Prepared by Dr. Kurt Schaberg

Soft Tissue Tumors

Overview

"Soft tissue" refers to the "connective tissues" surrounding other organs, including fat, muscle, fibrous tissue, blood vessels, lymph vessels and nerves.

Tumors arising in these sites often show mesenchymal differentiation.

Benign mesenchymal tumors far outnumber malignant tumors (i.e., sarcomas) by a factor of >100.

The most common benign tumor is Lipoma (30% of all soft tissue tumors), followed by fibrohistiocytic tumors (e.g., dermatofibroma), vascular tumors (e.g., hemangioma), and peripheral nerve sheath tumors (e.g., neurofibroma).

Benign tumors are *usually* superficial and <5 cm.
Sarcomas are *usually* > 5cm and/or deep-seated.

Soft tissue tumors considered challenging by many, likely in part due to the fact that they are relatively *rare* (particularly sarcomas), so we don't get to see many in training and practice, and they also have lots of *molecular* correlates, which most pathologists have limited experience with.

Always exclude (at least mentally) carcinoma, melanoma, lymphoma, and mesothelioma before making a sarcoma diagnosis.

Biologic Potential: *Beyond Benign and Malignant*

Particularly when it comes to soft tissue tumors, the division of tumors into only benign and malignant is an oversimplification ("false dichotomy"). Some tumors exhibit an "intermediate" or "borderline" behavior.

Most soft tissue tumors fit reasonably well into one of the 4 managerial categories below.

Category	Behavior	Examples
Benign	Almost always cured by complete *local* excision. Usually do *not* recur (and are non-destructive when they do). Exceedingly rare metastases.	Lipoma, Leiomyoma, Dermatofibroma, Neurofibroma
Intermediate (locally aggressive)	Infiltrative and locally destructive growth. Usually require *wide* local excision. Often recur locally. Very rarely (if ever) metastasize.	Desmoid fibromatosis
Intermediate (rarely metastasizing)	Often locally aggressive (see above), *and*, additionally, have a low rate of metastases (~2%) which is often unpredictable	Angiomatoid fibrous histiocytoma, Plexiform fibrohistiocytic tumor
Malignant (sarcoma)	Have substantial risk of distant metastases (depending on type and grade).	Myxofibrosarcoma, Leiomyosarcoma

Morphology frequently belies true biologic potential (with relatively bland tumors, like low-grade fibromyxoid sarcoma, exhibiting metastatic potential), so a firm histologic diagnosis is often necessary to predict behavior and assign a tumor into one of these categories.

It really depends on tumor type, location, etc… but many tumors of intermediate or malignant potential may be considered for adjuvant therapy (i.e., radiation or chemotherapy).

Approaches to typing

I take one of two approaches in trying to diagnose soft tissue lesions.

<u>Approach 1</u>: Identify a line of *differentiation*: I usually first start by trying to determine a line of differentiation, if possible, by morphology with the judicious use of immunohistochemistry, as necessary. For example, a lot of the time you can tell immediately if a tumor has adipocytic or vascular differentiation.

<u>Approach 2</u>: *Pattern-based* approach: Some lines of differentiation have overlapping morphology (e.g., some peripheral nerve sheath, smooth muscle, GIST, and fibroblastic tumors are all "Spindle cell" tumors). In these instances, I use IHC panels, with some morphologic hints.

Classification by Differentiation

This approach is what is taken by the WHO to classify tumors.

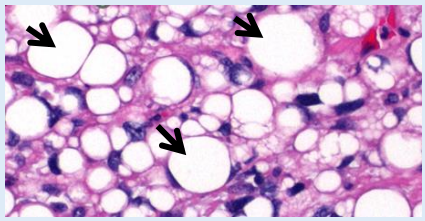
Cellular "***differentiation***" (**the specialized state of the cell** or **phenotype**; e.g., smooth muscle) may correlate with, but is not synonymous with, presumed "*histogenesis*" (cell of origin).

Histogenesis is hard to use for classification in reality as it requires assumptions *("It looks like X, therefore it must have <u>come</u> from X.")* and the fact that some tumors don't have a clear cell of origin.

Essentially, I try to find the line(s) of probable differentiation by morphology, possibly with supporting IHC, and then move to subtyping within that subdivision based on additional factors (e.g., atypia, components, etc…)

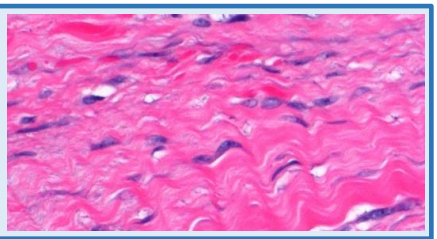
Adipocytic

Contain differentiated **lipocytes/lipoblasts (→)**.
Clear cytoplasmic vacuoles→ often distort or push aside nucleus
IHC: (+) S100 (but often not necessary)
Examples: Lipoma, Well-differentiated liposarcoma



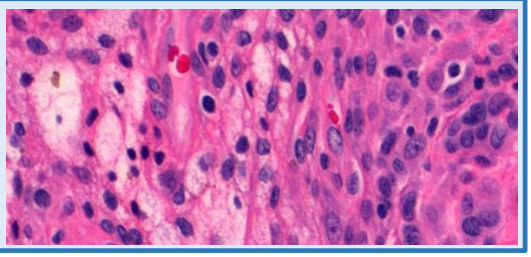
Fibroblastic/Myofibroblastic

Cells resemble fibroblasts or myofibroblasts (spindled cells in matrix)
Often have collagenous stroma
IHC: Variable, (+/-) SMA (with "tram track" pattern in myofibroblasts)
Examples: Fibroma, Inflammatory myofibroblastic tumor



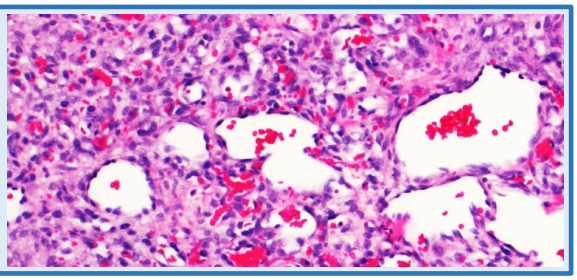
Fibrohistiocytic

Tumor cells **resemble histiocytes and/or fibroblasts**
Often more epithelioid to spindled cells.
IHC: Variable, (+/-) CD68
Examples: Dermatofibroma, Tenosynovial giant cell tumor



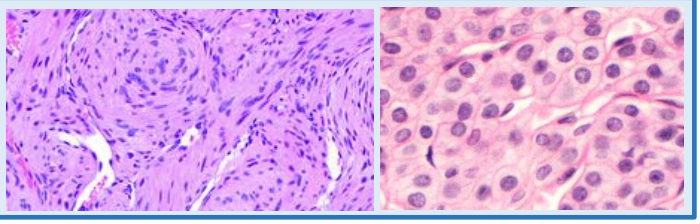
Vascular

Vessel formation by tumor cells
(includes slit-like spaces and intracellular lumens)
IHC: (+) ERG, CD31, CD34
Examples: Hemangioma, Angiosarcoma



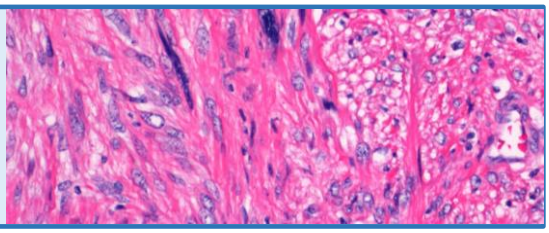
Perivascular/Pericytic

Modified vascular smooth muscle cells
Often dual **muscle** *and* **vascular** differentiation
IHC: Variable, (+) SMA,
Examples: Glomus, myopericytoma,



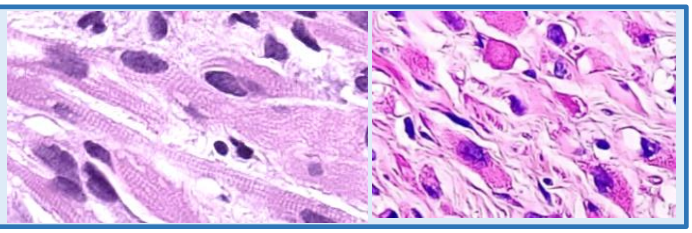
Smooth Muscle

Resemble smooth muscle: Cells arranged in **interesting fascicles**.
"Cigar-like" [dog dropping-like] nuclei
Required IHC: (+) Desmin, SMA, h-Caldesmon, and/or Calponin
Examples: Leiomyoma, Leiomyosarcoma



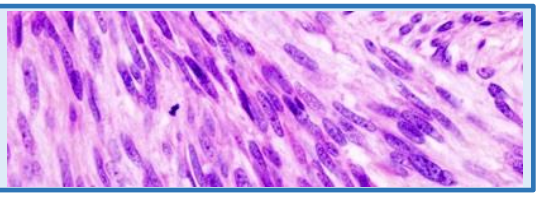
Skeletal Muscle

Cross-striated cells.
Rhabdoid cells to small round blue cells
Required IHC: (+) Myogenin, MyoD1, and/or Desmin
Examples: Rhabdomyoma, Rhabdomyosarcoma



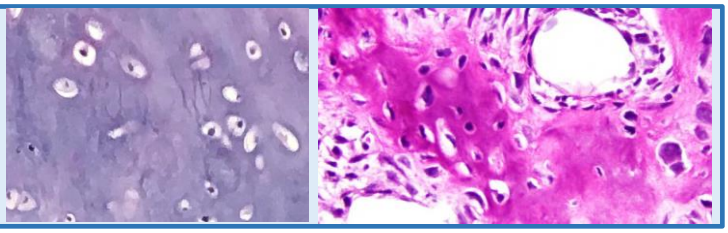
GIST

Derived from Interstitial cells of Cajal
Spindled to epithelioid cells. Usually arising in bowel wall
IHC: (+) CD117, DOG1, CD34



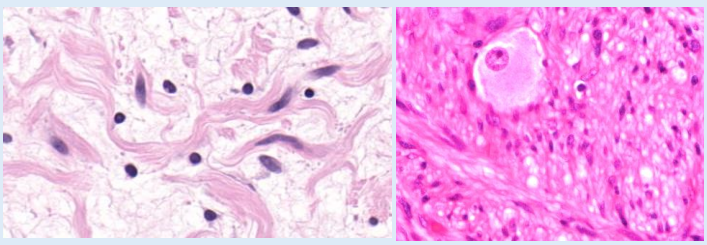
Chondro-osseous

Bone or cartilage production.
IHC: Cartilage (+) S100 (but often unnecessary)
Osteoblasts (+) SATB2 (but often unnecessary)
Example: Extraskeletal osteosarcoma



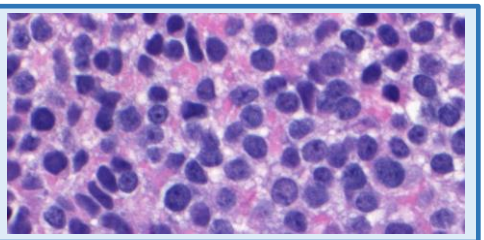
Peripheral Nerve Sheath

Spindled cells with **wavy, buckled nuclei**.
May see ganglion cells.
May see "parent" nerve
IHC: (+) S100, SOX10 (with some exceptions..)
Examples: Schwannoma, Neurofibroma, MPNST



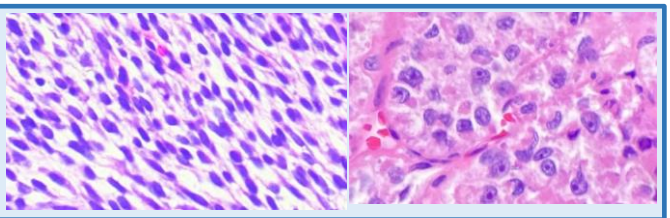
Small round cell sarcoma

Small **round cells** with **scant cytoplasm**.
Very **Blue**: High N:C ratio
IHC: Variable. Molecular: Fusions!
Examples: Ewing sarcoma, CIC-rearranged Sarcomas



Uncertain differentiation

Variable, often relatively unique morphology
IHC: Variable. Molecular: Fusions, often!
Examples: Synovial sarcoma, Alveolar soft part sarcoma



Pattern-Based Approach

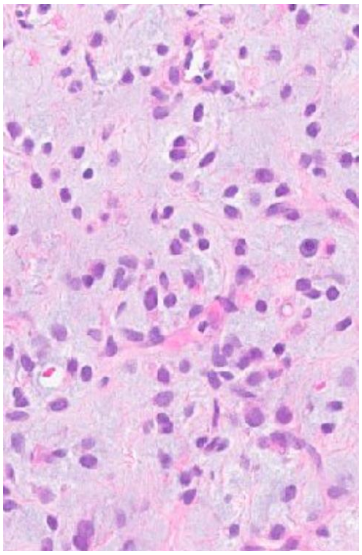
Modified from/inspired by: "Practical Soft Tissue Pathology" by Jason Hornick

Some tumor types show considerable morphologic similarities, requiring IHC to narrow things down. In these instances, I use a "pattern-based approach" with IHC panels (which I often tailor to each case).

Furthermore, it can be helpful to judiciously consider *mimickers* based on a pattern-based approach.

Myxoid

IHC to consider: S100, Desmin, CK AE1/AE3

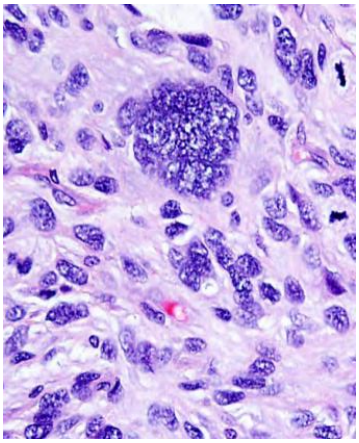


Myxoma
Neurofibroma
Perineurioma
Neurothekeoma
Spindle cell lipoma
Nodular fasciitis
Ossifying fibromyxoid tumor
Myxoid liposarcoma
Myxofibrosarcoma
Extraskeletal myxoid chondrosarcoma
Low-grade fibromyxoid sarcoma
Myoepithelioma
Myoepithelial carcinoma
Myxoinflammatory fibroblastic sarcoma
Aggressive angiomyxoma
Chordoma
Lipoblastoma
Nerve sheath myxoma
Intimal sarcoma
MPNST

Note: Some prefer SOX10 over S100

Pleomorphic

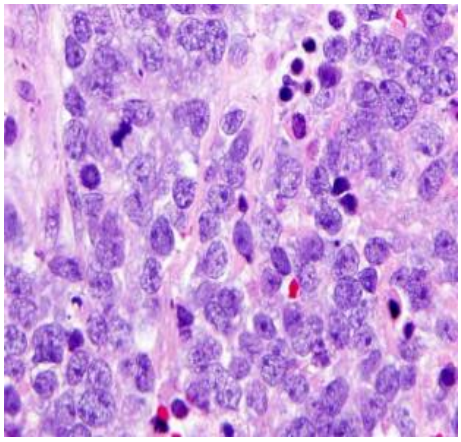
IHC to consider: S100, Desmin, Myogenin, CD45, CK AE1/AE3, ERG



Undifferentiated pleomorphic sarcoma
Pleomorphic leiomyosarcoma
Pleomorphic liposarcoma
Pleomorphic rhabdomyosarcoma
Dedifferentiated liposarcoma
Myxoinflammatory fibroblastic sarcoma
Pleomorphic angiectatic tumor
Myxofibrosarcoma
Angiosarcoma
Extraskeletal osteosarcoma
Pleomorphic fibroma
Pleomorphic dermal sarcoma
Atypical fibroxanthoma
Schwannoma/Neurofibroma (with ancient change)
Metastatic carcinoma
PEComa
Melanoma

Round cell

IHC to consider: S100, Desmin, CK AE1/AE3, CD45, CD99, TdT, WT-1, CD34, Synaptophysin, Myogenin,

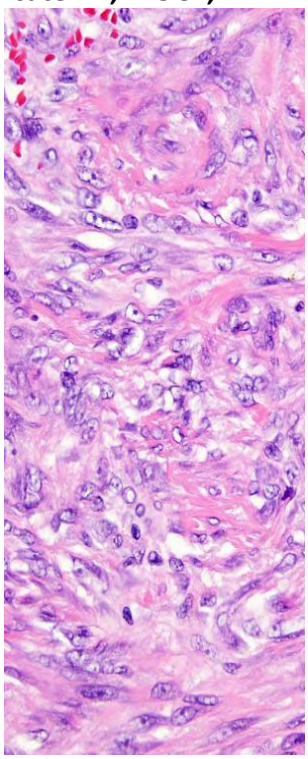


Ewing sarcoma
Alveolar rhabdomyosarcoma
Round cell (myxoid) liposarcoma
Desmoplastic small round cell tumor
Synovial sarcoma
Mesenchymal chondrosarcoma
CIC-rearranged sarcomas
BCOR-rearranged sarcomas
Lymphoma/Leukemia
Wilm's tumor
Neuroblastoma
Melanoma
Small cell carcinoma
Rhabdoid tumor

Spindled Cells

IHC to consider: S100, Desmin, SMA, CK AE1/AE3, p40, β-catenin, MUC4, CD34, CD31, CD117, STAT6,

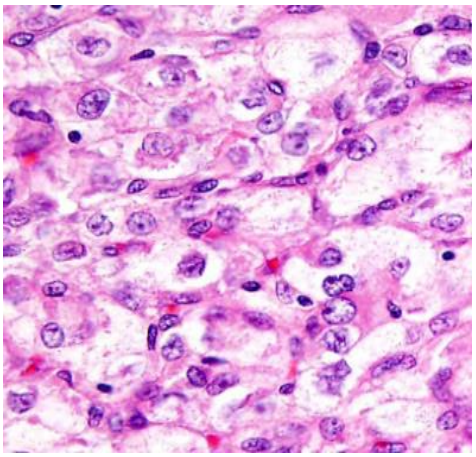
Nodular fasciitis
Inflammatory myofibroblastic tumor
Myofibroma/myopericytoma
Fibrous hamartoma of infancy
Calcifying aponeurotic fibroma
Fibromatosis
Schwannoma
Neurofibroma
Perineurioma
Ganglioneuroma
Spindle cell lipoma
Leiomyoma
Leiomyosarcoma
GIST
MPNST
Synovial sarcoma
Biphenotypic sinonsasal sarcoma
DFSP
Low-grade fibroblastic sarcoma
Embryonal/Spindled rhabdomyosarcoma
Kaposi sarcoma
Angiosarcoma
Fibrous histiocytoma
Dedifferentiated liposarcoma
Follicular dendritic cell sarcoma
Solitary fibrous tumor
Aggressive angiomyxoma
Myxofibrosarcoma
Fibroma (several kinds)
Myofibroblastoma (mammary-type)
Hemosiderotic fibrolipomatous tumor
Angiofibroma
PEComa



Epithelioid

IHC to consider: S100, Desmin, CD45, CK AE1/AE3, ERG, CD68, INI1, CD34

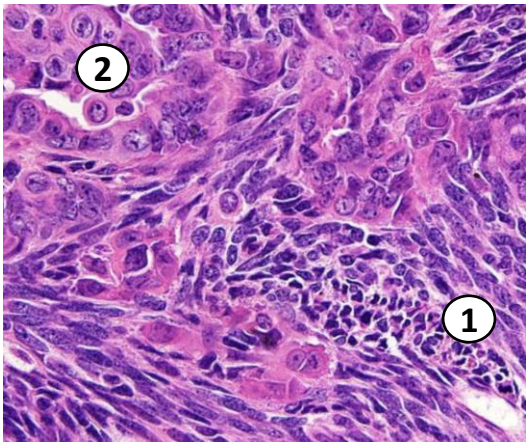
Epithelioid schwannoma
Epithelioid hemangioma
Epithelioid sarcoma
Extrarenal rhabdoid tumor
Epithelioid MPNST
Tenosynovial giant cell tumor
Myoepithelioma/carcinoma
GIST
PEComa
Meningioma
Clear cell sarcoma
Alveolar soft part sarcoma
Ossifying fibromyxoid tumor
Granular cell tumor
Juvenile xanthogranuloma
Glomus tumor
Epithelioid angiosarcoma
Epithelioid hemangioendothelioma
Metastatic carcinoma
Metastatic melanoma
Rhabdoid tumor



Biphasic

IHC to consider: S100, CK AE1/AE3, MDM2, SMA, H3K27me3

Carcinosarcoma
Biphasic synovial sarcoma
MPNST (with heterologous differentiation)
Ectopic hamartomatous thymoma
Dedifferentiated liposarcoma
Myoepithelioma/carcinoma
PEComa
(Biphasic) Mesothelioma
Leiomyoma
Schwannoma
Plexiform Fibrohistiocytic tumor
Angiomyofibroblastoma
Epithelioid sarcoma



Sarcoma Grading

For sarcomas, which are by definition malignant, histologic type alone often does not provide sufficient information for predicting clinical behavior and treatment planning. As such, the tumors must also be graded, most often using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system.

Grading is *ideally* done on resection specimens without pre-operative therapy (which may cause necrosis, thereby altering grade).

As tumors can be heterogeneous, only *minimum* grade can be assigned on a biopsy.

French Grading System (FNCLCC)

Tumor Differentiation	
Score 1	Sarcomas closely resemble normal adult tissue
Score 2	Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)
Score 3	Embryonal or undifferentiated sarcomas, sarcomas of doubtful subtype

Mitotic Count (per 40x field)	
Score 1	0-9 mitoses per 10 HPF
Score 2	10-19 mitoses per 10 HPF
Score 3	≥20 mitoses per 10 HPF

Tumor Necrosis	
Score 0	No necrosis
Score 1	<50% necrosis
Score 2	≥50% necrosis

Histologic Type	Score
Atypical lipomatous tumor/well-differentiated liposarcoma	1
Well-differentiated leiomyosarcoma	1
Myxoid liposarcoma	2
Conventional leiomyosarcoma	2
Myxofibrosarcoma	2
High-grade myxoid (round cell) liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Pleomorphic rhabdomyosarcoma	3
Poorly differentiated/pleomorphic leiomyosarcoma	3
Biphasic/monophasic/poorly differentiated synovial sarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Extraskeletal Ewing sarcoma	3
Malignant rhabdoid tumor	3
Undifferentiated pleomorphic sarcoma	3
Undifferentiated sarcoma, not otherwise specified	3

Total Score	Grade
2-3	Grade 1
4-5	Grade 2
6-8	Grade 3

Note: Tumors not included in the list, such as desmoplastic round cell tumor, alveolar rhabdomyosarcoma, and intimal sarcoma, are by definition high-grade.

Other tumors such as alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma, extraskeletal myxoid chondrosarcoma, low-grade fibromyxoid sarcoma, and sclerosing epithelioid fibrosarcoma are not assigned FNCLCC grade but may demonstrate late metastasis.

Grade is not used for angiosarcoma, as deceptively bland angiosarcomas may behave poorly, thus all are considered clinically "high-grade".

The prognostic significance of FNCLCC grading in malignant peripheral nerve sheath tumor is unclear.

***Modified from**: Collage of American Pathologists: Protocol for the Examination of Resection Specimens From Patients With Soft Tissue Tumors*

Sarcoma Genetics → Morphology

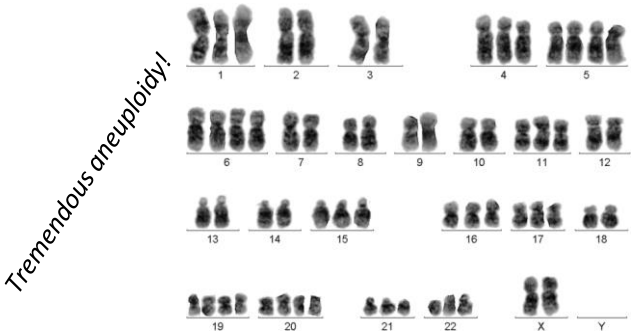
Broadly speaking, one can get a *hint* as to the genetics of a tumor by the basic morphology.
The more genetic changes a tumor has, often the more pleomorphic, heterogeneous, and "atypical" it will look. In contrast, tumors with a recurrent driver mutation/fusions often appear relatively bland and homogeneous/monotonous, with all cells having similar genetics.

"Complex" Genetics

Overall, **More common.**

Examples: Undifferentiated pleomorphic sarcoma, Myxofibrosarcoma,

***Lots* genetic changes!**
Often with many passengers and subclones

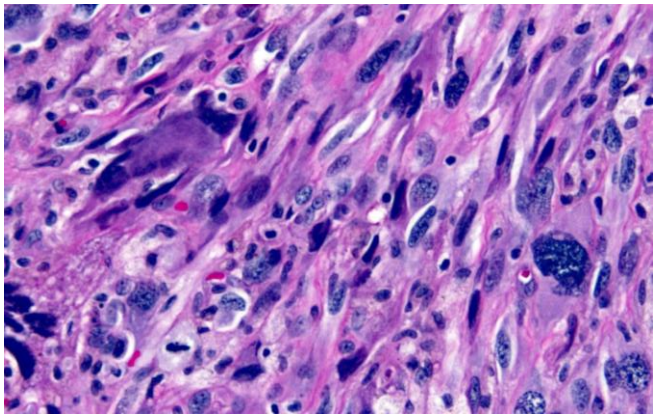


Very abnormal Karyotype with frequent **Aneuploidy**

Complex Genetics → Pleomorphic, heterogeneous Morphology

Significant **pleomorphism** and **heterogeneity**

IHC: Often weak, non-specific staining

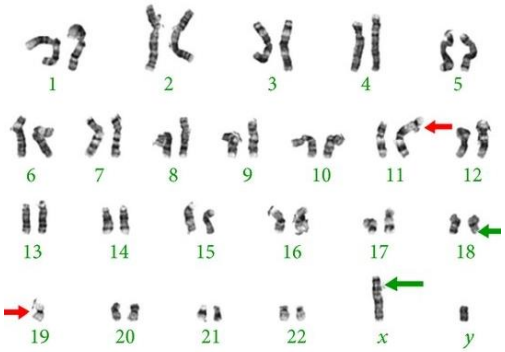


"Simple" Genetics

Overall, **Less common**
Most common in Sarcomas (~20%) and hematolymphoid tumors.

Examples: Synovial sarcoma, Infantile fibrosarcoma, Solitary Fibrous Tumor,

***Fewer* genetic changes**!
Often one main driver mutation, frequently a **fusion protein**.



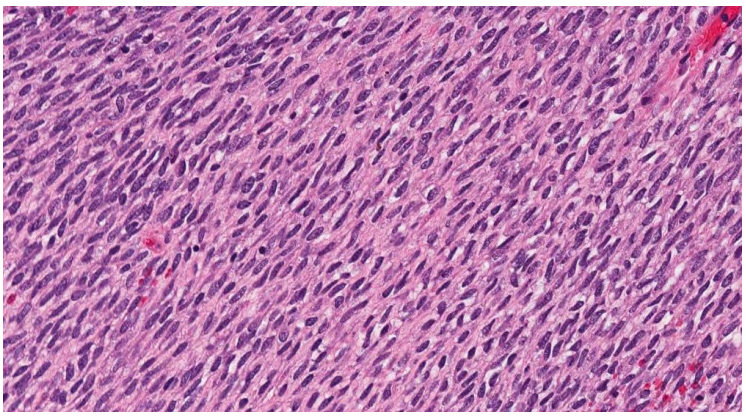
Synovial Sarcoma with X;18 translocation (green arrows) as well as association of chromosome 19 with telomere of chromosome 11 (red arrows).

Minimal Karyotype changes

Simple/monotonous Genetics → Monotonous, Consistent, Blander Morphology

Monotonous morphology with more bland cytology

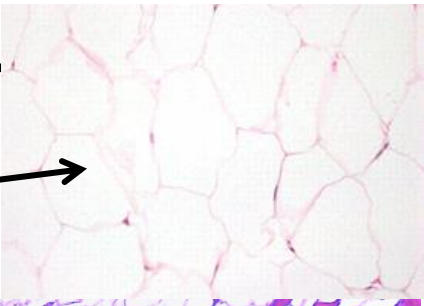
IHC: Frequently express multiple disparate makers (a helpful clue)



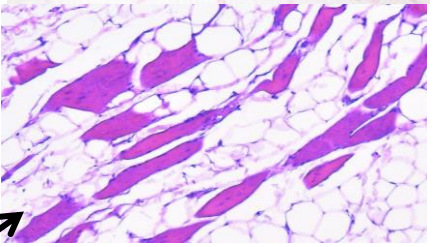
Adipocytic

Lipoma

Benign adipocytic tumors
Most are **mature** "white fat" with a single large lipid droplet.
No atypical, hyperchromatic cells. Usually superficial/subcutaneous.
Very **common**. Rare recurrences.



Although clinically form a mass, may be indistinguishable histologically from normal fat (so I often sign out as "Mature adipose tissue, compatible with lipoma")



Molecular: Various chromosomal aberrations. **HMGA2** often reactivated
Absence of giant marker/ring chromosomes and/or MDM2 activation

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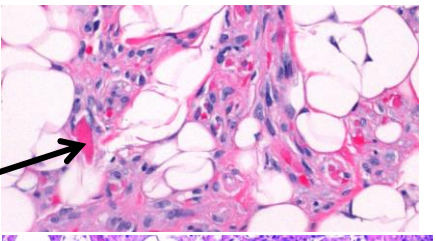
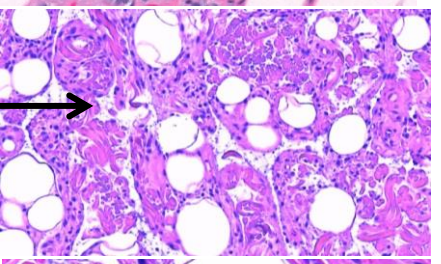
Additional lipoma types:

Intramuscular lipoma—within skeletal muscle. Often the thigh.
"Checkerboard" pattern of muscle and fat. Appear infiltrative.

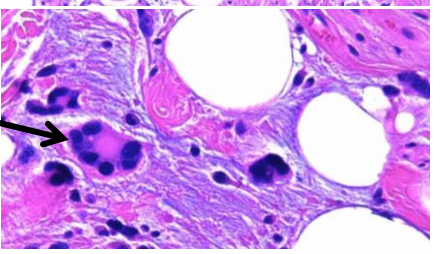


Angiolipoma—Fat + prominent branching network of vessels, often with fibrin thrombi. Usu. Tender nodule on forearm. Often young men.



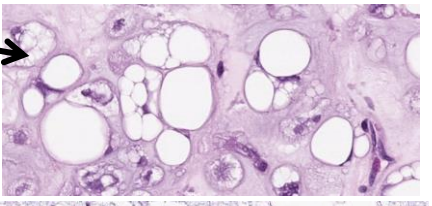
Spindle Cell Lipoma—Fat + bland spindle cells with ropey collagen in a variably myxoid background. Can be "fat-poor."

Note, these two subtypes (↑↓) exist on a spectrum. Classically, they are seen in older men in a "cape-like" distribution (neck, shoulder, back). Spindled and floret cells stain with CD34. Molecular: loss of RB1.

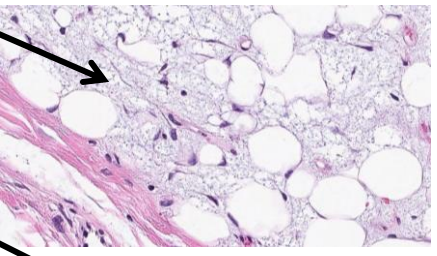


Pleomorphic Lipoma—Spindle cell lipoma + scattered, bizarre giant cells with floret-like arrangement of multiple hyperchromatic nuclei.

Myelolipoma—Fat + bone marrow elements. Most common in adrenal medulla.



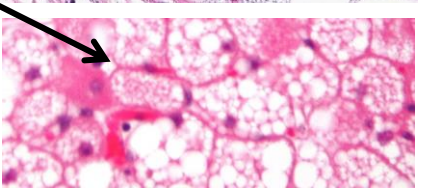
Chondroid Lipoma—Fat + lipoblasts in a myxochondroid background. Lobulated, circumscribed.



Lipoblastoma—Occurs in infants and resembles fetal adipose tissue. Lobules of immature fat cells separated by connective tissue septa with a loose myxoid appearance. *PLAG1* molecular rearrangements. Tendency to recur if incompletely excised. *Diffuse = Lipoblastomatosis*

Myolipoma—Fat + smooth muscle bundles

Hibernoma—Brown fat (multiple small vacuoles within polygonal cells with distinct cell membranes).



Lipomatosis of Nerve—Fat+ fibrous tissue growing *within* nerves. Surround and separate fascicles. Pseudo-onion bulbs. Usu. in arms.

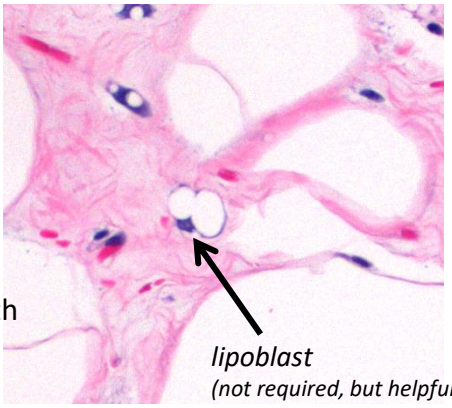
Lipomatosis—diffuse overgrowth of mature adipose tissue

Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma

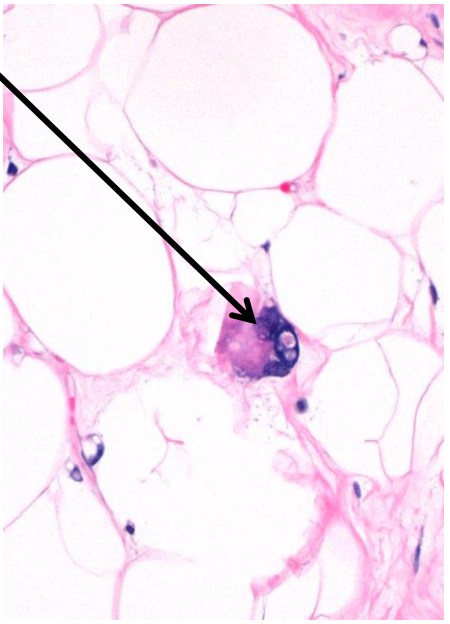
Most common adult sarcoma. Usually elderly.
Locally aggressive. Non-metastasizing (but recur/grow).

Deep soft tissue, most common in extremity, use ALT term: easier to excise, curable and less likely to recur.

In retroperitoneum, mediastinum, and spermatic cord: use WDL term, harder to excise, basically incurable.



Atypia! Variable amount of **lipoblasts** (cytoplasmic lipid-rich droplets with a hyperchromatic, indented/scalloped nucleus) and **hyperchromatic spindled cells.**



Can be lipoma-like (resembling mature fat), sclerotic (fibrous, non-lipogenic), or inflammatory (with associated brisk inflammatory infiltrate).

Molecular: Giant marker and ring chromosomes that contain amplified regions of 12q including MDM2 and CDK4 → Test for with MDM2 or CDK4 IHC, or, more commonly, FISH for **MDM2 gene amplification**. P16 is a sensitive (but not specific) marker as it is downstream from CDK4, so it is overexpressed.

Can De-differentiate and then have metastatic potential (see below).

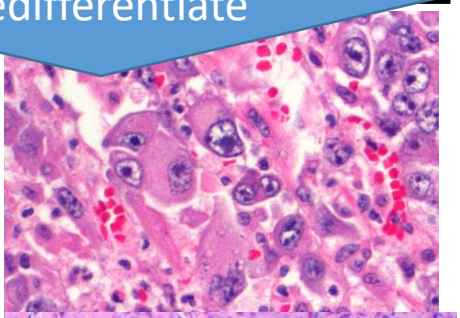
Fatty Tumors to FISH for MDM2

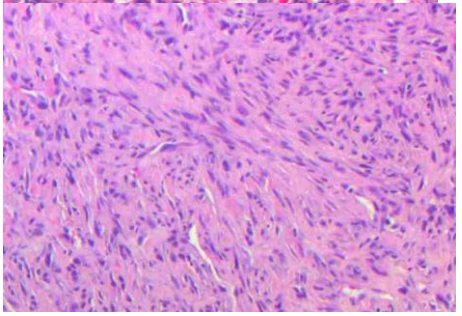
Use for suspicious/equivocal cases. No need to FISH classic cases with lipoblasts and/or atypia. PMID: 26146760

Lipomatous tumors with equivocal cytologic atypia
Recurrent lesions
Deep lesions without atypia that exceed 15 cm
Retroperitoneal or intra-abdominal lipomatous tumors lacking cytologic atypia *(Although retroperitoneal lipomas DO exist, they are very rare and a diagnosis of exclusion)*

Can Dedifferentiate

Dedifferentiated Liposarcoma





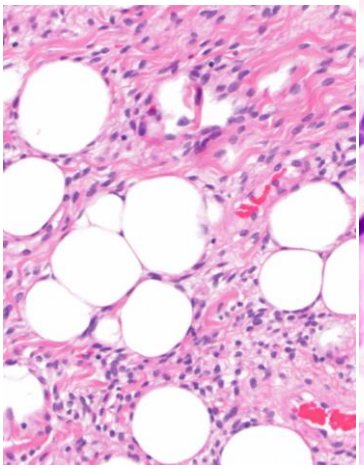
Transition from ALT/WDL, to another component, usually a spindle cell, **pleomorphic and non-lipogenic sarcoma** (of variable grade).

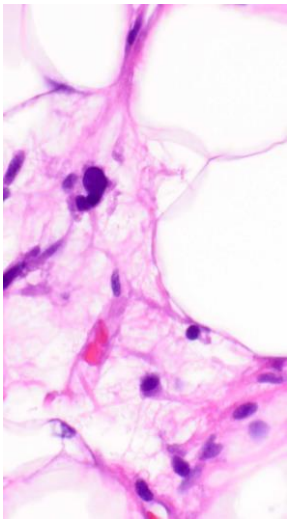
There is some controversy as to how to differentiate sclerotic (non-lipogenic) well-diff liposarcoma from De-diff. Some say de-differentiated areas should have a mitotic count of ≥5 mitotic figures per 10 high-power fields. PMID: 37057834

Molecular: Same underlying changes as ALT/WDL, so can use MDM2 FISH to support Dx if ALT/WDL component is inconspicuous.
Have *additional*, more complex, superimposed changes.

Most common in retroperitoneum→ most retroperitoneal pleomorphic sarcomas
Has Metastatic potential in addition to being more locally aggressive.

Atypical spindle cell/Pleomorphic lipomatous tumor





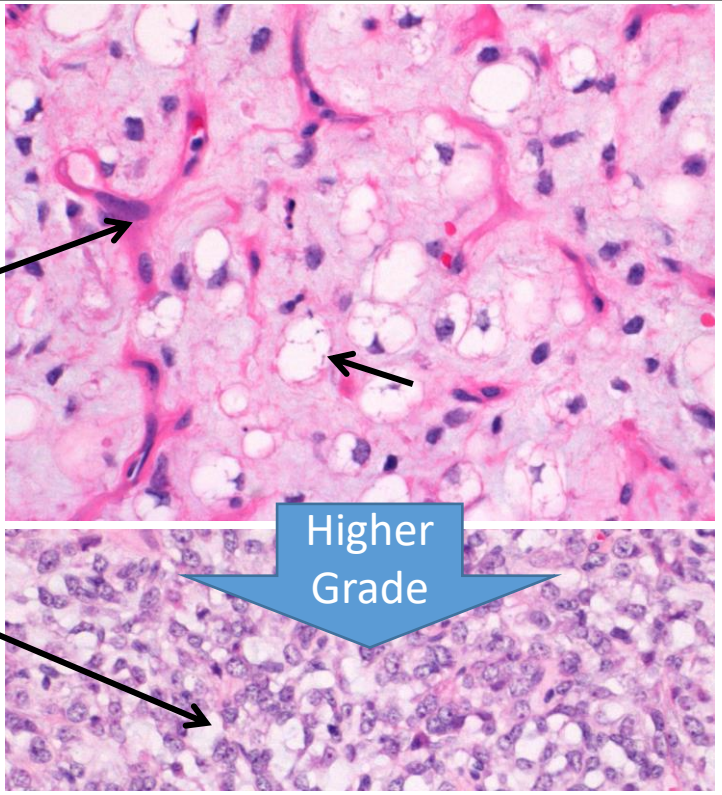
Benign (Non-metastasizing with low-rate of recurrence).
Do *NOT* de-differentiate.

Variable proportions of atypical spindled cells, adipocytes, lipoblasts, pleomorphic (multinucleated) cells , and myxoid to collagenous extracellular stroma
Mitoses usually rare.

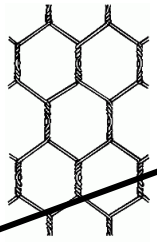
Usually **superficial** in **limbs** (esp. hands/feet)

Molecular: **RB1 loss**/deletion
No MDM2/CDK4 amplification
IHC: variable CD34, S100, Desmin

Myxoid Liposarcoma



Usually deep soft tissue of extremity, (esp. thigh).
Often younger.



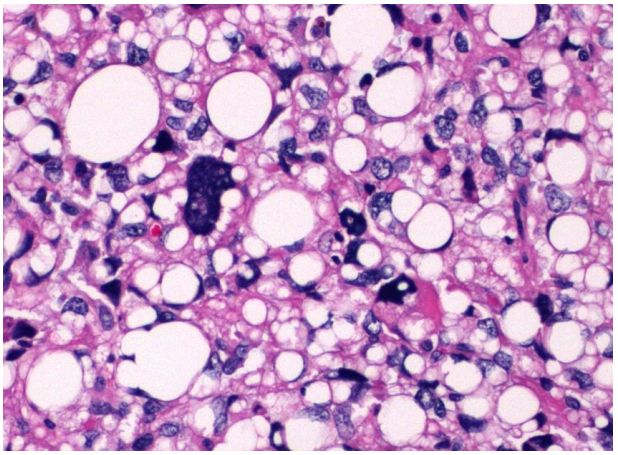
Resemble developing fat:
Abundant myxoid matrix,
Multinodular growth. Usually in fat.
Bland round cells.
Chicken-wire arborizing vasculature,
multivacuolar and univacuolar **lipoblasts**
Pools of mucin → "pulmonary edema-like"

As gets higher grade→ less myxoid component → composed of primarily round, overlapping cells → formerly "Round cell liposarcoma" (which is morphologically indistinguishable from other small round blue cell tumors).
>5% hypercellular component→ worse prognosis.

Molecular: DDIT3 fusions (usu. with FUS)

Frequently metastasize.

Pleomorphic Liposarcoma



Essentially, a pleomorphic high-grade sarcoma with scattered pleomorphic **lipoblasts**.

Sarcoma can be spindle cell, myxoid, epithelioid, etc…
Extreme pleomorphism including bizarre giant cells.
Least common liposarcoma.
Cannot have ALT/WDL component or other differentiation.

Malignant with frequent metastases.

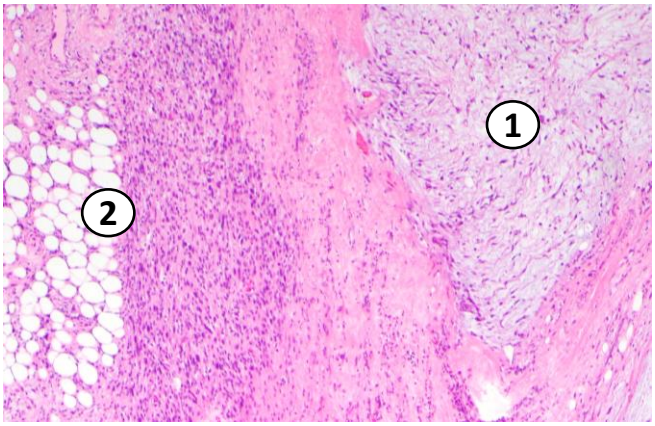
Molecular: Complex structural chromosomal rearrangements. NO MDM2 amplification

Myxoid Pleomorphic Liposarcoma

Very **rare**, usually in **Children** and adolescents
Aggressive with poor survival.

Two morphologic components:
1) Conventional myxoid liposarcoma
2) Pleomorphic liposarcoma

However, it lacks the DDIT3 gene fusions seen in usual myxoid liposarcoma and MDM2 amplification seen in ALT/WDL and De-diff liposarcoma.

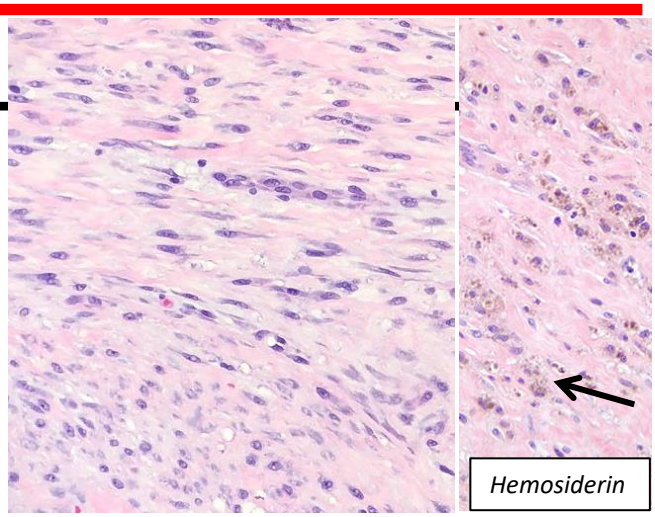


Lipomatous Tumor Comparison Table

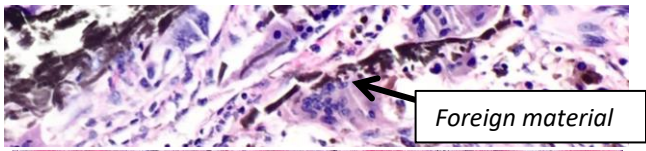
	Clinical	Morphology	Spindle cells	Myxoid areas	Lipoblasts	Genetics	Behavior
(Conventional) Lipoma	Extremely common. Usually older	Mature white fat	No	No	No	HMGA2 activated	Benign
Spindle cell/ Pleomorphic Lipoma	Usually old men on the back of the neck	Fat + spindled cells, ropey collagen, ± floret-like cells	Yes	Maybe	No	RB1 inactivation	Benign
Lipoblastoma	Infants. Trunk and extremities	Lobules of immature fat with loose myxoid appearance	Not much	Yes	Yes	PLAG1 fusions	Benign, can recur
Atypical spindle cell/Pleomorphic lipomatous tumor	Superficial. Limbs (esp. hands & feet)	Atypical spindle cells, adipocytes, lipoblast, multinucleated	Yes	Maybe	Yes	RB1 loss	Benign, can recur
ALT/ Well-differentiated liposarcoma	Deep soft tissue of extremity and retroperitoneum	Atypical spindled cells and lipoblasts	Often	Maybe	Maybe	MDM2 and/or CDK2 amplification	Locally aggressive and recur
Dedifferentiated liposarcoma	Most common in retroperitoneum	Transition from ALT/WDL to non-lipogenic sarcoma	Maybe	Usually no	Maybe	MDM2 and/or CDK2 amplification	Malignant
Myxoid liposarcoma	Deep soft tissue of extremities	Myxoid matrix with delicately arborizing vessels and lipoblasts	Maybe	Yes	Yes	DDIT3 fusions (usu. with FUS)	Malignant
Pleomorphic liposarcoma	Usually extremity of older adults. Rare.	Pleomorphic sarcoma containing lipoblasts	Maybe	Maybe	Yes	Complex genetics	Malignant

Fibroblastic/Myofibroblastic

Scar/Fibrosis

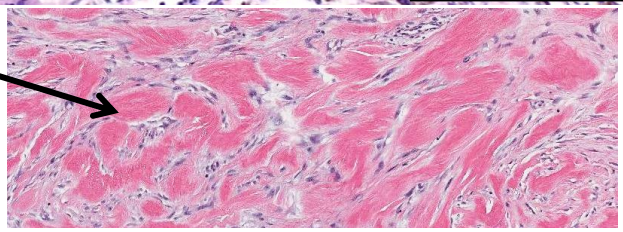


Site of prior <u>trauma</u> or <u>procedure</u>.
Fibroblasts in abundant extracellular collagen
Frequent <u>inflammatory cells</u>
± <u>Hemosiderin</u> laden macrophages
± <u>Foreign material</u> and/or foreign body giant cells
± Fat necrosis
Variable vascularity, but can be prominent.
Often lots of small capillaries and telangiectatic vessels



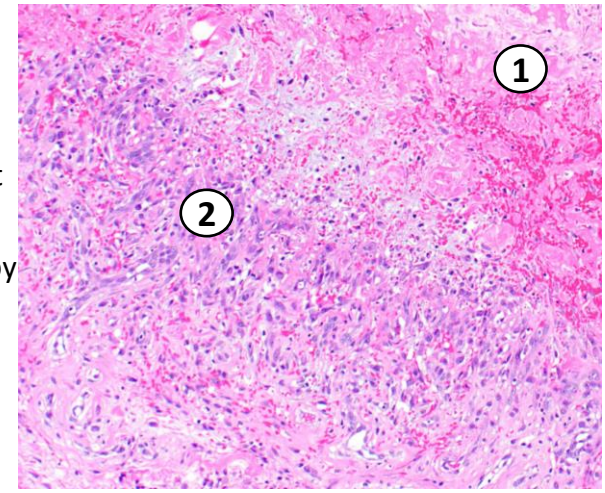
<u>In skin</u>: Epidermal atrophy and loss of adnexal structures
Horizontal running fibrosis with vertically oriented vessels

<u>Keloid</u>



Scar + Prominent thick, eosinophilic bundles of collagen
Most common in those with African heritage
Overgrows beyond wound.
Most common site is earlobe (e.g., after piercing)

Ischemic Fasciitis



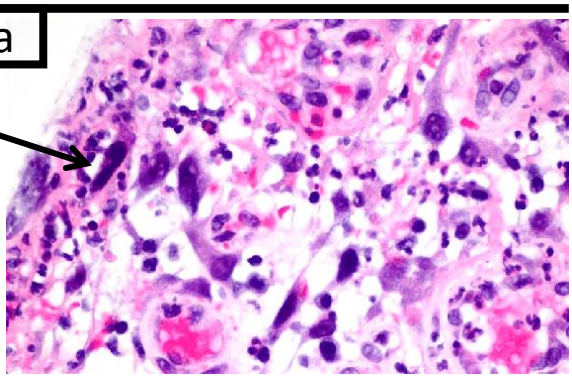
Non-neoplastic/reactive proliferation <u>overlying bony prominences of elderly and/or immobile patients</u>.

Often shoulder or sacral site in deep subcutis → intermittent ischemia with breakdown/regenerative changes.

Zonal growth with **1) central fibrinoid necrosis** surrounded by **2) proliferating blood vessels (granulation tissue-like)** and fibroblasts/myofibroblasts.

Can see scattered hyperchromatic atypical cells and mitoses, but no atypical mitoses.

Reactive "*Pseudosarcoma*" Stromal Atypia



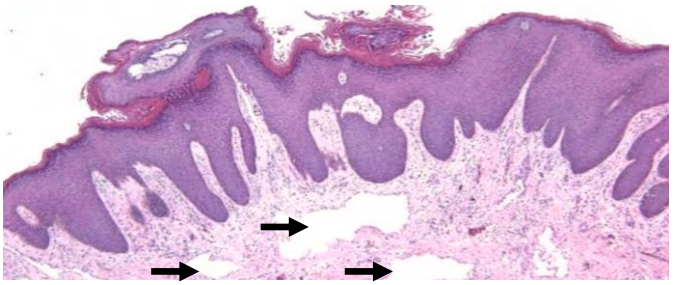
Bizarre, enlarged stromal cells, often seen in an area of <u>inflammation</u>/<u>ulceration</u>.
(easily <u>mistaken</u> for, but are <u>not</u> sarcoma)

Can be multinucleated. Spindled to epithelioid.
Commonly seen in colon inflammatory polyps or ulcers.

Can be mistaken for viral change or malignancy.

The main key to recognizing these as not tumor (despite the often eye-catching atypia!) is the inflammation and clinical context. Stains don't really help (except to rule out viral effect)

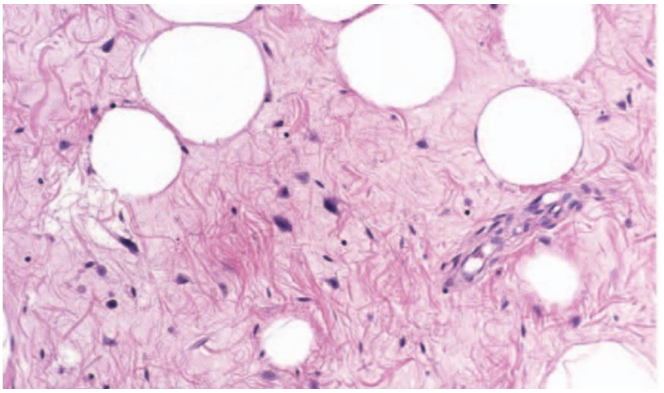
Localized Massive Lymphedema



Reactive (non-neoplastic), likely due **to lymphatic obstruction.**

Associated with **obesity** and immobilization→ thought that regional lymphatics become compressed and obstructed by heavy folds of dependent fat.

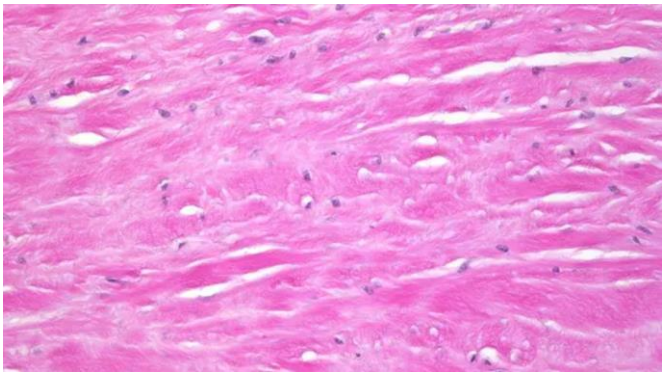
May present with generalized enlargement of medial portions of the arms and legs, including the groin,



Dermal edema with uniformly distributed cells.
Septae in subcutaneous fat are markedly expanded by edema fluid, plump fibroblasts, and collagen.
Dilated lymphatics (arrows).
Perivascular inflammation.

Can be confused for liposarcoma: shouldn't see lipoblasts or severely atypical stromal cells.

Desmoplastic Fibroblastoma



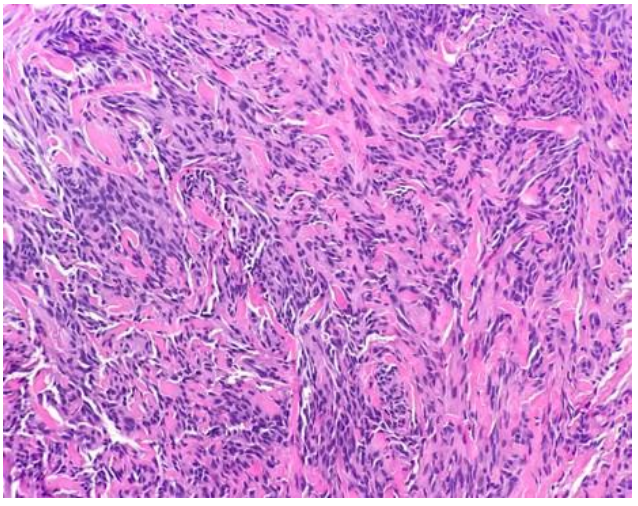
(aka Collagenous fibroma)

Benign.

Usually, slow-growing subcutaneous mass on extremity of an adult.

Paucicellular with **abundant collagen** or myxocollagenous matrix.
Scattered, bland stellate to spindled cells.

Myofibroblastoma



(aka Mammary-type Myofibroblastoma)

Benign. Frequently seen in **breast**.
Also, **inguinal/groin**. Usually well-circumscribed.

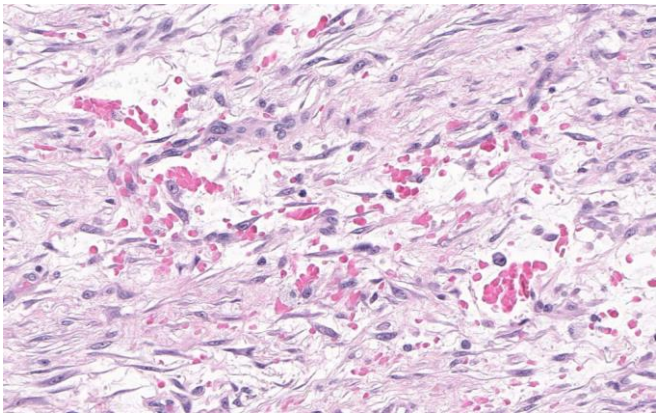
Haphazardly intersecting short fascicles of bland, short or elongated spindled cells.
Bands of hyalinized collagen.
Variable adipocytic component.
Can see Schwannoma-like nuclear palisading.

IHC: (+) CD34, Desmin

Molecular: Loss of RB1 (can show with IHC)

(Sounds like and looks sort of like, but is not…)
Intranodal Palisaded Myofibroblastoma
An intranodal benign spindle cell proliferation expressing actin(s); variably shaped dense collagenous bodies. Usually groin lymph nodes. Can see pink perinuclear vacuoles. Often nuclear palisading and collagen bodies.
IHC: nuclear β-catenin and/or cyclin D1 expression.

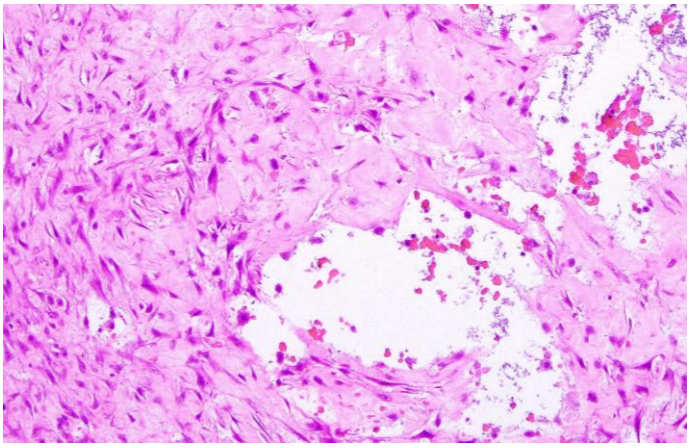
Nodular Fasciitis



Benign, **self-limited**, "transient neoplasia."

Rapidly growing, mass-forming **subcutaneous** lesion, sometimes after trauma, that self-regresses. Often upper extremity or head and neck of kids or young adults.

Can be misdiagnosed as a sarcoma because of rapid growth and mitotic activity. Previously thought to be reactive.



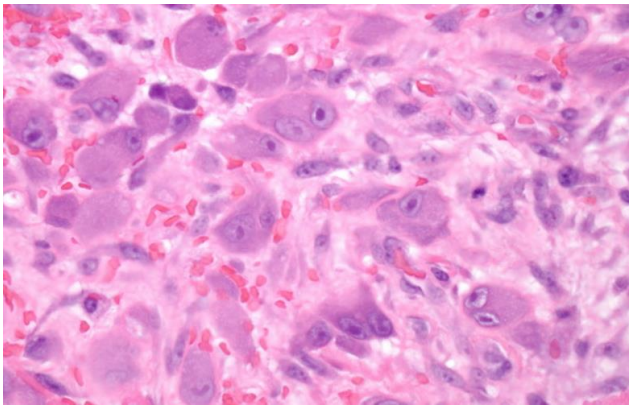
Bland spindled to stellate cells with variably cellular "**tissue culture-like" pattern** with microcystic changes.
"Torn stroma" resembling "S" and "C" shapes.
Extravasated RBCs. Variably myxoid.
Can see giant cells.
Older lesions may be scarred/collagenous.

Molecular: **USP6 gene fusions** (usually with MYH9)

IHC: **Actin (+)** (as myofibroblastic), but desmin (-).

Specific variants: Ossifying fasciitis (with metaplastic bone), Cranial fasciitis (on scalp of infants), and intravascular fasciitis (in vessels).

Proliferative Fasciitis/Myositis



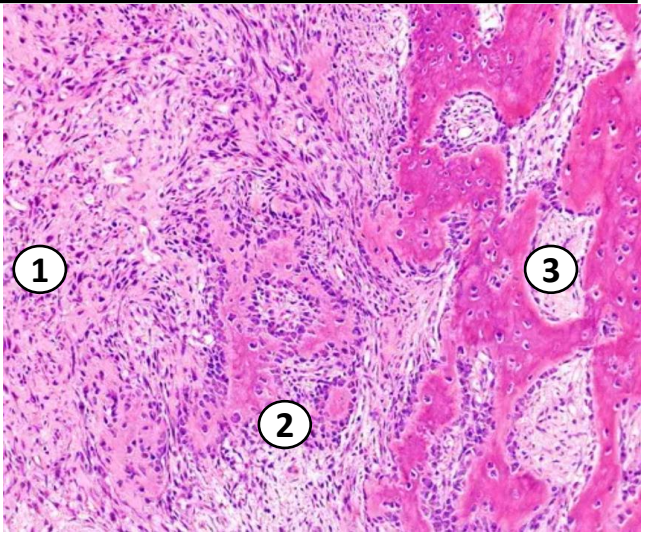
Benign. Subcutaneous soft tissue of adults usu. on arm.

Like nodular fasciitis (tissue culture-like)
Prominent large, basophilic ganglion-like cells with one or two vesicular nuclei and prominent nucleoli.
IHC: Similar to Nodular fasciitis. Not true ganglion cells (negative S100, etc…)

Molecular**: FOS** rearrangements

If in muscle, use "Proliferative myositis."

Myositis Ossificans



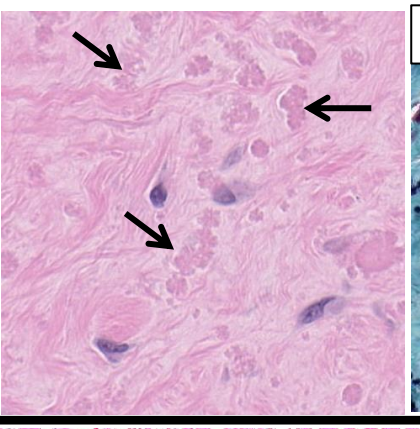
Benign. Self-limited Neoplasms.
Most common in **sites susceptible** to trauma, like buttock, elbow, thigh. Usually in skeletal muscle.
Usually **younger** patients. Grow rapidly.

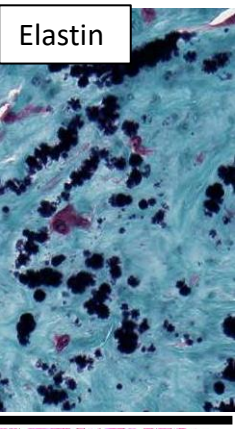
1) Central hypercellular fascicles of uniform spindle cells;
2) admixed **woven bone** and osteoblasts, maybe cartilage,
3) most mature at the periphery (Zonation).
Lots of mitoses. **Bland cytology**.

Molecular: **USP6 rearrangements**.

On finger?→ Fibro-osseous pseudotumor of digits

Elastofibroma



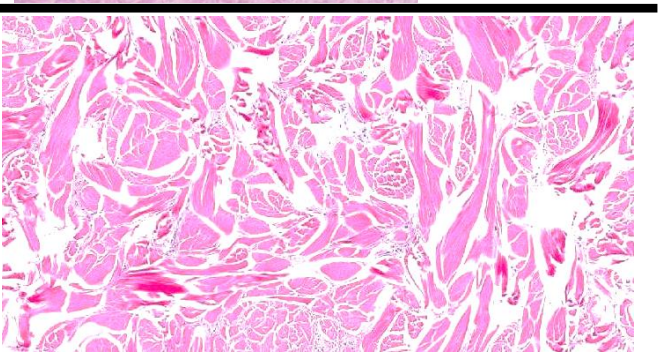


Benign (likely reactive/degenerative pseudotumor).
Usually under scapula of elderly patient. Ill-defined.

Eosinophilic collagen and **Elastin**.
Occasional fibroblasts, myxoid material, and fat.
Elastic fibers have a degenerative, "beaded" appearance that can fragment into flower-like disks

Stains: Can highlight Elastin with EVG.

Nuchal-type Fibroma

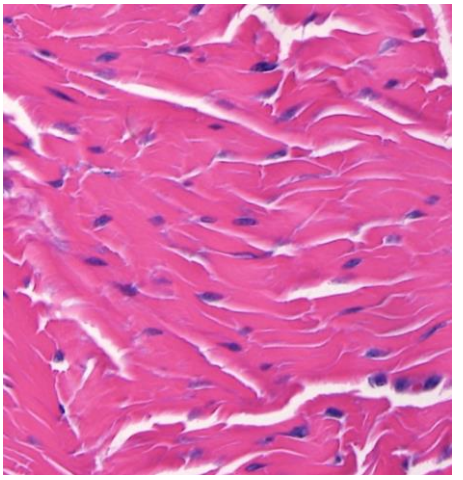


Benign. Usu. Posterior neck of adults. Painless mass.

Almost acellular densely collagenized with rare fibroblasts. Somewhat ill-defined entrapping adjacent structures.

IHC: Spindled cells usu. (+) CD34 and CD99. (-) actin.

Gardner-associated Fibroma



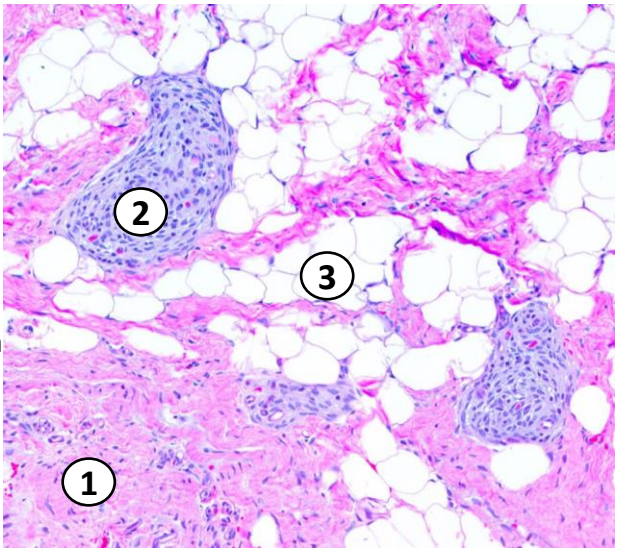
Benign.
Plaque-like mass in the **paraspinal region** or trunk of **young children**.
Strong association with FAP and desmoid tumors (Gardner syndrome).

Histologic overlap with nuchal-type fibroma.

Densely collagenized with sparse spindled cells with interspersed lobules of fat. Haphazard coarse collagen with Clefts & Cracks.
Can entrap other structures at periphery.

IHC: Spindled cells usu. **(+) CD34** and CD99.
Often **nuclear β-catenin** (like desmoids!)

Fibrous Hamartoma of Infancy



Benign superficial fibrous lesion occurring during **first 2 years of life**

3 components in organoid growth pattern:

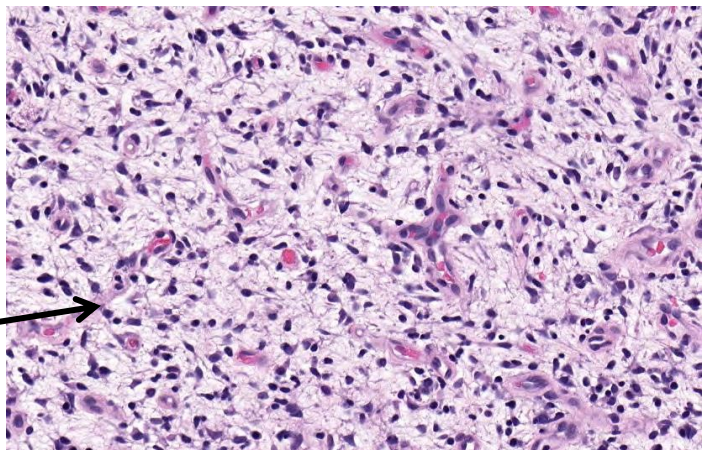
1)Intersecting bands of **mature fibrous tissue**, comprising spindle-shaped myofibroblasts and fibroblasts

2) Nests of **immature round, ovoid, or spindle cells** within loose stroma

3) Interspersed **mature fat**

Molecular: EGFR exon 20 insertion/duplication

Angiofibroma of Soft tissue



Benign.

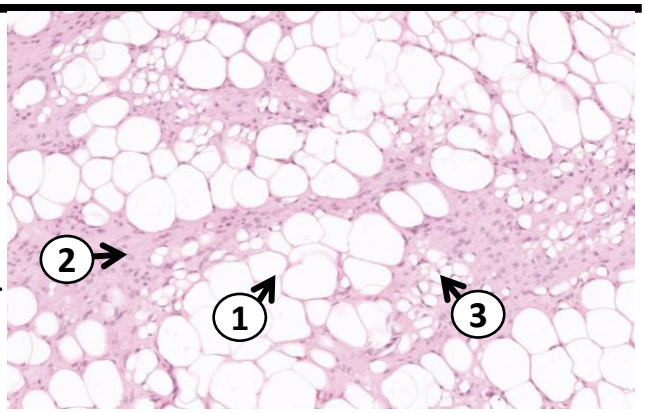
Subcutaneous. Usually on the **extremities**, usually near joints, especially the **knee**.

Variably myxoid or collagenous stroma
Bland spindled and uniformly **short spindled cells**
Innumerable small, thin-walled branching vessels.
Variable lymphoid infiltration.

Molecular: **NCOA2 gene rearrangements.**

IHC: (+/-) CD34, EMA

Lipofibromatosis



Rare. Benign, with <u>high rate of recurrence</u>.
Most often on the hands and feet of young children.
Painless subcutaneous mass.

Admixture of 1) mature fat, 2)short fascicles of bland spindle cells, and 3) lipoblast-like cells; infiltrative margins.

Vs fibrous hamartoma of infancy→ No primitive cells and + lipoblasts.

"Soft tissue tumors of the specialized Genital Mesenchyme"

These tumors all occur primarily in the **vulvar/perineum/pelvis**. Because of their similarities in name, morphology, location, and behavior, Dr. Richard Kempson would refer to them collectively as being derived from the "specialized genital mesenchyme" (of the GYN tract), which I think is conceptually helpful. <u>See my vulvar notes for more specific details on these tumors</u>, which are only outlined here.

<u>Angiomyofibroblastoma</u>: Benign. Well-circumscribed, prominent stromal vessels; round to spindled cells (often multinucleated) in a perivascular distribution. IHC: (+) Desmin

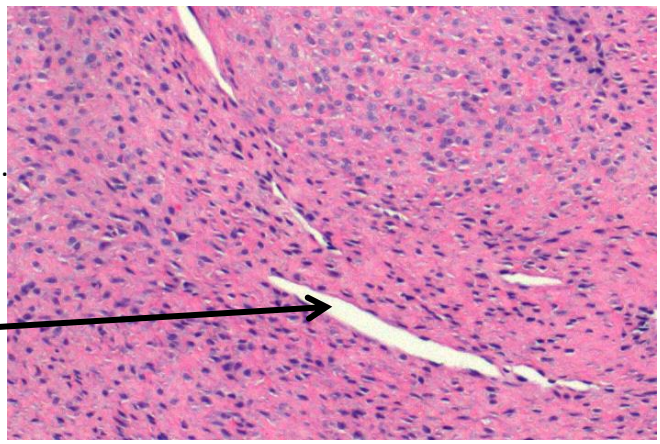
<u>Cellular angiofibroma</u>: Benign. Bland spindled cells, short bundles of delicate collagen fibers, and numerous small to medium-sized thick-walled vessels, with or without adipose tissue. Loss of RB1.

<u>Deep (Aggressive) Angiomyxoma:</u> Benign (despite name!), but with a tendency to recur after incomplete resection. Low-grade, hypocellular. Composed of small, bland spindled cells with scant cytoplasm. Numerous prominent blood vessels of varying sizes. IHC: (+)ER, PR, desmin. (+/-) CD34. Molecular: HMGA2 rearrangements

<u>Superficial Myofibroblastoma</u>: Benign. Oval to spindled cells with wavy nuclei and scant cytoplasm Fine collagenous stroma. Varied architecture. Thin-walled vessels, which might be dilated and "Stag-horn." IHC: (+) Desmin, ER/PR; (+/-) CD34

<u>Superficial Angiomyxoma</u>: Benign with localized recurrences. Exophytic polypoid mass centered in skin and subcutaneous tissue ("Superficial"!!). Multilobulated. Well-demarcated, but unencapsulated. Hypocellular myxoid nodules in dermis. Bland stellate and spindled cells and inflammatory cells (classically neutrophils) and numerous delicate vessels.

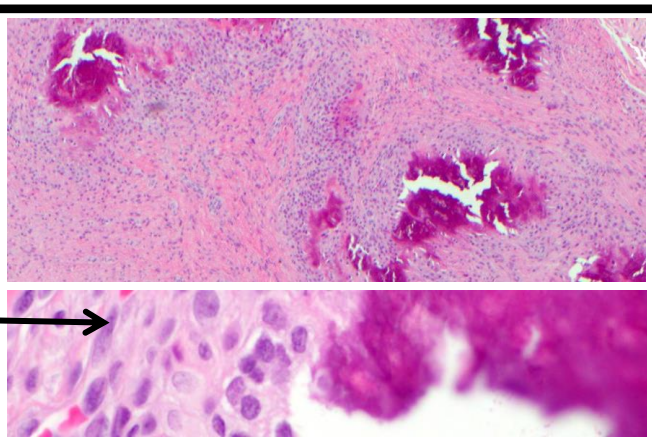
Fibroma of Tendon Sheath



Benign. Slowly growing **mass on tendon** sheath or aponeuroses.
Usu. **adults**, under 2 cm, and on extremities, often **hand**.

Well-circumscribed, lobulated.
Mostly hypocellular with spindled cells in densely collagenized stroma.
Characteristic cleft-like areas spaces, possibly vascular.
IHC: variable actin and CD68 (not too useful)
Molecular: USP6 rearrangements in some cellular ones

Calcifying Aponeurotic Fibroma

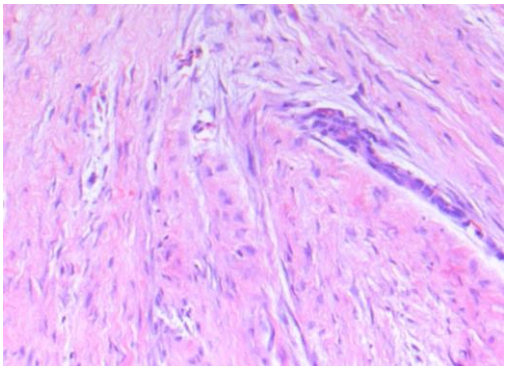


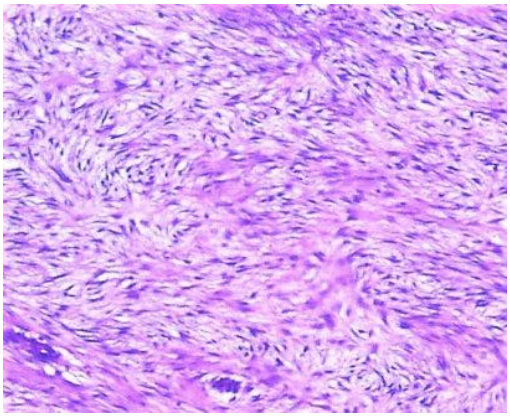
Benign. Primarily in Children. Can recur.
Slow-growing, painless mass on hands or feet attached to aponeurosis, tendons, or fascia

Variable cellularity throughout lesion.
Bland, plump fibroblasts with dense collagen.
Distinct areas of calcification (and cartilage) with surrounding plump fibroblasts. Infiltrative growth.

Molecular: FN1-EGF fusions

Desmoid Fibromatosis





Locally **aggressive**, but *non*-metastasizing
Classically treated with resection, but recurrence does not consistently correlate with margin status, and they can spontaneously stabilize/regress, so sometimes observed now.

Deep-seated: extremity soft tissue, retroperitoneum, trunk.

Infiltrative growth into surrounding structures (esp. skeletal muscle).
Broad, sweeping fascicles. (often span a whole 10x field!)
Uniform spindled cells with small, pale nuclei with pinpoint nucleoli.
Sometimes more stellate in shape.
Moderate amounts of collagen, surrounding cells, in slightly myxoid background. Thin-walled vessels. Can see keloidal collagen.
With age, less cellular and more collagen.
Microhemorrhages and scattered chronic inflammation.

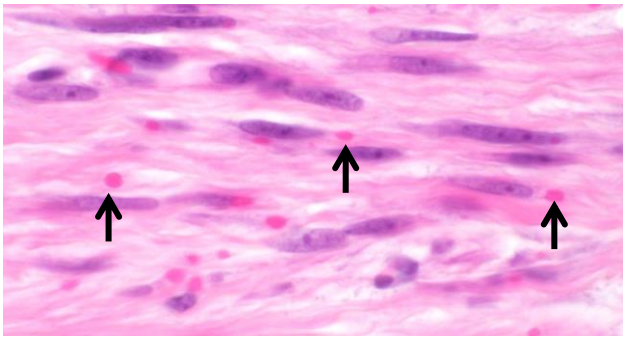
IHC: **Nuclear β-catenin** (~80%, often very focal).
Some actin (+)

Molecular: **β-catenin (CTNNB1) mutations** often.
Gardner syndrome have APC mutations (in same pathway)

Palmar/Plantar Fibromatosis

Benign. Nodular fibroblastic proliferation involving volar hands/fingers or plantar aponeuroses. Usually older men. Bland, variably cellular spindled cells in collagenous stroma. Can recur.

Rare Infancy/Childhood Fibromatoses

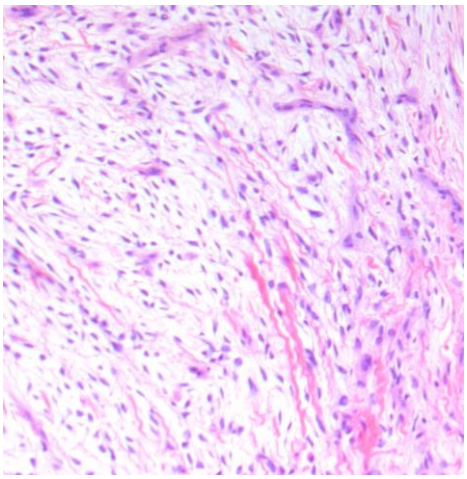


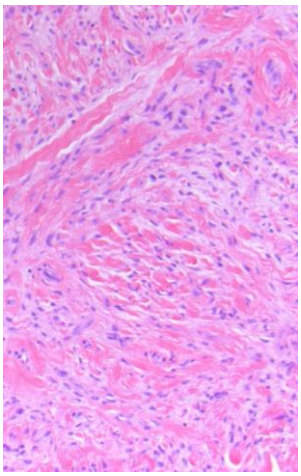
Inclusion body fibromatosis
(aka infantile digital fibroma)
Benign. Infants or Kids, usually on the digits. Sometimes multicentric, myofibroblastic tumor with characteristic intracytoplasmic inclusions. Can recur.

Juvenile hyaline fibromatosis
Extremely rare autosomal recessive syndrome that presents in infancy. Painful, disfiguring deposits of hyalinized fibrous material in dermis, soft tissue, and gingiva. Germline ANTXR2 mutations.

Fibromatosis colli
Benign, likely reactive, self-limited fibrous proliferation occurring in the sternocleidomastoid muscle of infants→ can shorten muscle causing torticollis.
Micro: paucicellular scar-like tissue with entrapped skeletal muscle

Acral fibromyxoma





Benign, but can recur.

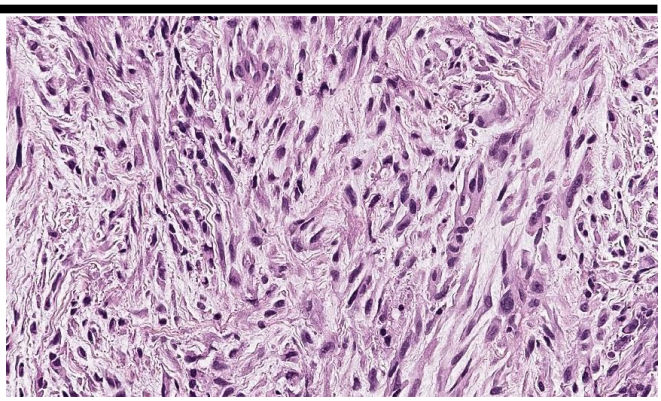
Acral, usually **periungal location**.
Dermal-based with infiltration of subcutis;

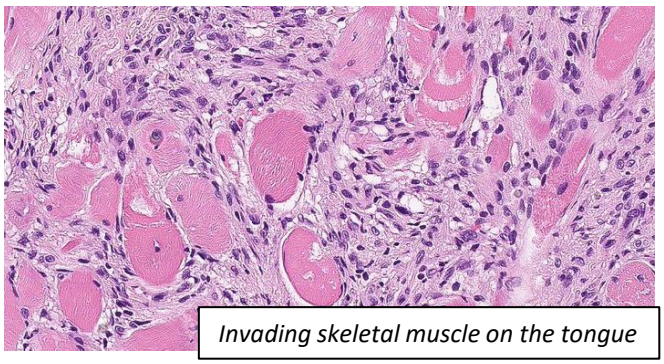
Lobulated architecture with vaguely storiform or fascicular growth. **Bland spindle cells** with a variably **myxoid or collagenous matrix**.

IHC: **(+) CD34**

Molecular: Frequent RB1 loss

Low-grade myofibroblastic sarcoma





Invading skeletal muscle on the tongue

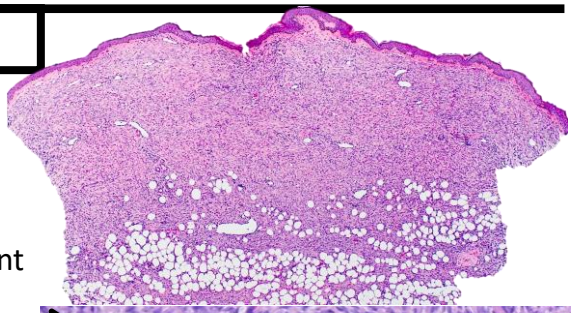
Rarely metastasizing sarcoma.
Usually **head/neck of adults**, esp. tongue/oral cavity.

Diffusely infiltrative growth, often between skeletal muscle fibers.
Cellular fascicles of spindle cells with pale eosinophilic cytoplasm.
At least focal **moderate nuclear atypia**
(hyperchromasia and pleomorphism)

IHC: (+/-) SMA, Desmin; Maybe focal nuclear β-catenin

DDX:
Fibromatosis→ Less infiltrative, no atypia
Leiomyosarcoma→ Diffuse muscle marker expression

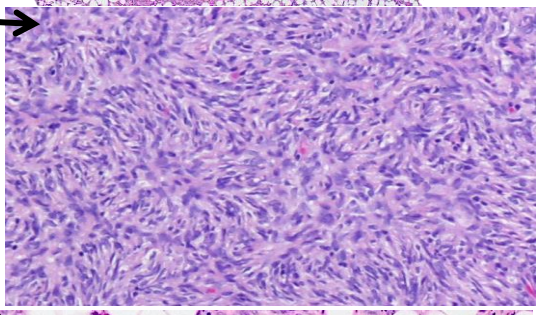
Dermatofibrosarcoma Protuberans (DFSP)



Benign, but locally aggressive and can **transform**.

Often **Young adults**. Plaque-like growth on the trunk.

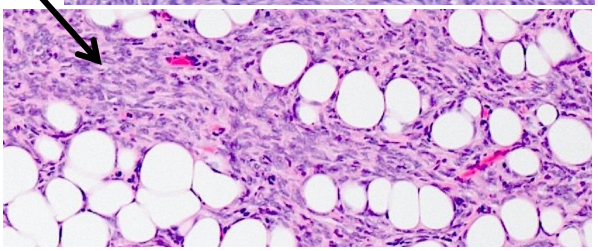
Spindle cell tumor Proliferation of **monomorphic** spindle-shaped cells with **deep dermal and subcutaneous** involvement
Arrayed in ***storiform*** or cartwheel patterns
Lesional cells typically lack significant atypia and pleomorphism



Infiltrative growth: Subcutaneous areas typically show honeycombing fat entrapment ("pearls on a string")

Various morphologies: Myxoid, "Pigmented," etc…

If loses storiform pattern→ herringbone pattern with more atypia & mitoses → consider *malignant transformation* to *fibrosarcoma* (malignant)

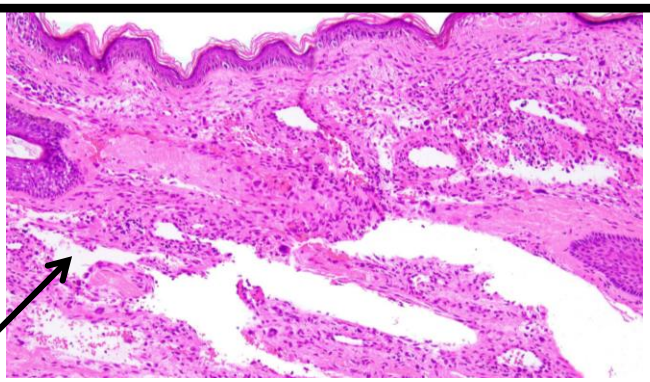


IHC: (+) Strong, diffuse CD34, (-) Factor XIIIA

Molecular: COL1A1-PDGFB fusion

← *This is what is meant by "storiform"*

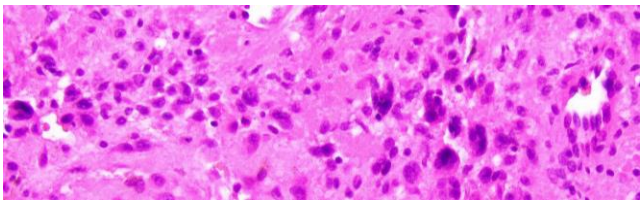
Giant cell fibroblastoma



Rare. Benign, but Locally aggressive.

Usually **Children** with a plaque-like mass on the trunk.
Closely related to DFSP molecularly.

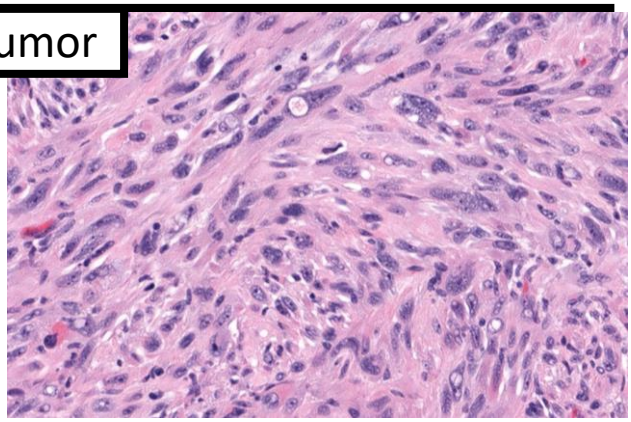
Infiltrative margins within the dermis and subcutis.
Hypocellular lesion with myxoid or collagenous stroma.
Bland spindled and stellate cells and scattered **multinucleated giant cells**, often lining **pseudovascular spaces**.



IHC: (+) CD34

Molecular: **COL1A1-PDGFB fusions**

Superficial CD34-positive Fibroblastic Tumor



Rare/New diagnosis. Good prognosis.

Skin & subcutis (very superficial)
Large eosinophilic cells with granular to glassy cytoplasm.
Fascicular to sheet-like growth.
Marked nuclear pleomorphism, but low mitotic count.

Classically: Middle-aged adults with slow growing leg mass

IHC: **(+)Diffuse CD34**; Frequent CK AE1/AE3

Solitary Fibrous Tumor ("SFT")

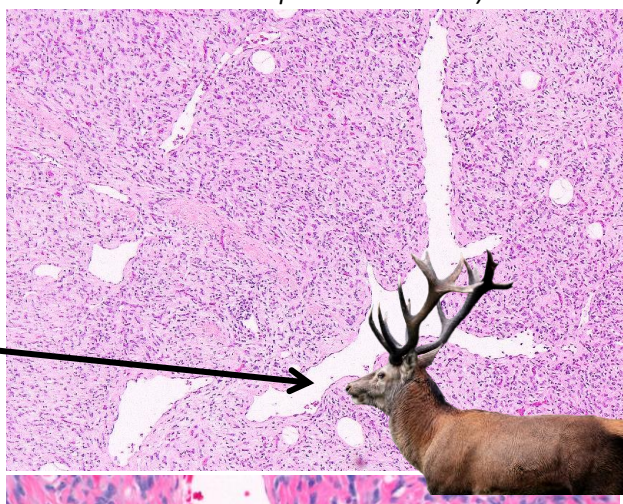
Old name: Hemangiopericytoma
(referred to cellular tumors on a spectrum with SFT)

Usually benign, but can recur and even metastasize.

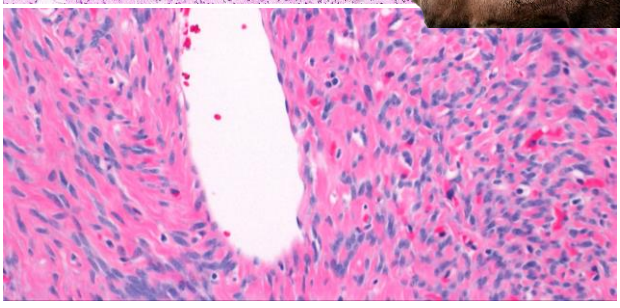
Can occur at any anatomical site, but most often **deep**.
Classic location: **Pleura**. Usually middle/older adults.

"***Patternless pattern***" of haphazard **bland spindled** to ovoid cells with varying amounts of collagenized stroma.

Prominent **"Staghorn vessels"** (dilated, thin-walled, branching vessels).



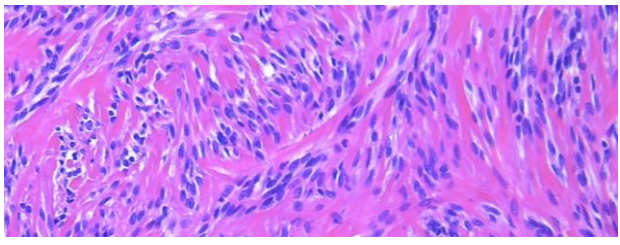
Wide histologic spectrum!
Can be hyalinized or myxoid. Can have keloidal collagen.
Can form fat or have giant cells.



IHC: (+) STAT6, CD34; Also, CD99 (but variable).

Molecular: **NAB2-STAT6 gene fusion**

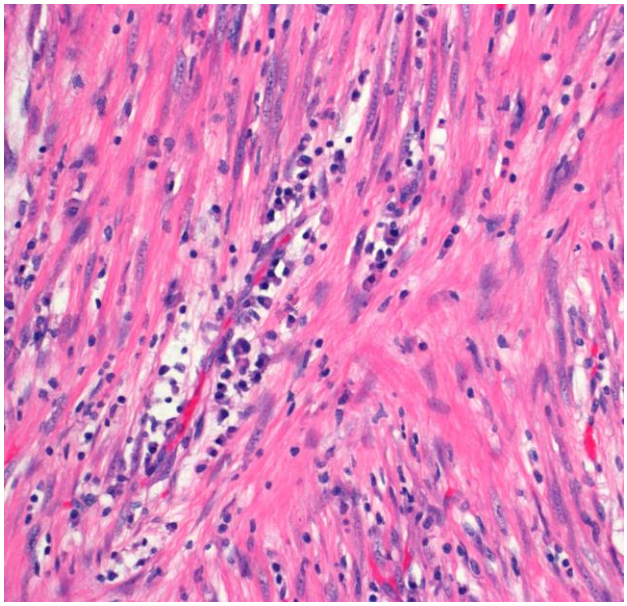
Factors associated with malignant behavior:
Age > 55, Numerous mitoses (esp. >4/10 HPF), Large size (esp. >15 cm), and tumor necrosis. PMID: 28731041



Dedifferentiated (anaplastic) SFT: transition to high-grade sarcoma (± heterologous elements).

Inflammatory Myofibroblastic Tumor

Borderline malignancy (tend to recur, rarely metastasize).

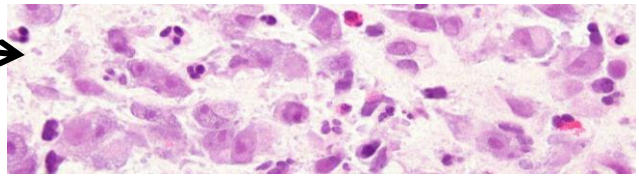


Most common sites: **Lung, mesentery, omentum**.
Any age, but **more common in children**.

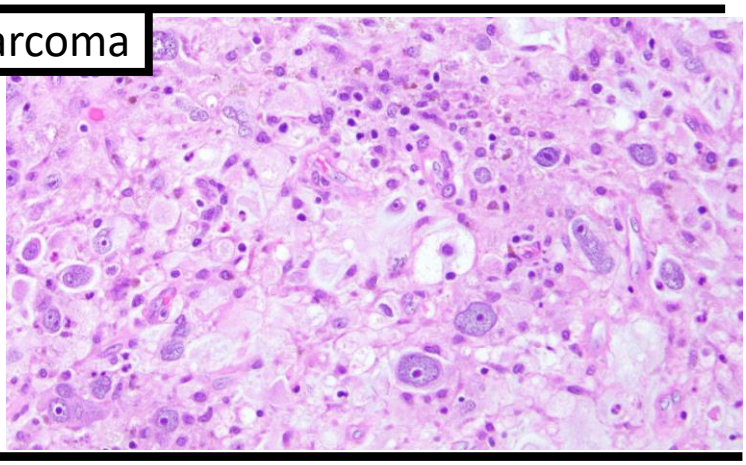
Bland spindled to stellate cells in myxoid to hyalinized stroma. Can have loose, fascicular, or storiform growth.
Prominent lymphoplasmacytic infiltrate.
May sometimes have large cells with prominent nucleoli.

IHC: Variable staining with actin/desmin. **ALK (+) in ~50%**
Molecular: ~50% have ALK gene rearrangements.
Other rearrangements include ROS1, NTRK3, etc..

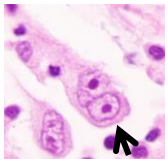
Aggressive subtype: *Epithelioid Inflammatory myofibroblastic sarcoma*: Plump epithelioid cells with vesicular chromatin and prominent nucleoli. Neutrophils. Usually in mesentery. Nuclear *membrane* ALK. Aggressive.



Myxoinflammatory Fibroblastic Sarcoma



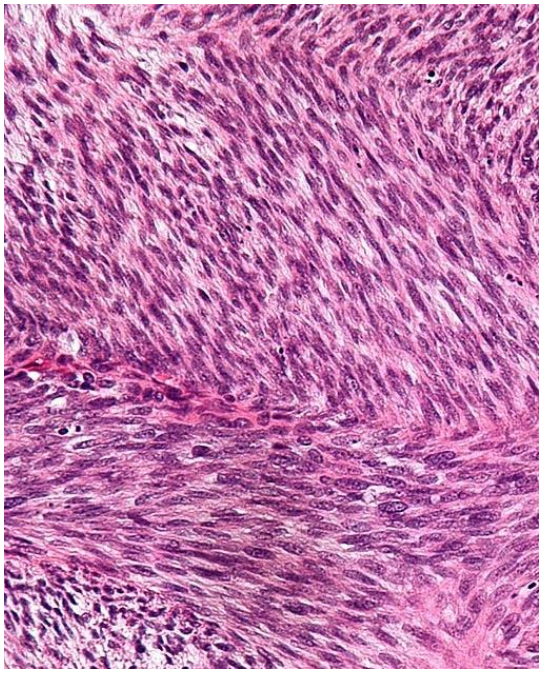
Local **recurrence common**. Very rare metastases.



Distal extremities, particularly hands.
Wide age range.

Infiltrative & multinodular.
Pleomorphic fibroblastic cells with macronucleoli
Variably myxoid to hyalinized matrix
Mixed **inflammatory infiltrate**.
Can see pseuodlipoblasts.

Fibrosarcoma (Adult)



"Almost defined out of existence" – Dr. Richard Kempson
(Many tumors previously called fibrosarcoma have been re-classified as synovial sarcoma, UPS, fibromatosis, or MPNST)

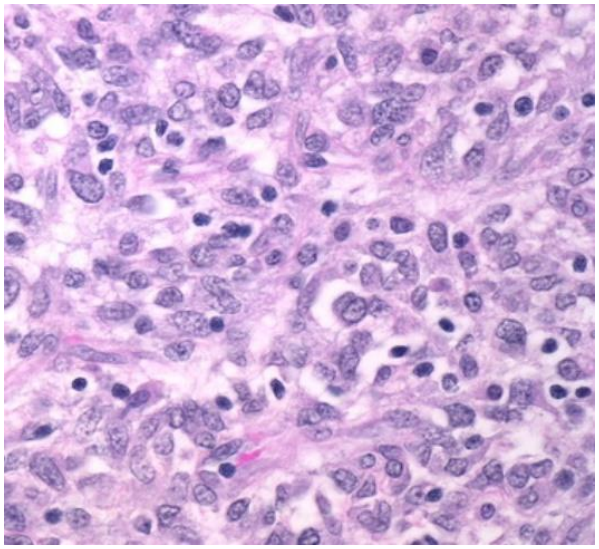
Now a diagnosis of exclusion!
Must do work up to exclude other diagnoses.

Uniform spindled cells with fascicular to herringbone growth.
Interwoven collagen fibers. Hyperchromatic nuclei.
No more than moderate pleomorphism.
Variable collagen.

No specific IHC of molecular.

Can get *Fibrosarcomatous* transformation of DFSP→ Loses storiform pattern and CD34 to become herringbone fibrosarcoma.

Infantile Fibrosarcoma



Locally aggressive, rapidly growing.
Only rarely metastasizes.

Newborns (congenital) or infants (<2yrs).
Usu. extremities.

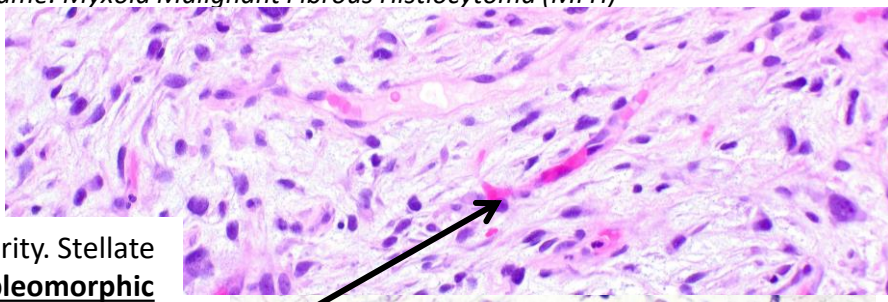
Sheets of **tightly packed spindled to ovoid cells** with herringbone/fascicular appearance.
Little pleomorphism. Mitoses present.
Often lymphocytic infiltrate. Staghorn vessels common.

Molecular: **ETV6-NTRK3 fusions** (same as in cellular mesoblastic nephroma) or other fusions with NTRK1, BRAF, and MET.

IHC: (+) pan-TRK; Otherwise non-specific.

Myxofibrosarcoma

Old name: Myxoid Malignant Fibrous Histiocytoma (MFH)

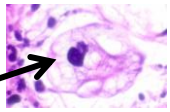


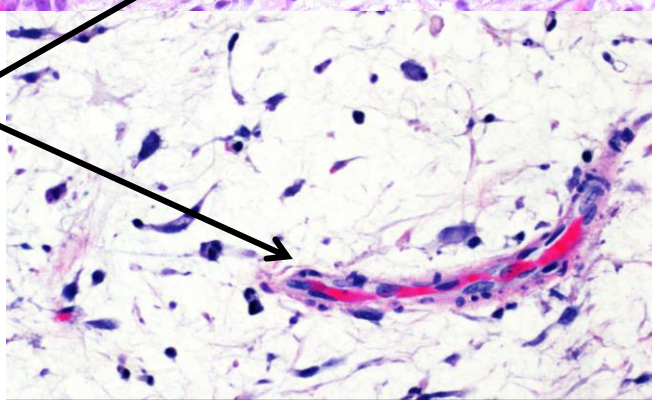
Malignant: recur and metastasize
Most common sarcoma of **elderly**.
Usually **extremity**, esp. near limb girdle

Multinodular, Infiltrative growth.

Myxoid background with varying cellularity. Stellate to spindled cells with **hyperchromatic, pleomorphic nuclei** with indistinct pink cytoplasm.

Characteristic **curvilinear vessels** that the tumor cells attach to like "melting wax."
More cellular/atypia? → High-grade





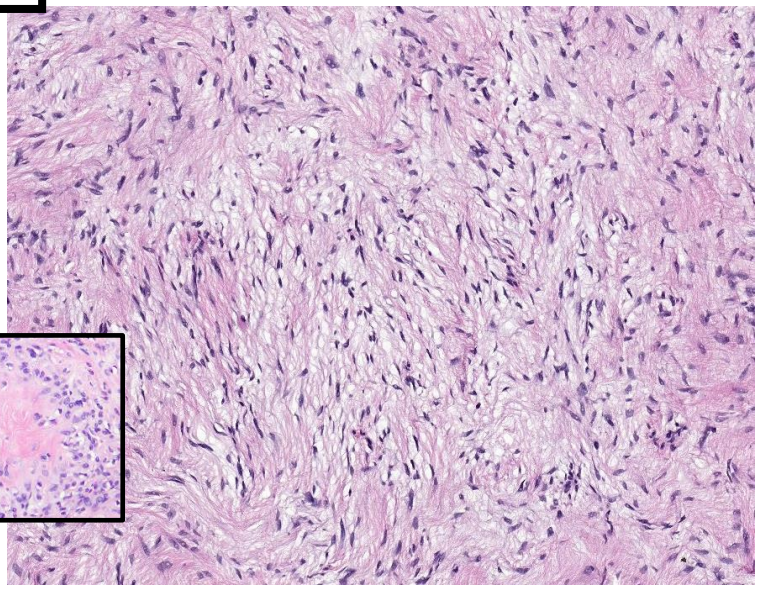
Variable inflammation.
Can have "pseudolipoblasts" with cytoplasmic *mucin*.

IHC: (+) focal SMA and/or CD34; (-) Desmin, S100

Molecular: **Complex karyotype**

Low-grade Fibromyxoid Sarcoma

Old name: Hyalinizing Spindle Cell Tumor with Giant Rosettes



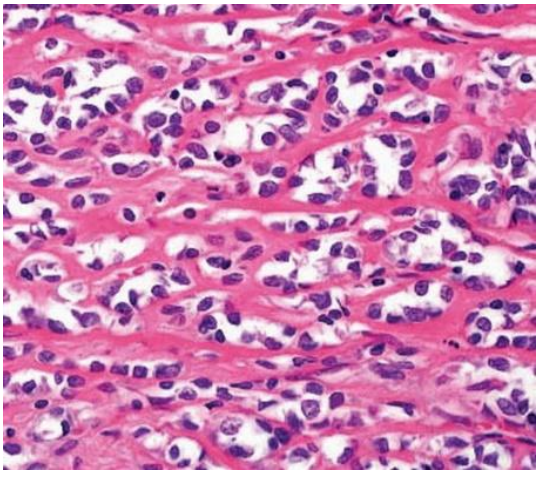
Malignant. Deep soft tissues of **extremity** of young to middle-aged adults.

Recur and can have late metastases.

Varying fibrous and myxoid areas, mostly fibrous though, with abrupt transitions.
Bland spindled cells with small hyperchromatic nuclei. **Whorled** to fascicular growth.
Myxoid areas have curvilinear, branching capillaries.
Can have large collagenous rosettes.

IHC: **(+) MUC4**, often EMA
Molecular: **FUS-CREB3L2 fusions** (or CREB3L1)

Sclerosing Epithelioid Fibrosarcoma



Malignant. Deep soft tissue of **limbs**. Middle-aged adults.

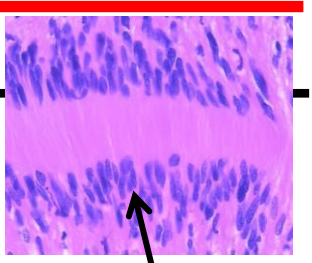
Densely hyalinized stroma with epithelioid cells arranged in cords and nests.
Cells have scant clear cytoplasm and angulated nuclei.

IHC: **(+) MUC4,** often EMA; (-) CK

Molecular: Somewhat diverse—many cases have FUS or EWSR1 and CREB fusions

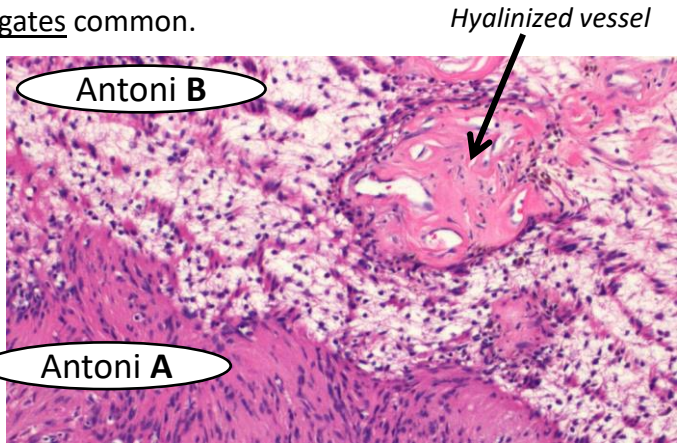
Nerve Sheath Tumors

Schwannoma



Benign. Composed *entirely* of **well-differentiated Schwann cells**.
Often associated with nerve in skin or subQ tissue. Can be associated with spine.
Usu. adults. Exceptionally low risk of transformation.
Usually **solitary** and sporadic. NF2-associated with bilateral vestibular schwannomas.

Typically encapsulated. Spindle cell tumor
Alternating compact spindle cells (Antoni A) and hypocellular less orderly areas (Antoni B)
Rows of nuclear palisading → Verocay bodies.
Hyalinized blood vessels and subcapsular lymphoid aggregates common.
Axons not present in lesion→ pushed to periphery.

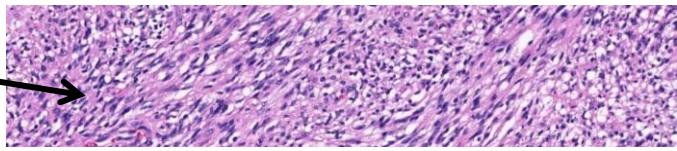


IHC: **Strong, diffuse S100** (and SOX10), scattered CD34, moderate calretinin. Neurofilament highlights displaced axons at periphery.

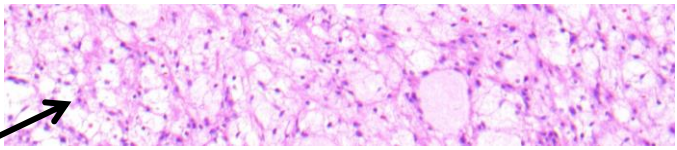
Subtypes:
Ancient Schwannoma- Degenerative atypia with bizarre large, hyperchromatic nuclei, but no mitoses

Plexiform Schwannoma- Usually sporadic (vs plexiform neurofibromas, which are often NF1 definitional)

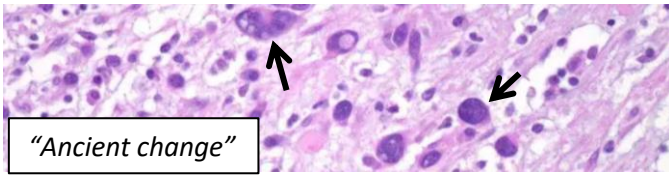
Cellular Schwannoma – Exclusively Antoni A areas.
No Verocay bodies. Usually large paravertebral nerves.
In contrast to MPNST, Ki67 <20%, HeK27me3 and P16 intact.



Epithelioid Schwannoma- Epithelioid cells.
Multilobulated growth.

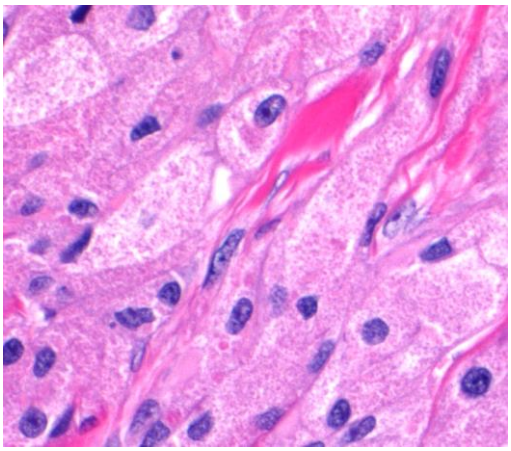


Microcystic/reticular Schwannoma- Usually visceral sites (e.g., GI tract). Microcyst-rich network.



Molecular: Frequent NF2 mutations, but this is non-specific and not used diagnostically.

Granular Cell Tumor



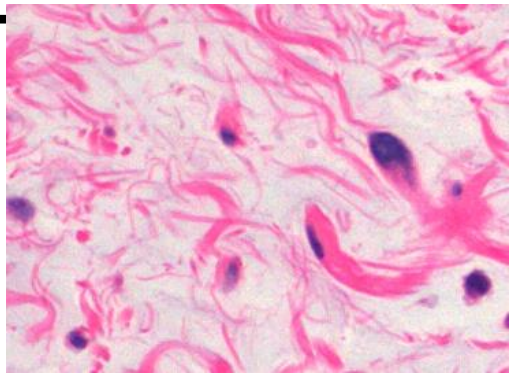
Benign (usually) neoplasm with neuroectodermal differentiation.

Epithelioid to spindled cells with **abundant eosinophilic granular cytoplasm** highlighted by PASd
Famous for inducing pseudoepitheliomatous hyperplasia that mimics squamous cell carcinoma.
Full of lysosomes due to inactivating mutations in ATP6AP1 or 2 (makes it so can't break down lysosomes)→ granular appearance

Stains: **(+) S100, SOX10, CD68**, Inhibin, Calretinin, MITF, (-) HMB45

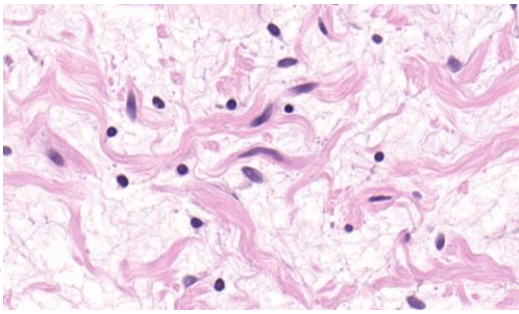
Congenital (Gingival) Granular Cell Tumor (Congenital Epulis):
Although looks similar, S-100 (-), located on gingiva at birth.

Neurofibroma



Benign. Most commonly solitary and sporadic.
Multiple NF is a hallmark of neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease.
Low risk of transformation (but higher than schwannoma)

Infiltrative, low-cellularity spindle cell neoplasm
Mixture of Schwann cells, perineurial-like cells, fibroblastic cells, and entrapped axons. (Schwann cells = neoplastic cells)
Randomly oriented spindled cells with **wavy, hyperchromatic nuclei**.
Often hypocellular and variably myxoid to collagenous matrix.
Thin and thick collagen strands ("shredded carrot collagen")
Entrapped axons are overrun by lesion and scattered throughout.
Can see "Ancient change" like in a Schwannoma.

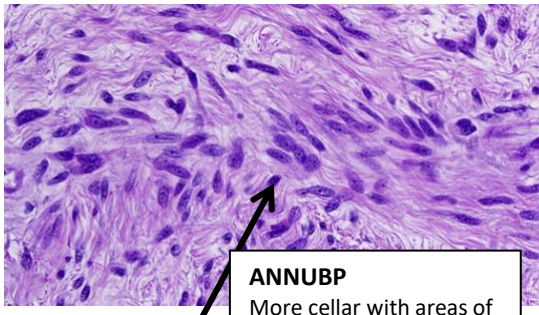


IHC: Diffuse S100 (+) (but less so than schwannoma). Moderate CD34.
Neurofilament shows entrapped axons within lesion.

Can be localized cutaneous (most common), intraneural, or diffuse.
Plexiform NF→ almost exclusively in NF1; higher risk of MPNST.

Types: Can be pigmented or show ancient change.

Molecular: NF1 biallelic inactivation



Spectrum of NF1-associated nerve sheath tumors:
Atypical Neurofibromatous Neoplasm of Uncertain Biologic Potential (ANNUBP)
Used in the *setting of NF1* to describe tumors that appear to be on the road to low-grade MPNST (but are not *quite* there)→ prompts additional sampling and further work-up clinically.

Definition: Schwann cell neoplasm with at least 2 of 4 features: 1)cytologic atypia, 2)loss of neurofibroma architecture , 3)hypercellularity, 4)mitotic index >1/50 HPFs and <3/10 HPFs

Loss of NF architecture refers to fascicular growth pattern and/or lack of CD34+ fibroblastic network; hypercellularity refers to "blue" appearance at low magnification and nuclear overlap at high magnification.

Ancillary testing: Loss of p16/CDKN2A expression, elevated Ki67 labeling, and extensive nuclear p53 staining. Also, decrease in S100 and CD34 staining. Loss of expression of H3K27me3.

Great consensus article on this: PMID: 28551330

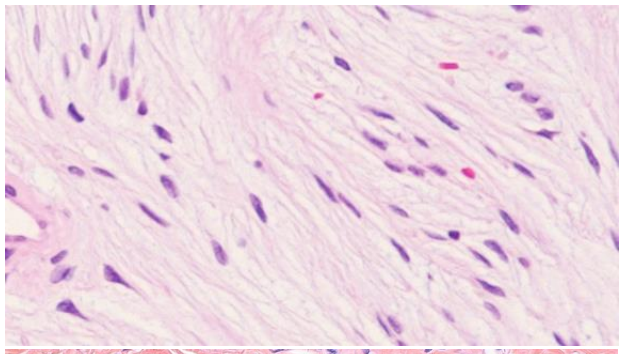
Diagnosis	Definition
Cellular neurofibroma	Neurofibroma with hypercellularity but retained architecture and no mitoses
ANNUBP	Schwann cell neoplasm with ≥ 2 of the following 4 features: cytological atypia, loss of neurofibroma architecture, hypercellularity, and mitotic index >1/50 HPFs and <3/10 HPFs
MPNST, low-grade	Features of ANNUBP, but with a mitotic count of 1.5–4.5 mitoses/mm^2 (3–9 mitotic figures per 10 HPFs) and no necrosis
MPNST, high-grade	MPNST with ≥ 5 mitoses/mm^2 (≥ 10 mitotic figures per 10 HPFs) or 1.5–4.5 mitoses/mm^2 (3–9 mitotic figures per 10 HPFs) combined with necrosis

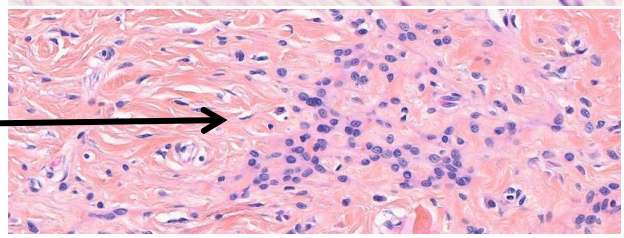
Adapted from: Who Classification of tumors of Soft tissue and Bone. 5th ed.

Perineurioma

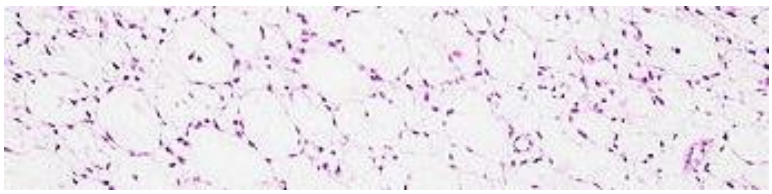
Benign. Can be intraneural or soft tissue. Sporadic.

Composed entirely of perineurial cells.
Elongated, slender spindle cells with bipolar cytoplasmic processes.
Storiform, whorled and lamellar architecture.
Wavy/tapering nuclei. Perivascular whorls.
Think: "*Fingerprint*"





Specific patterns/variants:
Sclerosing- epithelioid cells in dense collagenous stroma
Reticular- lacy architecture



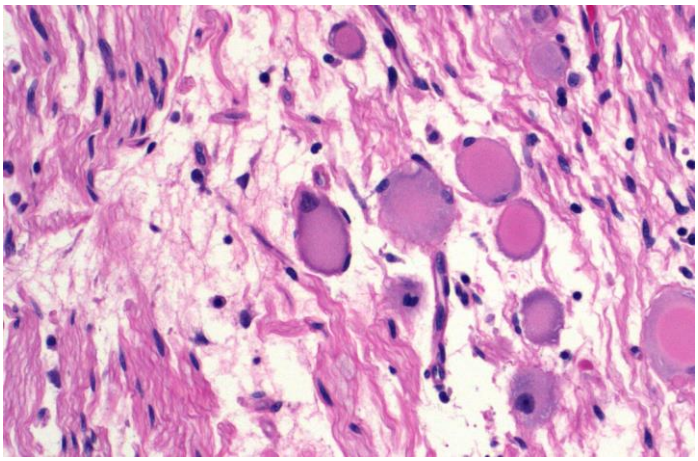
IHC: (+)EMA, Claudin-1, GLUT-1,
(+/-) CD34. (-)S100

Ganglioneuroma

Benign. Usually posterior mediastinum or retroperitoneum. No immature neuroblastic element (unlike ganglioneuroblastoma). Although some likely represent matured neuroblastoma, it is thought that most are *de novo*.

Mature ganglion cells in neuromatous stroma
(unmyelinated axons with Schwann cells).
When multiple/diffuse and/or syndrome-related (MEN 2b, Cowden, and NF1)→ *Ganglioneuromatosis*

Stains: Schwann cells (+) S100, Ganglion cells (+) Synaptophysin, neurofilament

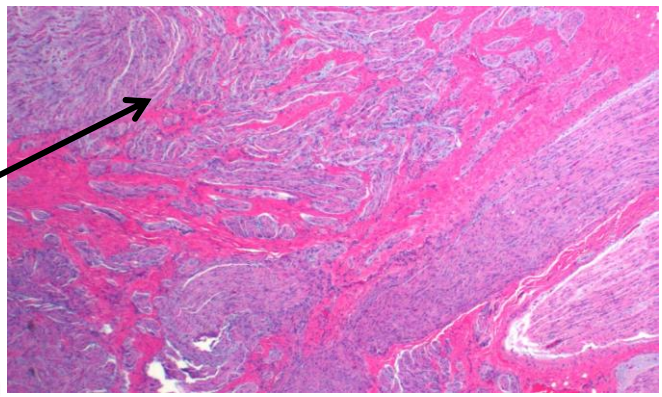


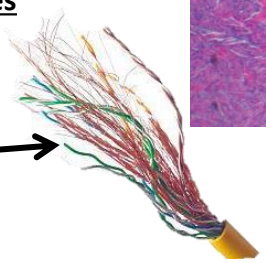
Traumatic (Amputation) Neuroma

Non-neoplastic nerve proliferation after trauma (nerve is growing to try to reestablish connection).

Haphazard proliferation of nerve fascicles including axons and perineurial cells.
Damaged nerve often easily identified.

***Think*: Frayed electrical wire!**

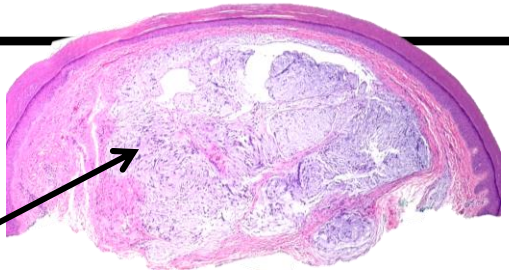


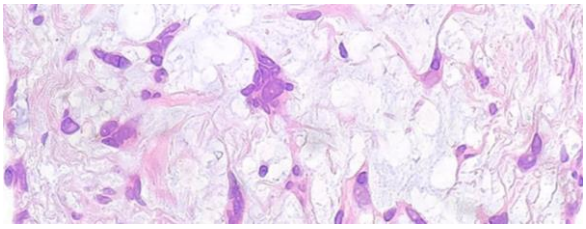


Hybrid Nerve Sheath Tumor

Intermingled features of <u>two</u> types of benign nerve sheath tumors.
For example: Perineurioma/Schwannoma, Schwannoma/Neurofibroma

Dermal Nerve Sheath Myxoma



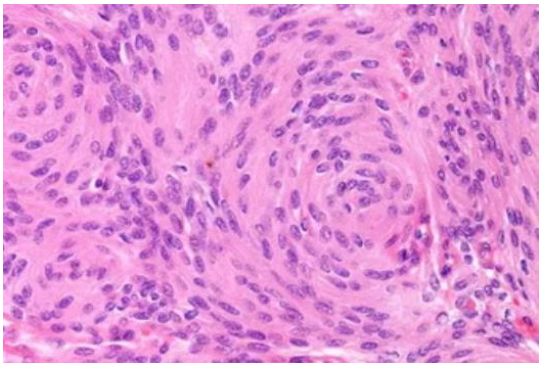


Benign.

Young adults with small superficial lesions on the distal extremities (usually **<u>fingers/toes</u>**). Rare.

<u>Myxoid</u> neoplasm with **<u>multilobulated</u>** growth.
Bland spindle, ring-like, and epithelioid Schwann cells
IHC: (+)S100

Ectopic Meningioma

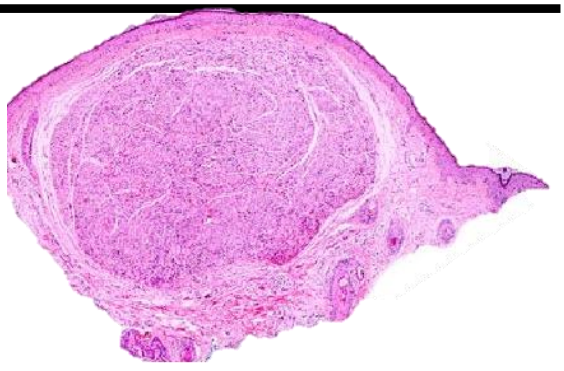


Benign. Essentially a meningioma in soft tissue (<u>outside of CNS</u>).
Whorled architecture. Oval nuclei.
Occasional nuclear pseudoinclusions.

Meningothelial hamartoma represents a developmental rest, composed of non-neoplastic arachnoid cells.

IHC: EMA, PR, and SSTR2A (+)

Solitary Circumscribed Neuroma

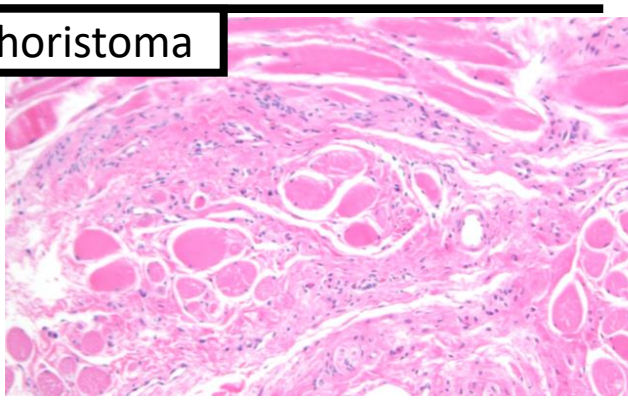


aka Palisaded encapsulated neuroma
Benign. Usually on the <u>skin of the face</u>.

Circumscribed cutaneous lesion of Schwann cell-rich fascicles of nerve fibers with or without partial encapsulation;
Focal palisading and artefactual clefting

IHC: (+)S100, Focal Neurofilament in trapped axons.

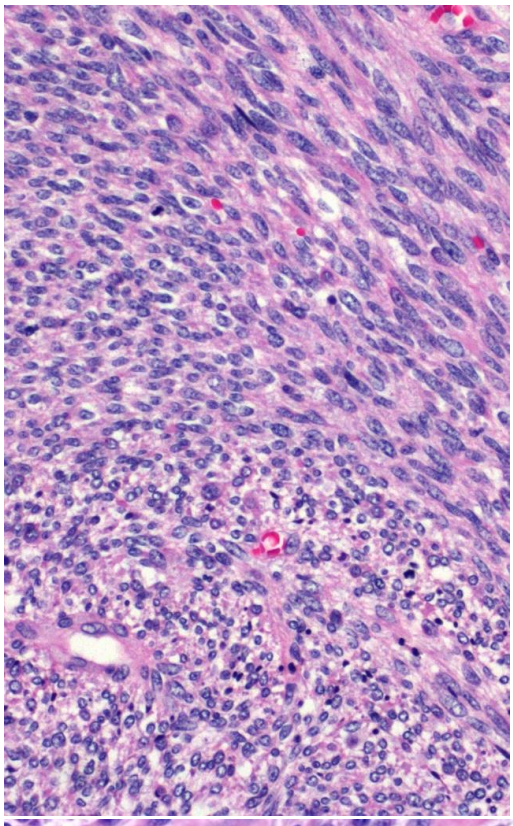
Benign Triton Tumor/ Neuromuscular Choristoma



<u>Extremely rare</u>. Benign.
Intimate interposition of mature skeletal muscle and nerve fibers within the endoneurium of a nerve.
Intact perineurium around fascicles.
Can get superimposed fibromatosis.

IHC: (+) Desmin in muscle. Nuclear β-catenin often.

Malignant Peripheral Nerve Sheath Tumor (MPNST)



Malignant. Adults. Frequently in setting of **NF1**.
Often poor prognosis.

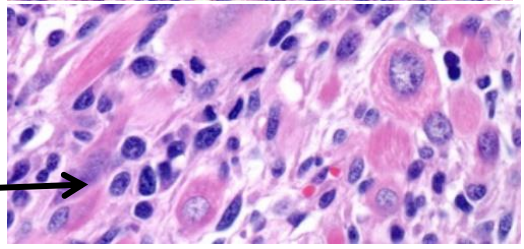
Sarcoma arising from a peripheral nerve *or* pre-existing peripheral nerve sheath tumor or displaying histologic/IHC evidence of nerve sheath differentiation or in a patient with NF1.

Variable appearance, can resemble undifferentiated pleomorphic sarcoma or fibrosarcoma.

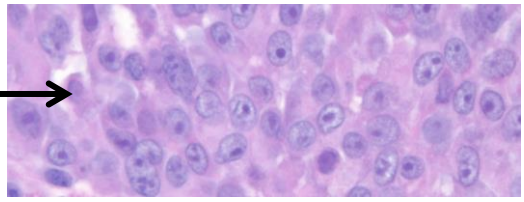
***Usually*: Spindled** cells arranged in sweeping **fascicles**.
Densely **cellular** areas alternate with less cellular areas giving a "marble-like" effect.
Can have herringbone architecture.
Wavy, buckled nuclei *(as with many Schwannian tumors)*
Often *limited* pleomorphism.
Geographic **necrosis** and/or **mitotic activity** (often greater than 10/10 HPFs)

See Neurofibroma section for spectrum of disease seen in NF1, including ANNUBP and low-grade MPNST.

IHC: **Patchy/focal S100 and SOX10.**
Loss of H3K27me3 expression in high-grade MPNST (associated with worse prognosis. Fairly specific—due to PRC2 inactivation).
Express PRAME (vs negative in most benign PNSTs)
Molecular: Also, inactivation of NF1 and CDKN2A (P16)

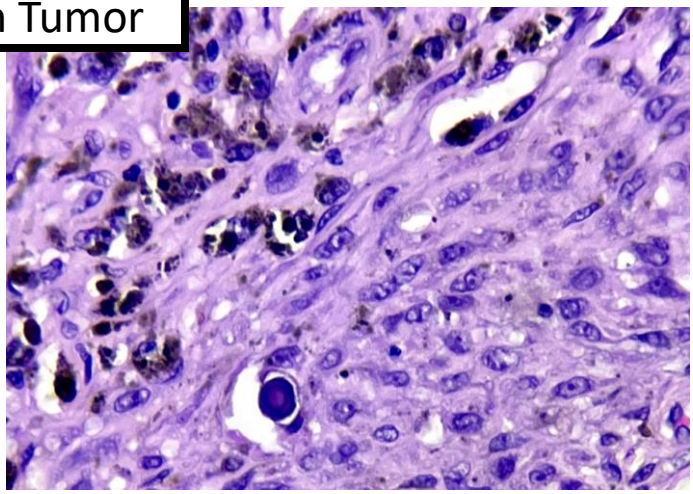


Frequent heterologous elements. Most classic:
MPNST with rhabdomyoblastic differentiation ("*Malignant triton tumor*")



Epithelioid MPNST—composed of polygonal, epithelioid cells.
Sporadic (not NF1). Unique strong, diffuse S100 staining and loss of SMARCB1 (INI1).

Malignant Melanotic Nerve Sheath Tumor



Rare. PNS tumor composed of Schwann cells with Melanocytic differentiation. Malignant.
Associated with Carney Syndrome.

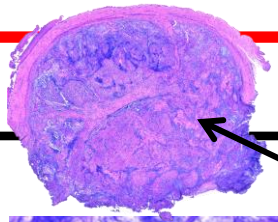
Frequent origin from paraspinal or visceral autonomic nerves (e.g., GI tract).

Fascicular to sheet-like proliferation of heavily pigmented, relatively uniform plump spindled cells

IHC: (+) coexpression of S100/SOX10 and melanocytic makers (e.g., HMB45, melan-A)

Molecular: PRKAR1A loss

Perivascular/Pericytic Tumors

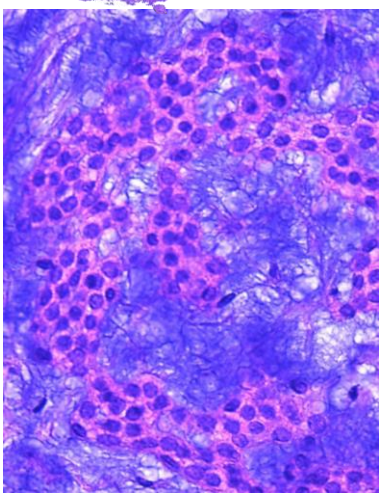


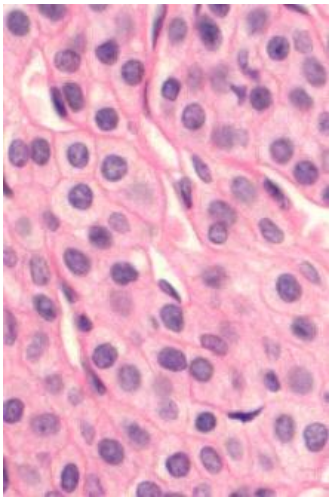
Grossly circumscribed, round nodules

Glomus tumor

Benign. Tumor derived from glomus body (modified smooth muscles of that help regulate heat).

Often red-blue nodules in the deep dermis of extremities. **fingers/toes**. Often **painful**.





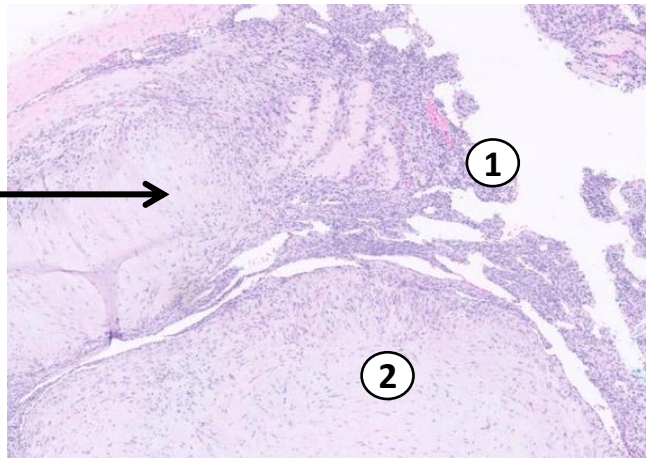
Monomorphic round to epithelioid cells.
Centrally placed, round nuclei.
Well-defined cell borders. Eosinophilic cytoplasm.
Arranged in **perivascular nests**.

IHC: **(+)SMA**, other smooth muscle markers variable.
Molecular: Frequent NOTCH gene rearrangements

Variants:
Glomangioma (Glomuvenous malformation)—dilated vascular spaces lined by glomus cells.
Malignant glomus tumors— Spindle or round cells, sarcomatous phenotype with atypia and mitoses.
Also, Symplastic glomus tumor, Glomangiomyoma, Glomangiopericytoma, Glomangiomyomatosis.

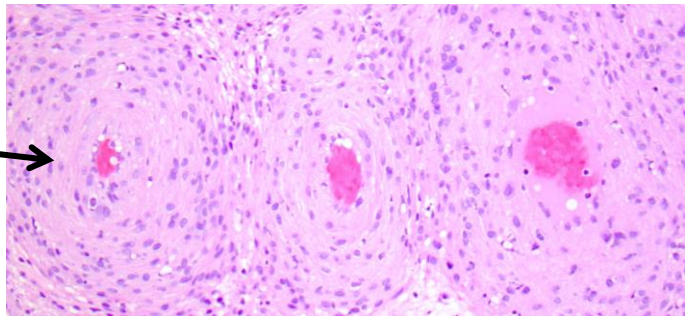
Myopericytoma/Myofibroma

Benign. Exist on a **spectrum**.



Myofibroma: Usu. Head/neck in first year of life.
Multinodular, well-circumscribed.
Biphasic: 1) Cellular, immature-appearing, plump spindled cells with staghorn vessels, 2) surrounding hyalinized/chondromyxoid nodules of myoid spindled cells. Can see necrosis, Calcs, mitoses.

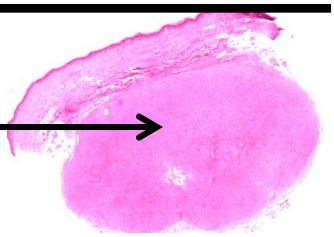
Myopericytoma: Superficial mass in adults.
Nodular, well-circumscribed.
Bland, myoid-appearing spindled cells growing in a concentric pattern around numerous small vessels.
Very richly vascular



IHC: **(+)SMA;** usually (-) Desmin.
Molecular: **PDGRFB mutations** common.

Angioleiomyoma

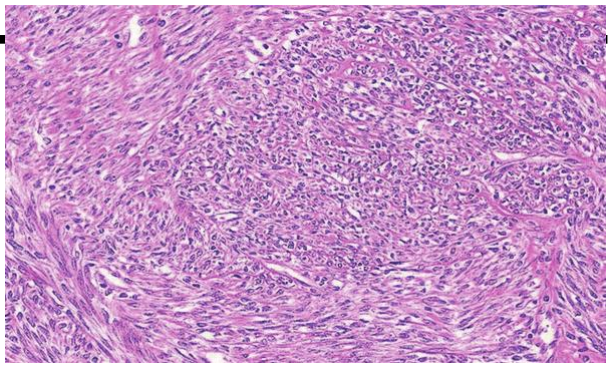
Well-circumscribed neoplasm composed of mature, cytologically bland smooth muscle cells arranged concentrically around prominent blood vessels.
Classically painful and on the lower leg of a middle-aged woman.



Smooth Muscle

IHC: (+) SMA, Desmin, H-Caldesmon, Calponin

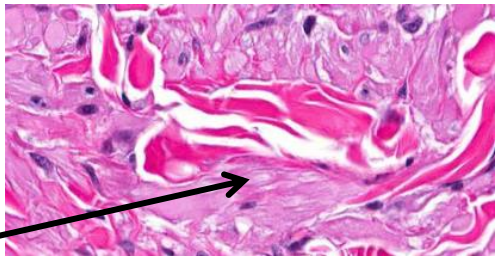
Leiomyoma



Benign.
Common in dermis. Relatively uncommon in *deep* soft tissue.

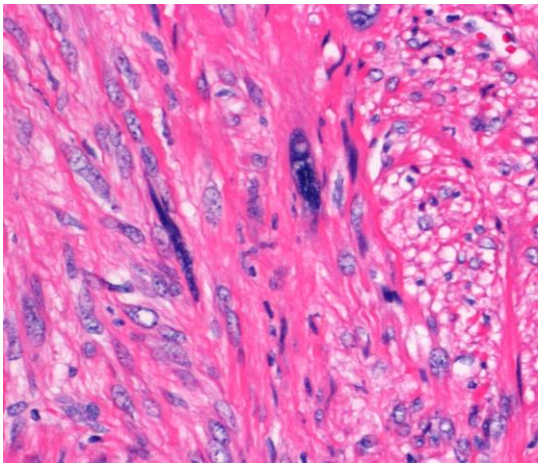
Cytologically bland spindled cells with cigar-shaped nuclei.
Fascicular architecture.
No nuclear atypia or necrosis.
At most very rare mitoses (<1/50 HPF)

Retroperitoneal tumors usually (+) ER, PR, WT1 (like in uterus)



Pilar Leiomyoma
Ill-defined, dermal nodule composed of haphazardly arranged smooth muscle bundles/fascicles. Derived from pilar muscles. Often painful. Fascicles often dissect between dermal collagen

Leiomyosarcoma



Malignant. **Poor prognosis**. Usually older adults.
Often in retroperitoneum of adults. Often arise from veins.

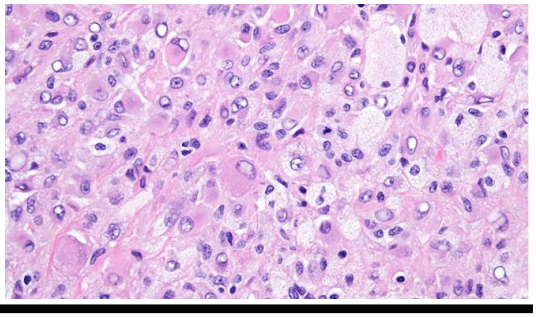
Intersecting perpendicular **fascicles** of eosinophilic spindled cells with blunt "cigar-like" nuclei. Usually very **cellular**.
Variable, but often notable **pleomorphism**.
Mitotic activity, often atypical mitoses. Necrosis.

Can dedifferentiate, losing normal morphology/IHC, requiring a better differentiated area to make a Dx.

IHC: (+) at least one myogenic marker, ideally two

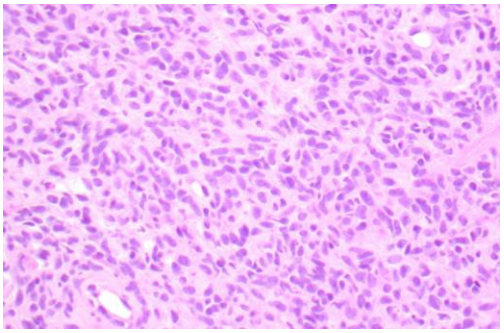
Molecular: Complex karyotype (genomically unstable).

"Inflammatory Leiomyosarcoma"



Very rare. Better prognosis. Fascicular proliferation of variably atypical eosinophilic spindled cells, which show mitotic activity; dense inflammatory infiltrate, variable, most often lymphoid or xanthomatous. Near haploid.
Can express skeletal muscle markers, so some suggest calling "*Inflammatory Rhabdomyoblastic Tumor*"

EBV-associated Smooth Muscle Tumor



Generally Benign, but patients can get multiple primaries.
Seen in setting of **immunodeficiency** (e.g., HIV, post-transplant, etc)

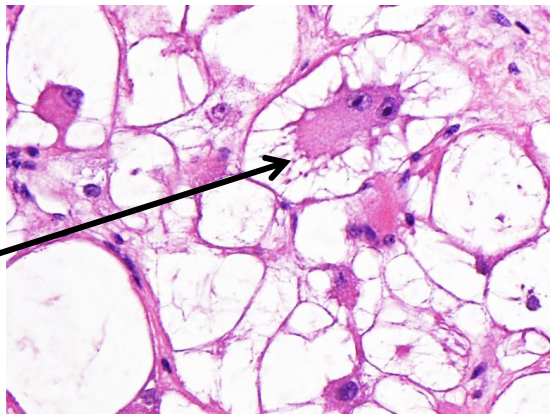
Mostly typical smooth muscle appearance (fascicular architecture, blunt-ended nuclei). Can see tumor-infiltrating lymphs and more "round cell" areas.

Molecular/IHC: Need to confirm **EBV** in tumor with **EBER**

Skeletal Muscle Tumors

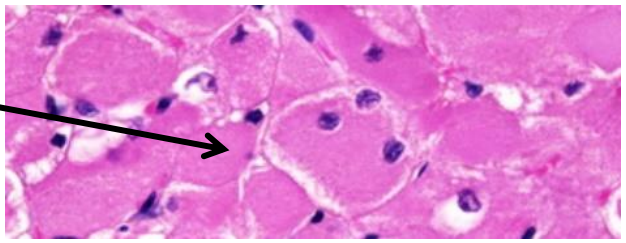
IHC: Most specific Myogenin, MyoD1
Also, general muscle markers (e.g., Desmin, Actin)

Rhabdomyoma

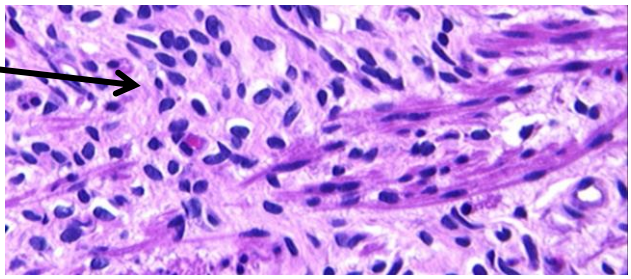


Benign. (But location/growth may cause problems)
Well-circumscribed, with no invasion of adjacent structures.
Mature rhabdomyoblasts. Unencapsulated, lobular.
No significant atypia, mitotic activity, or necrosis.

Cardiac-type Rhabdomyoma:
Occur in hearts of infants and young children, often in the setting of Tuberous sclerosis.
Large, polygonal, vacuolated, cleared out, "spider cells"



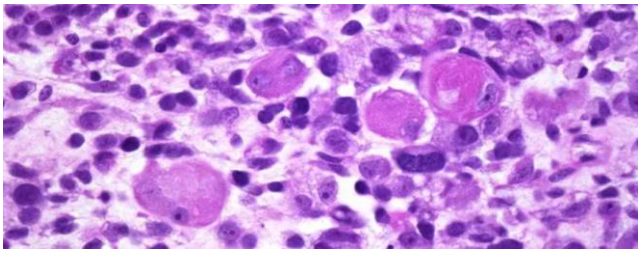
Adult-type Rhabdomyoma:
Mature skeletal muscle differentiation.
Usu. Head and neck. Often pharynx or tongue.
Large, polygonal cells with abundant granular eosinophilic cytoplasm. Well-defined cell borders. Some spider cells



Fetal-type Rhabdomyoma:
Usu. Head and neck. Any age.
Irregular bundles of immature skeletal muscle.
Myxoid background.

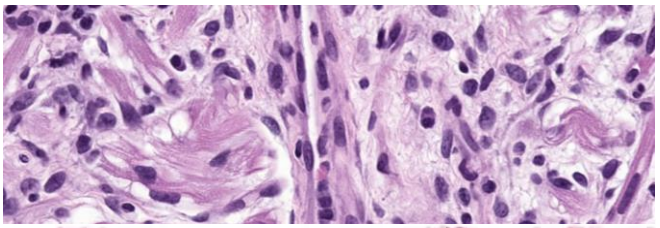
Genital-type Rhabdomyoma: (usually in vagina)
Small (<2cm), without a cambium layer.

Embryonal Rhabdomyosarcoma

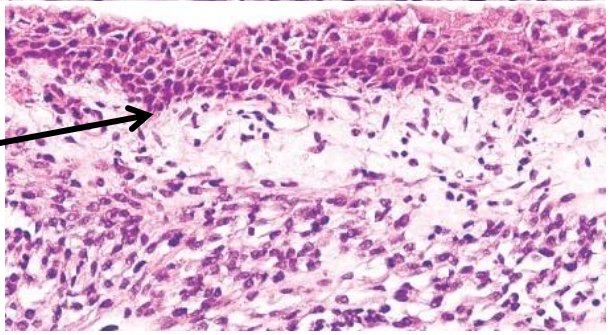


Malignant.

Most common soft tissue sarcoma in kids/teens.
Occasionally adult.
Usu. Head/Neck (e.g., nasal, tongue, etc..) or Genitourinary (e.g., bladder, prostate, etc…)



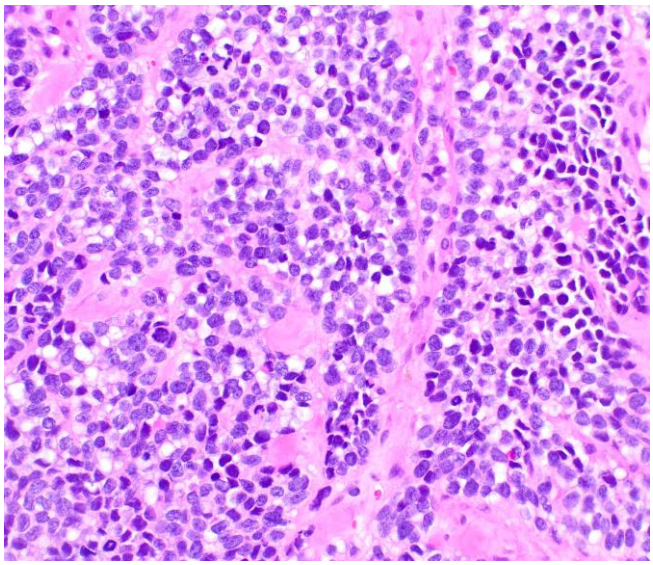
Resembles embryonic skeletal muscle cells.
Primitive round and spindle cells. Often myxoid stroma.
Scattered differentiated **rhabdomyoblasts**
rhabdoid cells with abundant, eccentric eosinophilic cytoplasm, "tadpole cells," and "strap cells" (with cross striations). Can see cartilage. Often "matures" post-chemo



Botryoid type: Densely cellular layer below epithelial surface ("cambium layer") separated by hypocellular area. Polypoid surface nodules ("grape-like"). Usually projecting into mucosa-lined spaces (like vagina or nasal cavity)

Molecular: Complex, with frequent RAS mutations

Alveolar Rhabdomyosarcoma



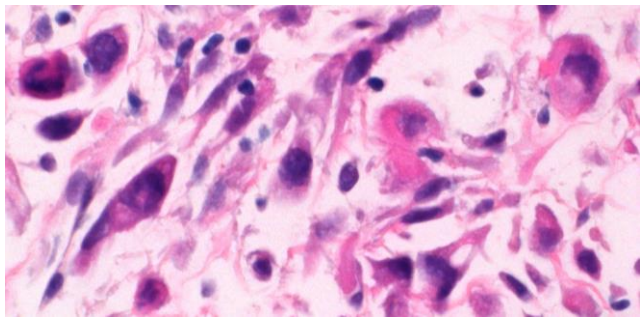
Malignant. More aggressive than Embryonal Rhabdo.
Often adolescents and young adults in deep soft tissue of extremities and head/neck.

Highly cellular "**small round blue cell**" tumor.
Uniform primitive round cells
Often nest-like arrangement (hence "**alveolar**").
Notable *absence* of strap cells, tadpole cells, etc…

Molecular: **FOXO1** fusions with either PAX3 or PAX7

IHC: **Strong, diffuse Myogenin** suggests this Dx (often patchier in embryonal). Often patchy neuroendocrine staining.

Pleomorphic Rhabdomyosarcoma

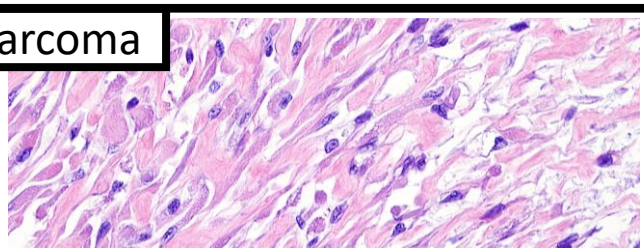


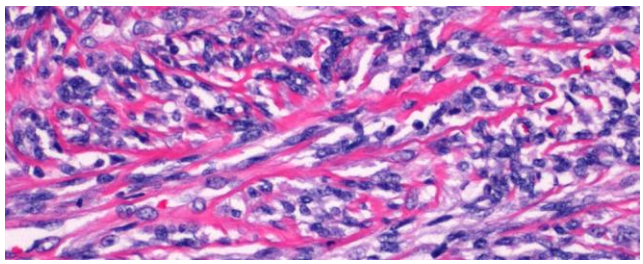
Malignant. Older adults. Deep soft tissue. Aggressive.

High-grade pleomorphic sarcoma: sheets of large, atypical cells. Eosinophilic polygonal cells to tadpole-like.

No embryonal or alveolar component. Resembles heterologous differentiation in carcinosarcomas.
Complex genetics.

Spindle Cell/ Sclerosing Rhabdomyosarcoma





Cellular spindle cell fascicles
Variably sclerotic collagenous background.

IHC: Of note, in some cases MyoD1 is strongly positive, while Myogenin and desmin are only focal often.

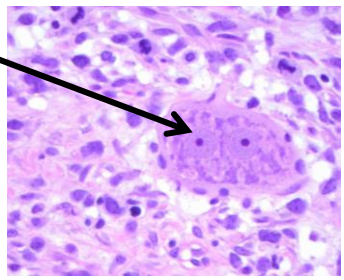
Two main clinical/molecular patterns:

1) **Paratesticular** or head/neck of kids
Fusion-related (e.g., NCOA2)→ favorable prognosis

2) Head/Neck or extremity of younger adults
MyoD1 mutated→ more aggressive

Ectomesenchymoma

Ganglion cell!



Very rare. Kids in the pelvis.

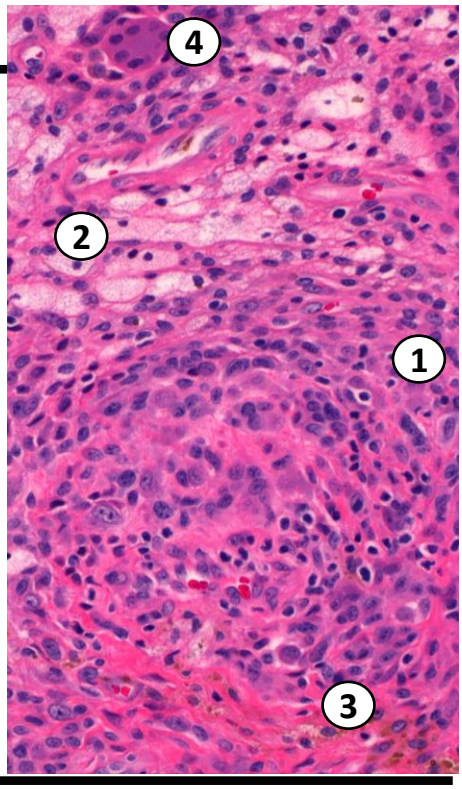
Composite of: **1) Embryonal rhabdomyosarcoma**, with
2) Neuroblastic elements (neurons, ganglioneuroma, neuroblastoma)

IHC: (+) Muscle/Neural markers in *different* zones

I conceptualize this as sort of the opposite of a "malignant triton tumor," which is an MPNST making muscle… this is a rhabdomyosarcoma making neural elements.

Fibrohistiocytic Tumors

Tenosynovial Giant Cell Tumor



Benign, but can be locally destructive. Younger/Middle-age adults.

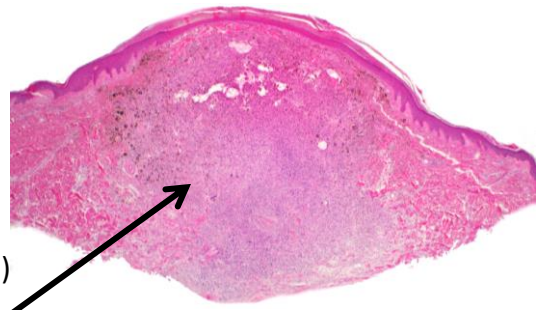
Mixture of 1) bland mononuclear cells, 2) foamy macrophages, 3) hemosiderin-laden macrophages, and 4) osteoclast-like giant cells. Mononuclear cells are spindled to round with reniform/grooved nuclei. Mitoses common. Variable hyalinization.

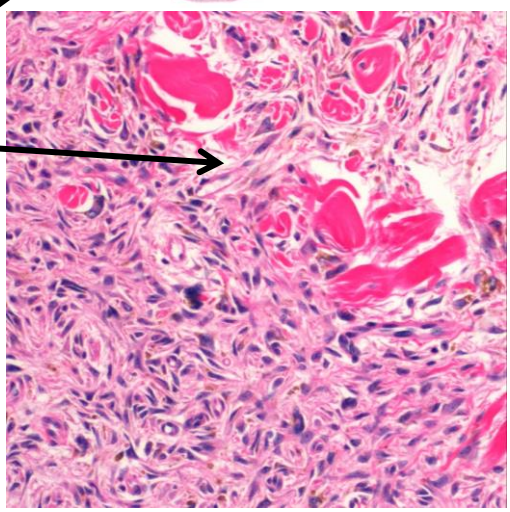
IHC: Mononuclear cells CD68, CD163 (+), scattered Desmin.
Molecular: **CSF1 gene rearrangements**

Localized-type: Discrete, rounded proliferation. Usually occurs in digits. Less aggressive. Often cure with excision.

Diffuse-type: Grows in expansive sheets. Often in or around knee. Often intraarticular. Large. Destructive. Treat more aggressively.
Old name: "Pigmented Villonodular Synovitis" (PVNS)

Fibrous Histiocytoma





Benign (generally).
Neoplasm or Neoplasm-like (some seem to occur after trauma)

Fibroblastic and histiocytic cells arranged in short fascicles or storiform growth.

Dermatofibroma ("DF", Benign/cutaneous fibrous histiocytoma)
In Dermis (most common site by far)
Looks like a "blue haze" in the dermis
Tumors are grossly circumscribed but microscopically have irregular, often jagged borders. Collagen trapping at periphery
Frequent staghorn vessels.
Overlying epithelial basilar induction with hyperpigmentation

Lots of variants: Epithelioid, Cellular, Aneurysmal, etc…
IHC: FXIIIA(+), CD163(+), CD68(+), CD34(-)

"Deep Fibrous Histiocytoma:" If in deep soft tissue. Very rare. May occasionally metastasize! PRKCB or PRKCD rearrangements often. (+)CD34 often (unlike DF). Sometimes SMA.

Plexiform Fibrohistiocytic tumor: Plexiform architecture in deep soft tissue/dermis. (+) SMA

Giant Cell Tumor of Soft Tissue

Morphologically similar to Giant cell tumor of bone, but genetically unrelated (No H3F3A mutations). Superficial soft tissue of extremities. Multinodular: Cellular nodules separated by fibrous stroma. Round to ovoid mononuclear cells with osteoclast-like giant cells. Hemosiderin deposition and metaplastic bone.

Vascular Tumors

Endothelial cells stain with: CD31, ERG, FLI1, often CD34

Vascular Malformations

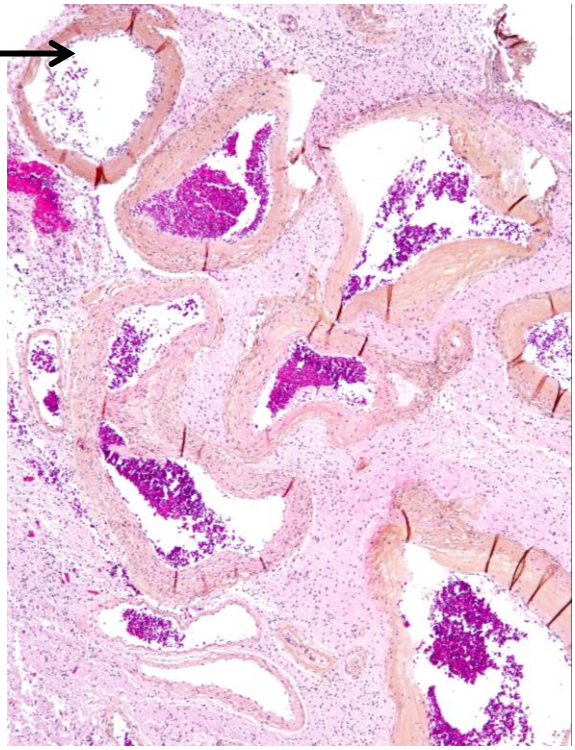
Malformations: Most are **congenital** and thought to be ***Developmental*** abnormalities (occur during embryogenesis in utero), that grow *with* the host. They are static and do not regress.
Sometimes syndrome-associated.
Can still regrow/recur, particularly if large and not entirely resected.

Hemangioma: used for lesions due to cellular proliferation on the presumption that they are **neoplasms**. Most commonly composed of capillaries. Grow faster than patient. *Can* spontaneously involute.

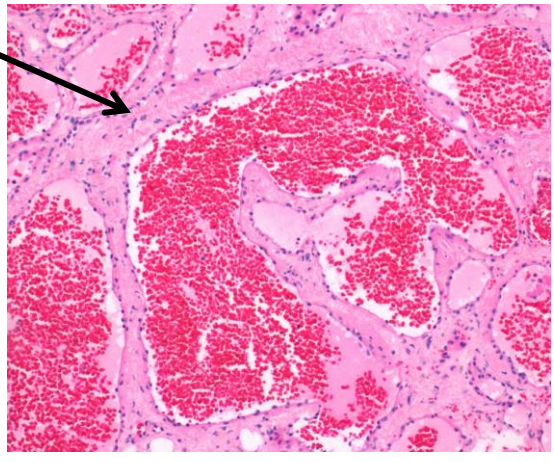
That said, because of their unclear nature (developmental vs neoplastic), the names "malformation" and "hemangioma" are alternatively used sometimes. Lesions called "hemangiomas" that are likely actually malformations include: intramuscular hemangioma, spindle cell hemangioma, cavernous hemangioma.

Radiology (and specifically arteriography or venography) can be very helpful in categorizing lesions.

Arteriovenous Malformation/Hemangioma (AVM/H)
Many vessels of different sizes including arteries and veins:
Large, tortuous arteries with thick-walled veins.
Fast flow (due to arteries) with Arteriovenous shunts.
Fibrointimal thickening of veins due to higher pressure.
Variable small vessel component.
Most common in head/neck and brain.
Can cause heart failure and consumptive coagulopathy.
Mostly appear to be congenital malformations, but some appear to be acquired.
Elastin stain can highlight IEL of arteries.
Multiple tissue planes→ Angiomatosis



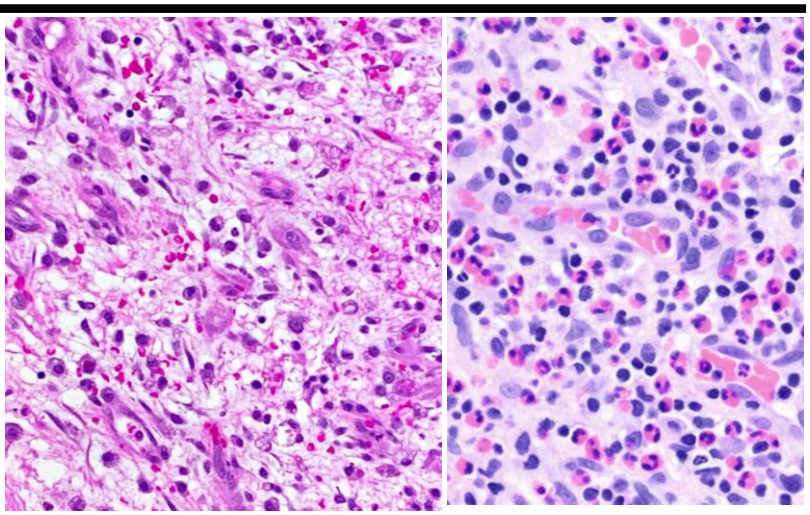
Venous Malformations (Venous Hemangiomas)
Ill-defined collection of abnormally thick, muscular veins.
Vary in size/dilation. No internal elastic lamina (by EVG).
Slow flow → thrombi and calcifications.
Includes: **Cavernous hemangiomas** (collection of large, dilated veins with thin walls, common in the liver)



Cutaneous Capillovenous Malformation
E.g. Telangiectasia. Often diagnosed clinically.
Associated with a variety of conditions (e.g., HHT)

Hereditary hemorrhagic telangiectasia (HHT) (Osler-Weber-Rendu disease): Vascular abnormalities of capillaries and veins of skin and mucosal membranes. Inherited, Autosomal dominant

Granulation Tissue

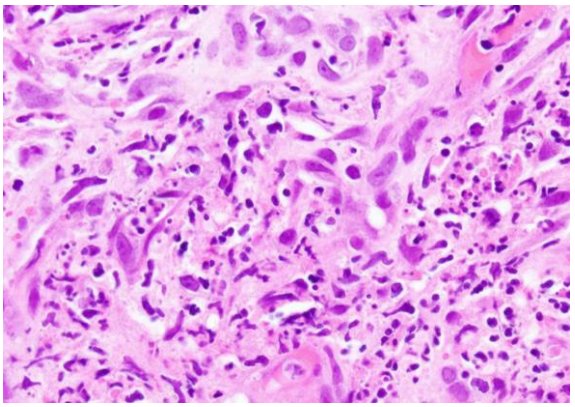


Part of *normal* healing process and scar formation **at sites of injury** (Reactive/Non-neoplastic)

Mixture of
1)Proliferating capillaries
2) Proliferating Fibroblasts
3) Inflammation (Acute and/or Chonic)
4) Variable myxoid to fibrous stroma

Sometimes *mistaken* for vascular neoplasms

Bacillary Angiomatosis



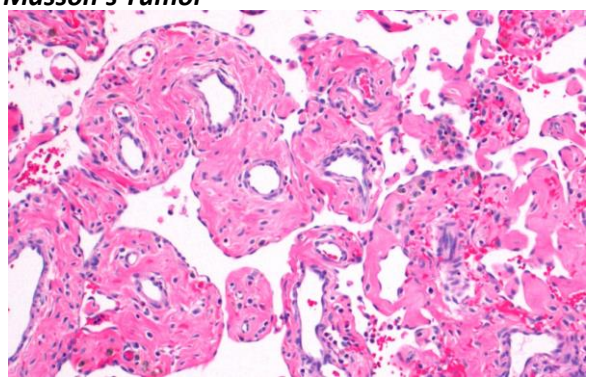
Non-neoplastic vascular proliferation caused by **Bartonella** (Gram-negative bacilli, also causes Cat scratch disease). Almost exclusively in immunocompromised adults, often AIDs. Often in skin/soft tissue.

Nodular growth. Lobules of capillary-sized vessels with plump endothelium. Associated neutrophilic infiltrate.

Stains: Warthin-starry highlights organisms

Papillary Endothelial Hyperplasia

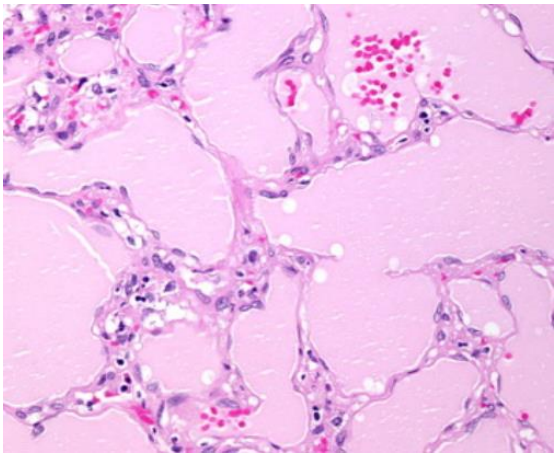
aka Masson's Tumor



Manifestation of **organizing thrombus**→ Intravascular exuberant **proliferation of endothelial cells with fibrin**. Small papillae covered by a single layer of endothelium with a collagenized fibrin core. No atypia or mitoses. Papillae can fuse, forming anastomotic channels.

Main importance is that it can *mimic* angiosarcoma histologically. However, can be distinguished by exclusively intravascular growth and lack of mitoses/atypia.

Lymphangioma



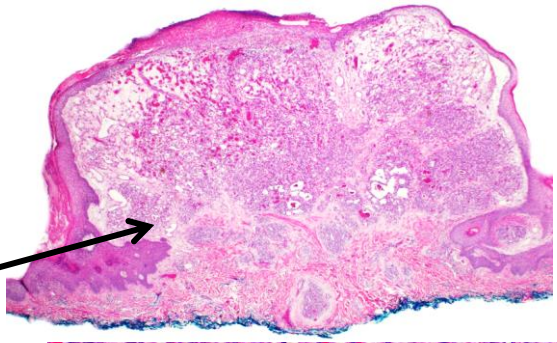
Benign. Often in kids during the first year of life.
Associated with Turner syndrome (XO).

Thin-walled, **dilated lymphatic** vessels of different sizes, lined by flattened endothelium. Frequently surrounded by lymphoid aggregates.
Contain grossly "milky" lymphatic fluid.

IHC: Endothelium expresses **D2-40** and PROX1 (specific for lymphatics). Also CD31. Variable CD34.

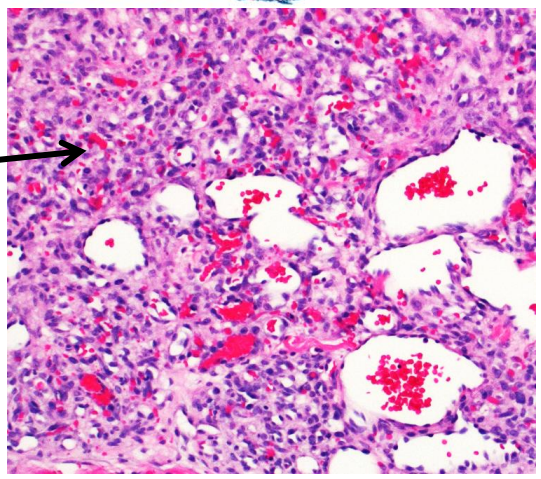
Lymphangiomatosis→ multicentric or extensively infiltrating, usually involving multiple tissue planes/organs.

Hemangiomas



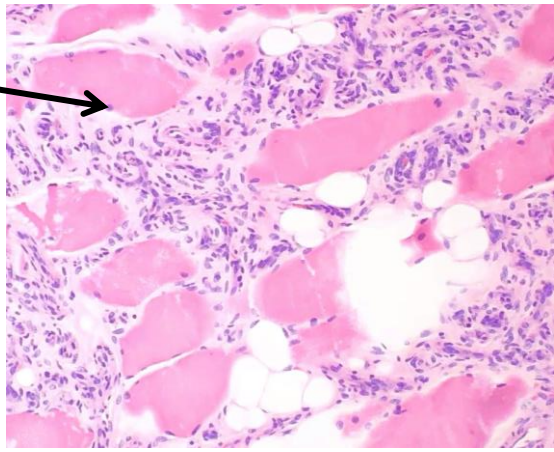
Benign vascular neoplasms. Often grow faster than patient.
Categorized by vessels size/appearance.

Lobular Capillary Hemangioma *("Pyogenic granuloma")*
Polypoid, exophytic on skin and mucosal surfaces.
Unclear if truly neoplastic.
Lobular arrangement of small capillaries with larger "feeder" vessel.
Myxoid stroma with inflammatory cells. Often eroded surface.



Infantile (Juvenile) Hemangioma
Starts as flat, red mark soon after birth→ grows to look like "strawberry" over several months → regress over several years.
Multinodular masses fed by single arteriole.
Appearance varies depending on phase (proliferative vs involutional).
IHC: Unique expression of GLUT1 (not in other hemangiomas)

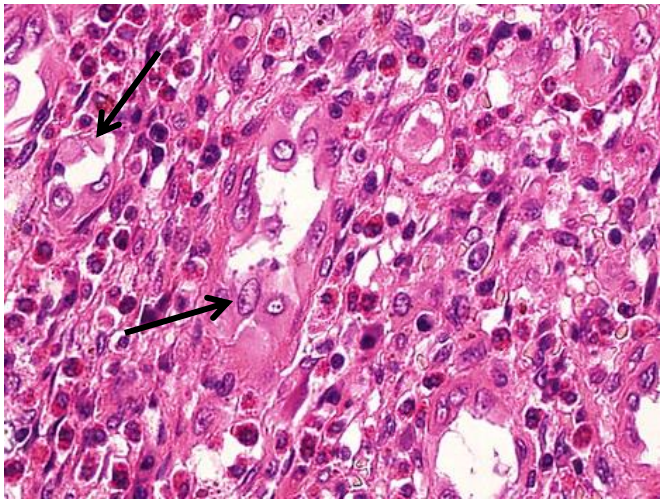
Intramuscular hemangioma
Mixed vessels, large and small with lymphatics within muscle.
Can have prominent adipose tissue (mimicking lipoma)
Often recognized in young adulthood. Present with exercise pain.
Often large with diffuse infiltration.
Most are probably AV malformations and congenital.



Congenital Hemangioma
Present at birth and don't grow. Can be "rapidly involuting" or "non-involuting." Well-defined lobules of capillaries with central draining vessels, surrounded by fibrous tissue.

Epithelioid Hemangioma

aka Angiolymphoid hyperplasia with eosinophils



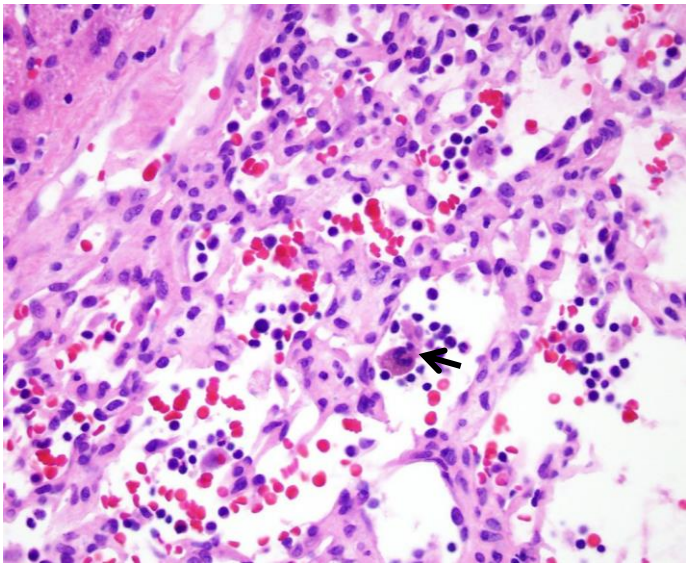
Benign.
Often young adults in superficial head and neck.
Circumscribed, subcutis. Large and deep.

Lobules of capillaries centered around larger vessel.
Endothelial cells are plump ("epithelioid"), projecting like tombstones into vessels. Round nuclei. Abundant eosinophilic cytoplasm. Vesicular chromatin.

Associated inflammatory infiltrate rich in **eosinophils**.

Molecular: **Frequent FOS/FOSB rearrangements**.
IHC: (+) FOSB

Anastomosing Hemangioma



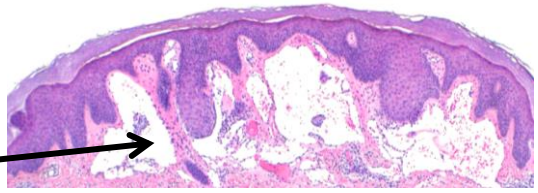
Thin-walled Anastomosing vessels line by hobnail endothelial cells.
Hyaline globules and extramedullary hematopoiesis common, so look out for megakaryocytes (→).

Can see anywhere. Most common in GU/GI tracts. Lobulated, with some focal infiltration of adjacent tissue.

Molecular: GNAQ or GNA14 mutations

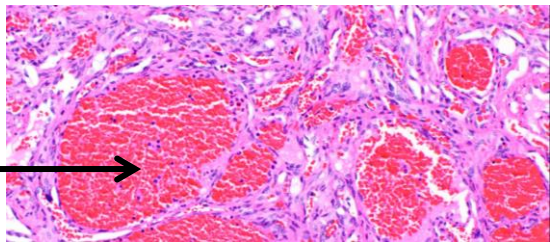
In contrast to Angiosarcoma: No atypia (hyperchromasia, pleomorphism), mitoses, or multilayering of endothelial cells.

Rare Vascular lesions



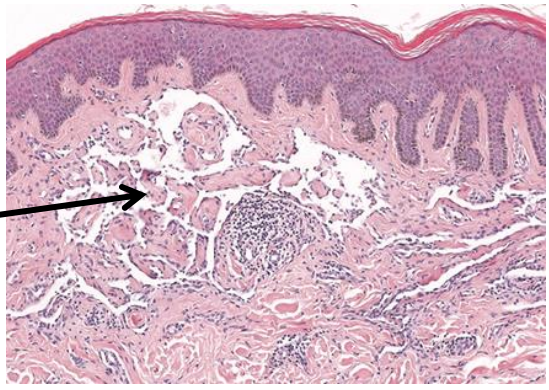
Synovial hemangioma: Benign proliferation of blood vessels in a synovium-lined surface. Congested, variably-sized vessels.

Hobnail hemangioma: Benign. Superficial dilated vessels with thin walls. Lined by small, bland, hobnail endothelial cells. Focal papillae ok. Usually young adults on the leg.

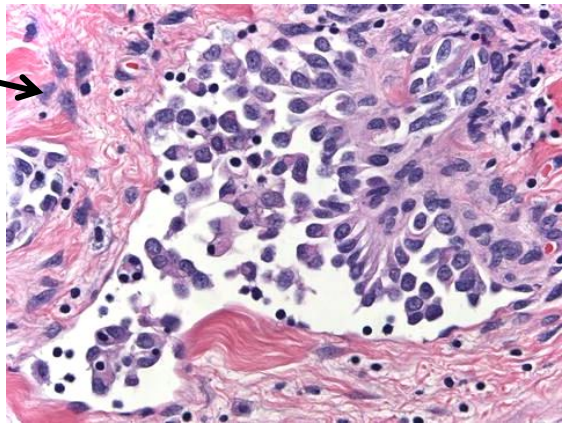


Spindle cell hemangioma: Benign vascular tumor with both cavernous and cellular, mostly spindled, zones. Usu. Young adults on extremities, SubQ. Frequent IDH1 mutations (associated with Maffucci syndrome).

Other rare hemangiomas: Acquired tufted hemangioma, Microvenular hemangioma, Sinusoidal hemangioma, Glomeruloid hemangioma,



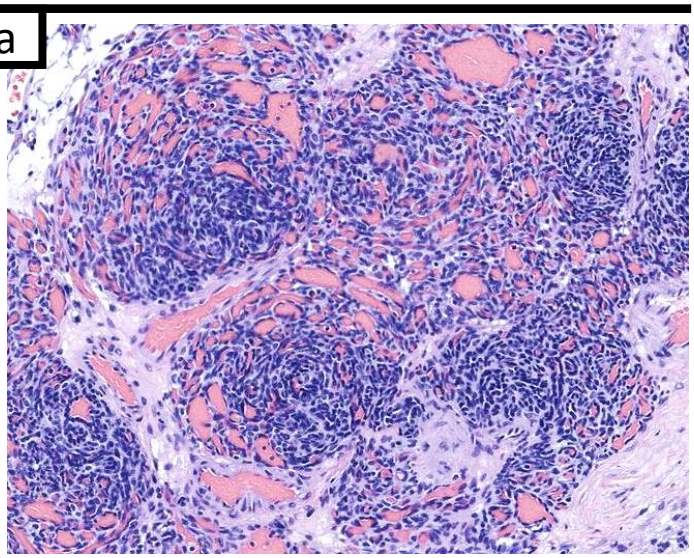
Retiform hemangioendothelioma: Rare. Locally-aggressive, rarely metastasizing vascular lesion. Elongated and narrow arborizing vascular channels resembling rete testis (hence name). Lined by bland hobnail cells. Usu. Skin/SubQ of kids.



Papillary intralymphatic angioendothelioma:
aka "Dabska tumor" or PILA
Rare. Rarely metastasizing. Tufting and hobnail endothelial cells within superficial lymphatics. Background lymphangioma.
Polarized "matchstick-like" columnar endothelial cells.
Lots of intraluminal lymphocytes.
IHC: (+)Pan-endothelial and lymphatic markers

Composite Hemangioendothelioma
Admixture of two histologically distinct components (e.g., EHE)

Kaposiform Hemangioendothelioma



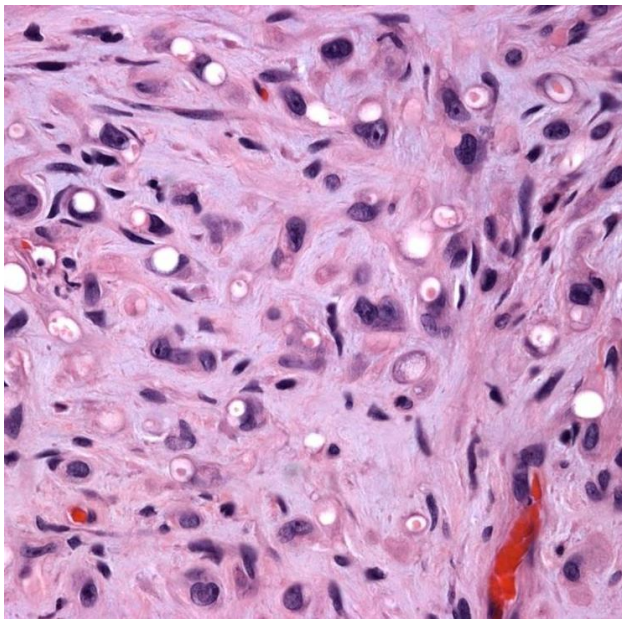
Locally aggressive vascular tumor.
Rare. Exclusively in **children**. Deep-seated.
Often associated with Kasabach-Merrit phenomenon (consumption of platelets→ thrombocytopenia)

Infiltrate soft tissue in lobular "cannon-ball fashion." Different areas have features of both capillary hemangioma and Kaposi sarcoma (plump spindled cells that form slit-like lumina with RBCs, hence the name). Associated with lymphatic spaces.

Tightly coiled glomeruloid-like areas.
IHC: (+)Vascular *and* lymphatic markers

Tufted angioma→ superficial version of KHE

Epithelioid Hemangioendothelioma



Malignant (but less aggressive than angiosarcoma).

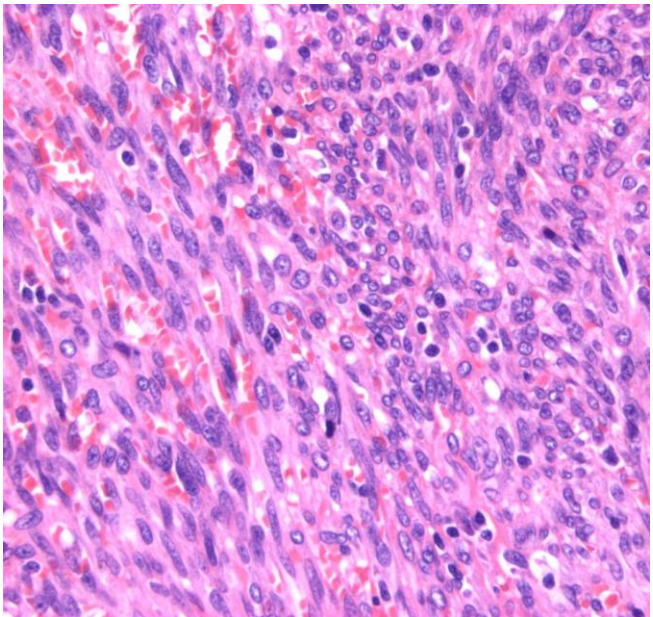
In soft tissue, often angiocentric, expanding wall and obliterating lumen. Also common in liver and lung.

Cords or nests of epithelioid endothelial cells in myxohyaline stroma. Moderate amounts of eosinophilic cytoplasm.
Eosinophilic cells with **vacuoles** containing erythrocytes ("Blister cells").

IHC: CAMTA1 stain specific. (-/+) CK, SMA
Molecular: recurrent **CAMTA1-WWTR1 fusions**

A subset have YAP1-TFE3 fusions. Stain with TFE3. Well-formed vessels. Seem to be more aggressive.

Kaposi Sarcoma



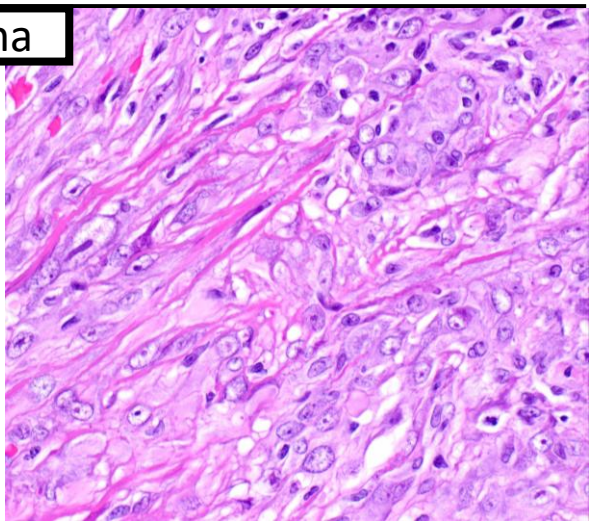
Locally aggressive. Often multiple cutaneous lesions, but can involve viscera and lymph nodes.
Caused by **Human Herpes Virus 8** (HHV8) in all cases.

Can be Classic/Endemic, which are usually indolent, or associated with **immunosuppression** (usually **AIDs**), which is more aggressive often.

Proliferation of small slit-like vessels lined by mildly atypical cells surrounded by bland spindled cells; **Extravasated RBCs** and patchy chronic inflammation. Frequent hyaline globules (intra or extracellular).

IHC: **HHV8** (nuclear, speckled)

Pseudomyogenic Hemangioendothelioma



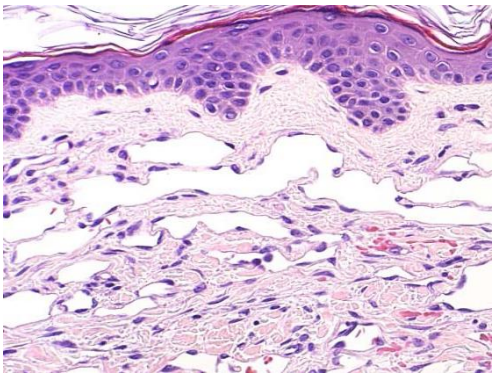
Rare. Rarely metastasize. Often multiple nodules in same anatomic region. Often young men on leg.

Plumps spindled to epithelioid cells with **vesicular chromatin** and **abundant eosinophilic cytoplasm** (resembling rhabdomyoblasts, hence the name!). Fascicular or sheetlike-growth.

Abundant brightly eosinophilic cytoplasm. Vesicular nuclei.

IHC: (+) AE1/AE3, ERG, **FOSB**. INI1 intact.
Molecular: SERPINE1 and **FOSB genes fusion**

Atypical Vascular Lesion

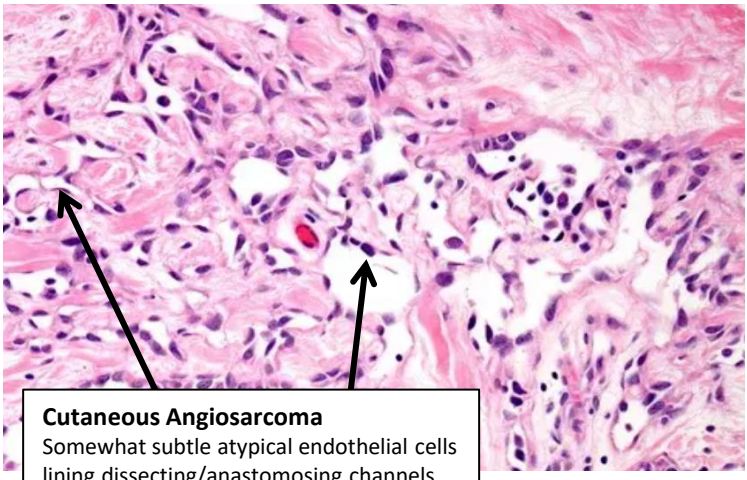


Benign. Occur in **irradiated skin** (often of breast).
Often **small**, superficial dermal, symmetrical.

Irregularly-shaped thin-walled vessels with branching and anastomosing growth. Lined by a single layer of endothelium with some hobnailing and hyperchromasia.
NO endothelial cell multilayering, mitoses, or true cytologic atypia

IHC/Molecular: No MYC overexpression/amplification.

Angiosarcoma



Cutaneous Angiosarcoma
Somewhat subtle atypical endothelial cells lining dissecting/anastomosing channels

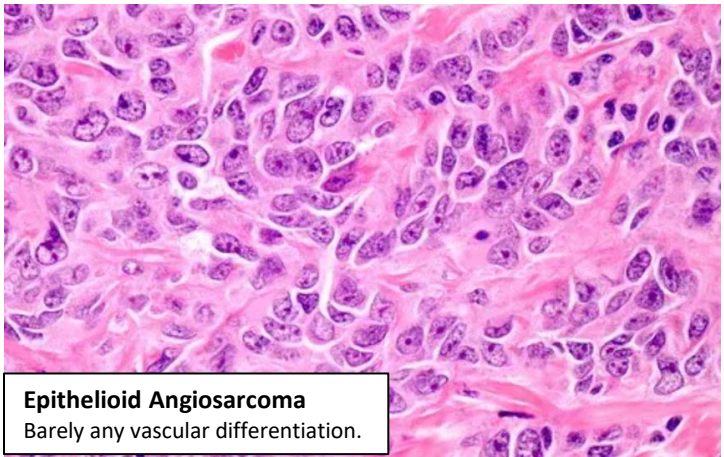
Malignant. Very aggressive. Typically elderly.

Variable degrees of **vascular differentiation**.
Some areas show well-formed anastomosing vessels, while other areas may show solid sheets of high-grade cells with only IHC evidence of vascular differentiation.
Can be epithelioid or spindled.
Often extensive hemorrhage. Infiltrative.

Unlike benign lesions: significant cytologic **atypia**, **necrosis**, endothelial cells piling up, and/or mitotic figures (although mitoses can be seen in some benign tumors)

Grade does **not** predict prognosis (*all* aggressive)

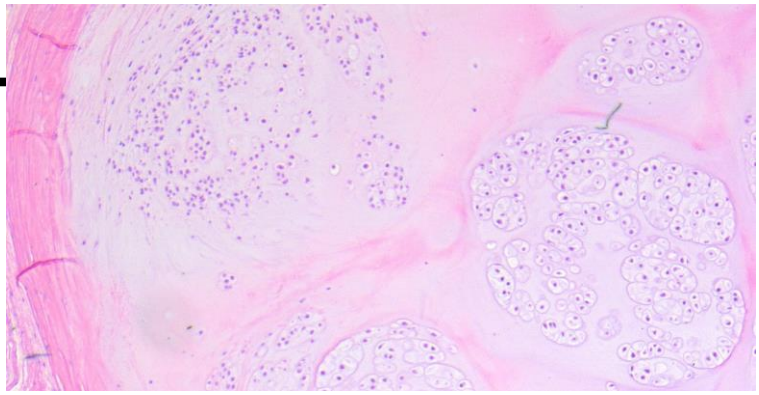
Post-radiation angiosarcoma of the breast:
Occurs after radiation (usu. ~5yrs).
High-level amplification of MYC (by IHC or FISH) is a hallmark of this lesion. Also seen in lymphedema-associated angiosarcoma.



Epithelioid Angiosarcoma
Barely any vascular differentiation.

Chondro-Osseous Tumors

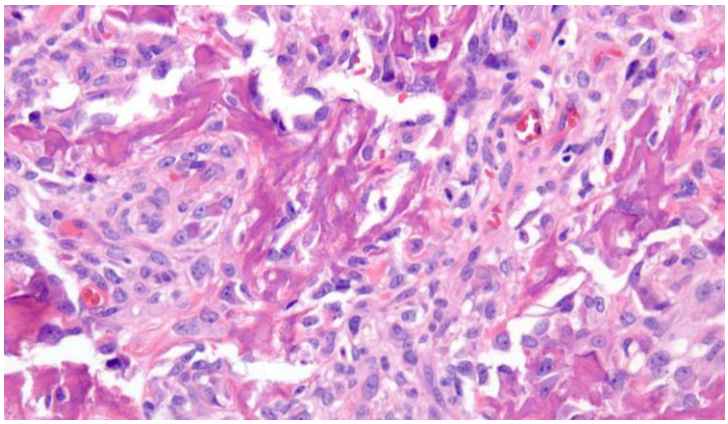
Chondroma (of Soft tissue)



Soft tissue mass composed of nodules of well-differentiated cartilage.
Hyaline or myxoid matrix. May calcify.
Chondrocytes show limited atypia and mitoses.

Most common in fingers (like enchondromas)

Extraskeletal Osteosarcoma

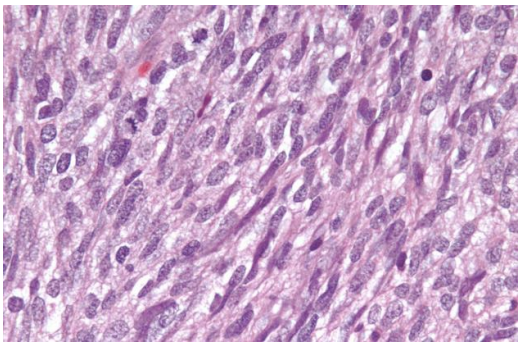


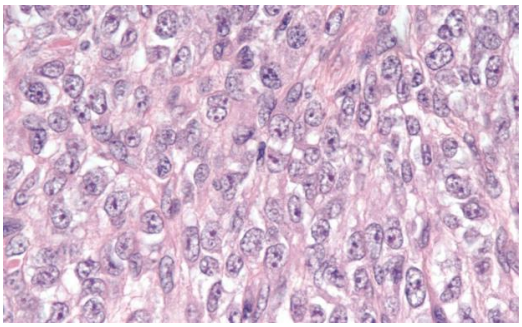
Malignant cells associated with neoplastic bone/osteoid.
Not associated with skeletal system.
Otherwise unclassifiable sarcoma.

IHC: (+) SATB2 in osteoblasts (can be helpful to distinguish osteoid from collagenous stroma)

Complex genetics. Poor prognosis.

Gastrointestinal Stroma Tumor (GIST)





Derived from **interstitial cells of Cajal** (pacemaker cells of GI tract)
Most common in Stomach (60%) followed by Small Bowel (30%)
Most often **spindled**, but can be epithelioid or pleomorphic
Gastrointestinal: Intramural, submucosal, or subserosal location

Molecular: Mutually exclusive **cKIT** (80%) or **PDGFRA** (10%) receptor tyrosine kinase mutations→ Can shrink pre-operatively with receptor tyrosine kinase inhibitors (e.g., imatinib)
Mainstay therapy = surgery, but can use RTK inhibitors if metastatic/recurrent
Increased in NF1 patients

IHC: **(+) CD117 (cKit), DOG1**, CD34

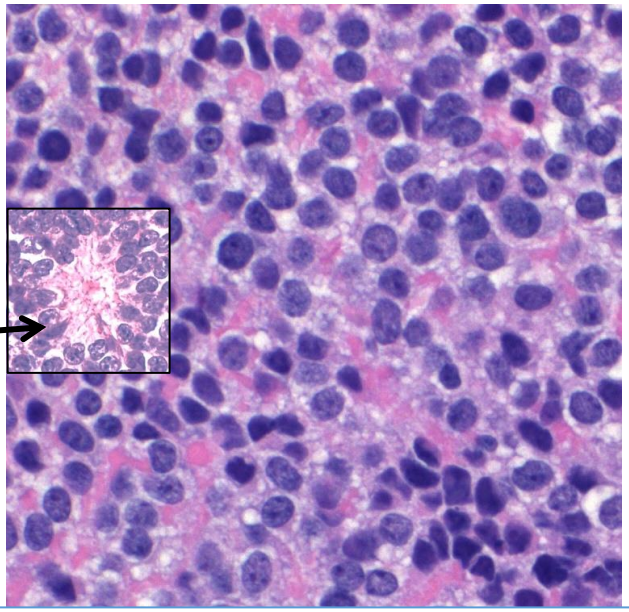
Variable behavior→ estimate risk of progressive disease based on size, mitoses, location (see table below)

SDH-mutated GIST (without a cKit mutation)→ **pediatric**/familial
Epithelioid, **multinodular**, **metastasize to lymph nodes**, don't respond to RTK inhibitor therapy (no cKit mutations!), but overall more indolent; Characterized by **loss of SDHB IHC staining**

Carney-Stathakis syndrome→ paraganglioma and GIST with germline SDH mutation
Carney's Triad→ GIST, pulmonary chondroma, paraganglioma, somatic SDH mutation

Undifferentiated small round cell sarcomas of bone and soft tissue

Ewing Sarcoma



Malignant. Variable neuroectodermal differentiation.
Often arises in the **bone of young** (but can see in many organs/sites; Chest wall = *Askin tumor*).
Old name: Primitive Neuroectodermal tumor (PNET)

Usually uniform, small, round, blue cells with sheet-like to lobular, growth pattern with variable necrosis.
Even chromatin without nucleoli.
Can see pseudorossettes

IHC**: Strong, membranous CD99 staining** (Sensitive, but not specific staining). NKX2-2 (more specific)
Cytoplasmic glycogen stains with PAS.

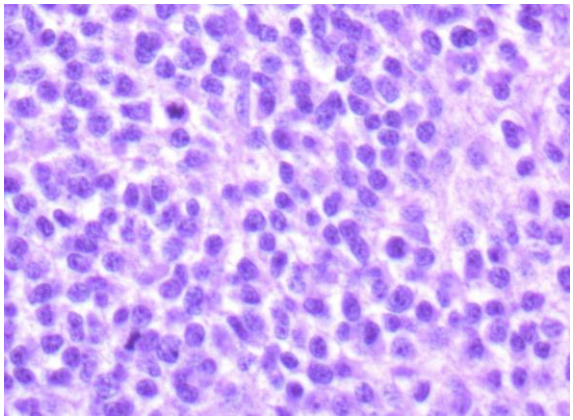
Molecular: Fusion of FET gene (EWSR1, FUS, TAF15) with a ETS gene (FLI1, ERG, etc..)
Most common by far: EWSR1 fusion (with FLI-1, most common, or ERG) t(11;22)

Round cell sarcoma with "EWSR1-non-ETS fusions"
Round and spindle cell sarcomas with EWSR1 or FUS fusions involving partners unrelated to ETS family.
Often, NFATC2 (bone) or PATZ1 (soft tissue)

When I'm thinking Ewing, I usually start with EWSR1 FISH to confirm the diagnosis as it's cheap & fast.

Break apart FISH is still positive in "EWSR1-non-ETS fusions" though. If FISH is negative, or there's anything strange about it, consider doing a sarcoma fusion panel to identify both partners and look for other genes.

CIC-rearranged Sarcomas

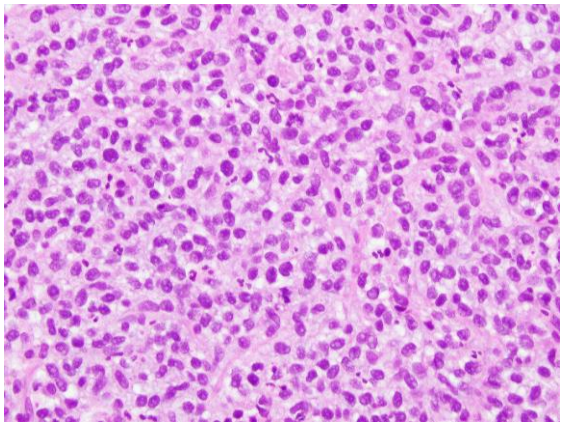


Malignant. More aggressive the Ewing.
Often young adults in soft tissue.

Solid to lobulated proliferation of small round cells (like Ewing sarcoma, but often more prominent nucleoli).
Scant eosinophilic to clear cytoplasm. Sometimes spindled.
Geographic necrosis usually present. Lots of mitoses.

IHC: WT1 (+ nuclear), ETV4, variable CD99,
Molecular: **CIC fusions**, mostly commonly with DUX4

BCOR-rearranged Sarcomas



Malignant. Similar outcome to Ewing. Young. Usually in bone.

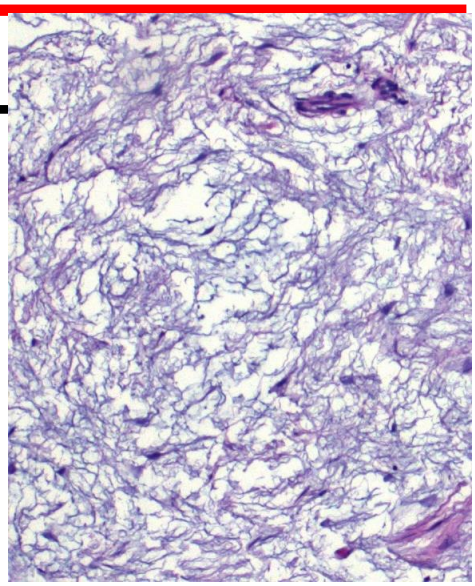
Solid proliferation of mostly small round cells with monomorphic round nuclei, fine chromatin, and delicate capillary network.
Sometimes partially spindled. Variably myxoid.

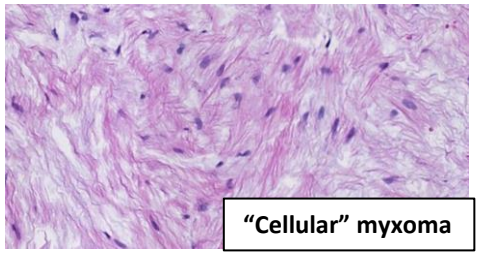
Molecular: BCOR fusion with either CCNB3 or MAML3 or a BCOR internal tandem duplication.

IHC: SATB2, BCOR, CyclinD1

Tumors of Uncertain Differentiation

Myxoma





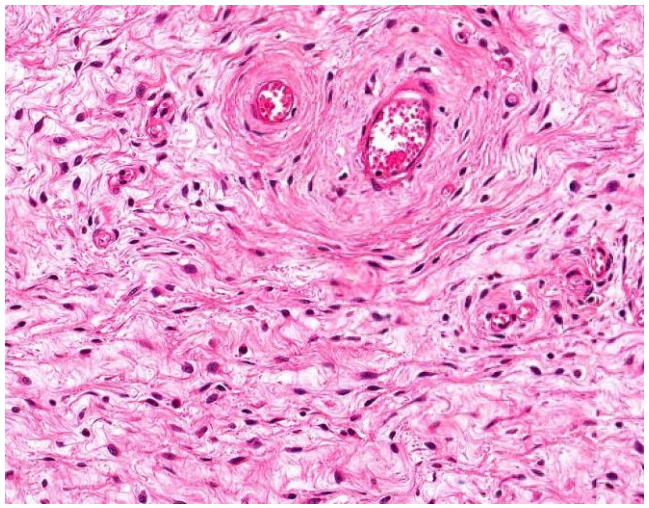
"Cellular" myxoma

Benign. Adults, middle-aged.
Uniform, cytologically bland, small spindled to stellate cells in **abundant myxoid stroma**. **Hypocellular** and **hypovascular**.
Can show cystic change and/or have more slightly more cellular areas.
Grossly look like jelly. Can be infiltrative. Occasional muciphages.
Notably, No atypia or mitoses (otherwise consider myxofibrosarcoma)
IHC: (+/-)CD34; (-)Desmin, S100

Intramuscular myxoma:
Within muscle. Often female. Frequent GNAS mutations.
Can sometimes be "cellular" with more cells and collagen.
Intramuscular myxoma + fibrous dysplasia = Mazabraud syndrome (both have GNAS mutations)

Juxta-articular myxoma:
Vicinity of a large joint (usu. Knee)
Lacks GNAS mutations.

Deep ("Aggressive") Angiomyxoma

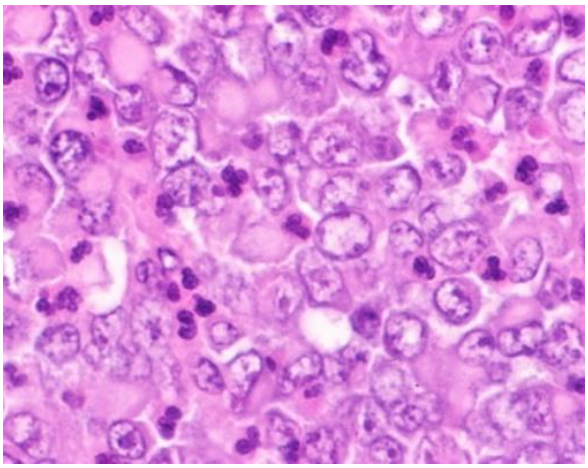


Benign (despite name!), but frequent recurrences
Adult women in pelvicoperineal region. Usu. >10cm.

Poorly-marginated. Hypocellular with myxoid matrix.
Small spindled to stellate cells.
Scattered medium to large-sized vessels with occasional hyalinized walls.
Scant eosinophilic cytoplasm with processes.
Larger spindled myoid cells congregate around larger vessels and nerves.

IHC: (+) ER, PR, Desmin; (+/-)SMA, CD34
Molecular: HMGA2 rearrangements frequently.

Extrarenal Rhabdoid Tumor



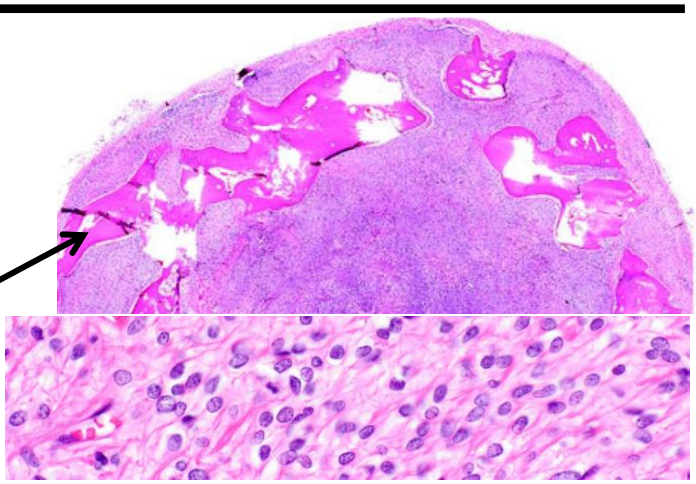
Malignant. Very aggressive! Mainly infants and children.

Characteristic **"rhabdoid" cells** (Large, round/polygonal cells with abundant, eccentric, glassy eosinophilic cytoplasmic inclusions and vesicular nuclei with prominent nucleoli). Often discohesive.

Morphologically/genetically identical to Rhabdoid tumors in kidney and brain of kids.

IHC/Molecular: **SMARCB1 (INI1) loss/inactivation**
CAM5.2 (+) in inclusions.
(+/-) CK, EMA, SALL4, Glypican-3, CD99, Synaptophysin.

Ossifying Fibromyxoid Tumor

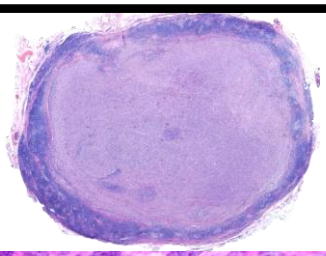


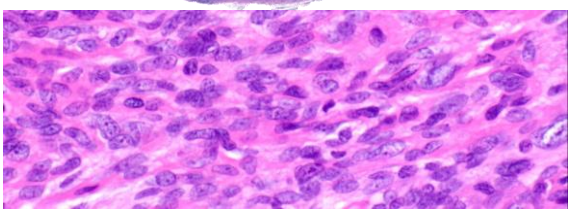
Rare. Wide age range/locations.
Usually benign with potential with recurrence.

Lobules of uniform, monomorphous round to spindled cells arranged in cords surrounded by fibromyxoid stroma.
Circumscribed mass with peripheral ossification.

IHC: **(+) S100**, (+/-) Desmin
Mosaic loss of SMARCB1 (INI1).
Molecular: PHF1 rearrangements

Angiomatoid Fibrous Histiocytoma





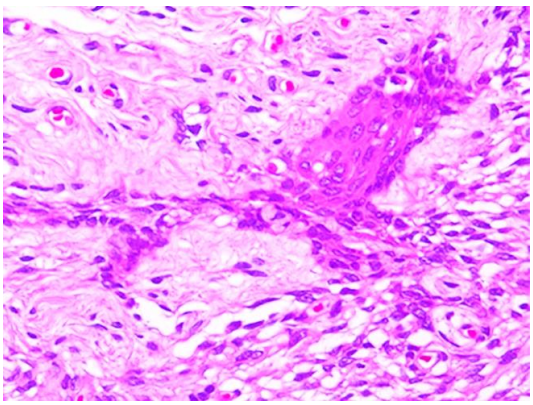
Rare. Usually indolent (rare metastases).
Most commonly young. Small **subcutaneous** nodule.

Often pericapsular cuffing of **lymphocytes** (mimicking a lymph node)
Nodules of epithelioid/ovoid cells in syncytial sheets.
Pseudoangiomatoid spaces full of blood. Thick fibrous capsule.

IHC: Variable desmin, CD99, and EMA.

Molecular: **EWSR1 fusions**, usually with CREB1.

Ectopic Hamartomatous Thymoma

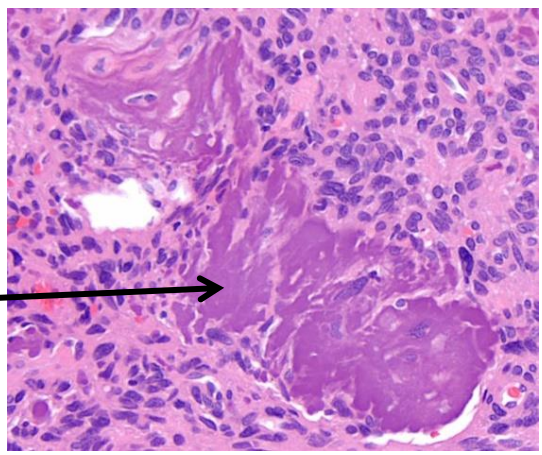


Benign. Exclusively in the lower neck region. Often adults.
Despite name, no evidence of thymic origin/differentiation.

Haphazard blending of spindle cells, epithelial islands and adipocytes.
Some spindled cells show "lattice-like" growth. Islands of often squamous epithelium blend with spindled cells.

IHC: Epithelium stains with keratins. Plump spindled cells express actin. Delicate spindled cells express CD34.

Phosphaturic Mesenchymal Tumor

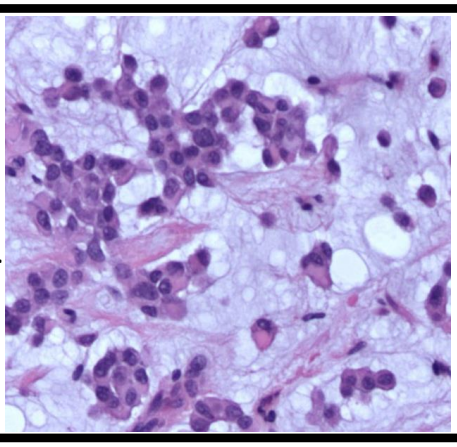


Most tumors are benign (but cause significant side-effects!).
Produce **FGF23** →inhibiting renal proximal tubule phosphate reuptake → tumor induced **Hypophosphatemia** and **osteomalacia** (corrected by excision)

Bland spindled to stellate cells. Rich vascular network
Unusual hyalinized "smudgy" matrix with "grungy" or flocculent calcifications.

FGF23 can be demonstrated by testing blood or by IHC.
Molecular: FN1 fusions.
IHC: (+/-) CD56, ERG, SATB2, and/or SSTR2A

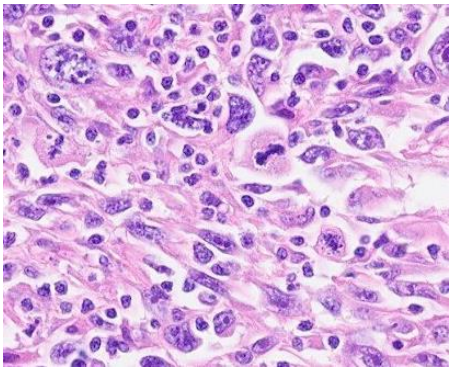
Myoepithelial Tumors

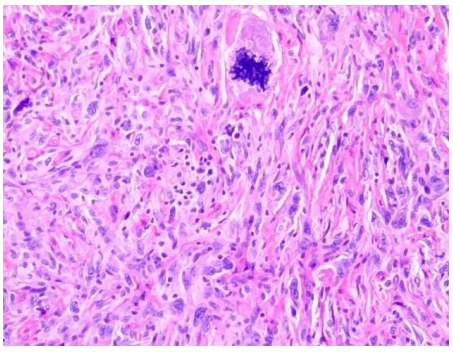


Rare. Resemble counterparts in salivary gland and skin.
Wide morphologic spectrum. Spindled to epithelioid cells.
Often reticular or trabecular growth with prominent myxoid stroma.
Myoepithelioma→ Benign
Myoepithelial carcinoma→ Have atypia, nucleoli, mitoses and necrosis.
Ductal component? → Mixed tumor

IHC: (+) CK, S100. (+/-) GFAP, EMA, SOX10, Calponin, SMA
Molecular: **EWSR1** (myoepithelial tumors) or PLAG1 (mixed tumors)

Atypical Fibroxanthoma (AFX)





Dermal-based mesenchymal neoplasm. Tumors that meet strict criteria generally behave in a benign fashion.

Requirements: (Can only make on an excisional specimen)
1) **Strict confinement to Dermis** (*No* SubQ invasion)
2) **Negative IHC for keratins, S100, and SOX10**
3) **No Tumor necrosis, LVI, PNI**

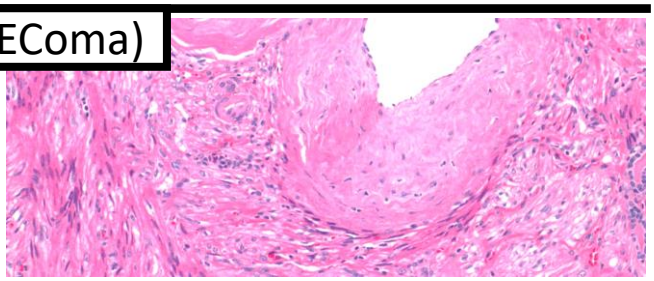
Well-circumscribed, nodular. Often ulcerate.
Sheets and fascicles of highly pleomorphic cells. Lots of mitoses

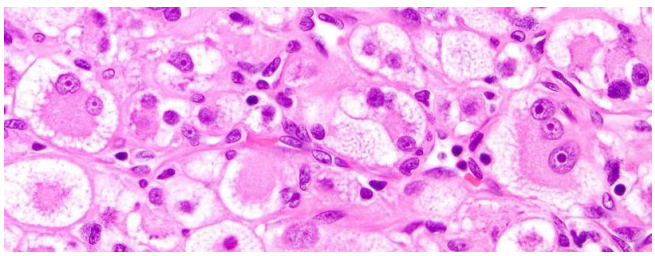
Arises in sun-damaged skin (UV-induced) of head and neck: in a disease spectrum with Pleomorphic Dermal Sarcoma (same thing, but in subQ).

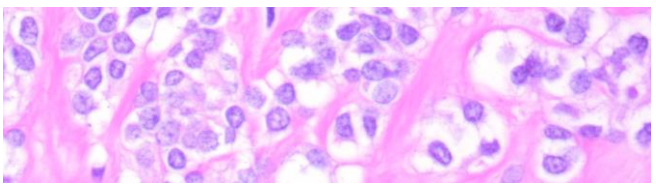
IHC: Mostly to *exclude* other diagnoses (-) CK, S100, SOX10, CD34, ERG, Desmin (excluding carcinoma, melanoma, angiosarcoma,and leiomyosarcoma, respectively)
(+/-) Non-specific stains CD10, p53, SMA.

Molecular: TP53 mutations.

Perivascular Epithelioid Cell Tumor (PEComa)







Benign, usually (Unless frankly malignant)

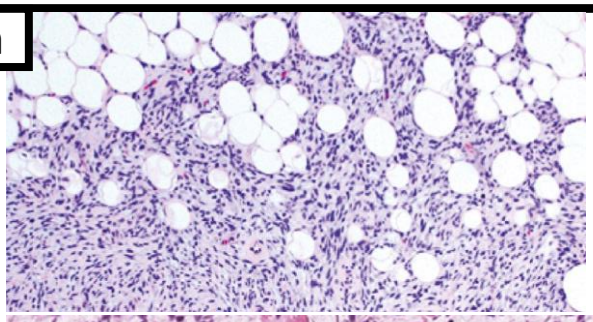
Often areas of epithelioid tumor cells with abundant granular eosinophilic to clear cytoplasm with round nuclei with small nucleoli. Sometimes spindled.
Associated with vessel walls in radial arrangement.

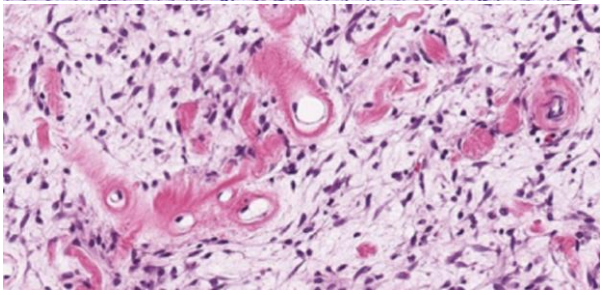
IHC: Variably express **melanocytic** (usu. HMB45, variable MelanA), and **smooth muscle** (Actins, desmin, etc..) markers. TFE3 positive in subset with TFE3 fusions.
Cathepsin K→ sensitive/strong, but not specific

A subset of cases are associated with Tuberous Sclerosis.

Can see in many sites/organs.
Includes Angiomyolipoma, Clear cell "sugar" tumor, and lymphangioleimyomatosis.

NTRK-rearranged spindle cell neoplasm





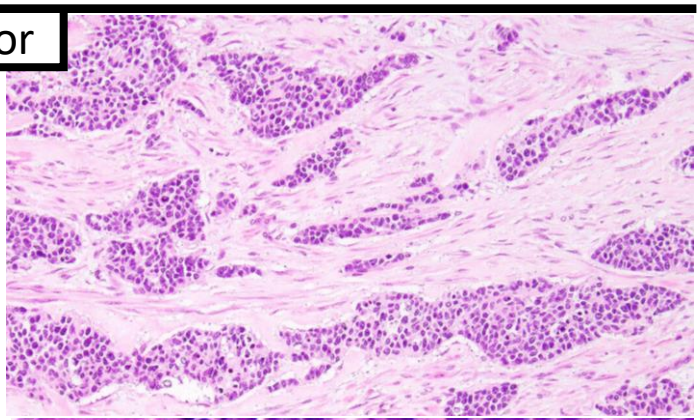
Emerging group of molecularly-defined tumors (outside of infantile fibrosarcoma)

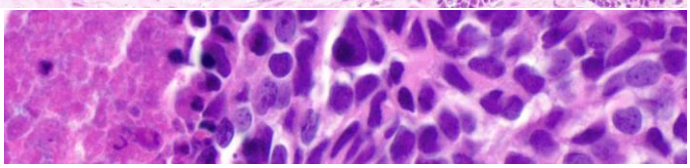
Wide morphologic spectrum.
Haphazardly arranged monomorphic spindle cells.
Infiltrative growth within fat.
Distinctive stromal and perivascular keloid collagen

IHC: (+) S100, CD34, pan-TRK; (-) SOX10
Molecular: **NTRK fusions (needed for Dx)**
Tumors with NTRK1 fusions stain with NTRK1 IHC.

Closely resemble (and were previously thought to be) peripheral nerve sheath tumors (given IHC, appearance)

Desmoplastic small round cell tumor





Malignant. Aggressive with poor survival.

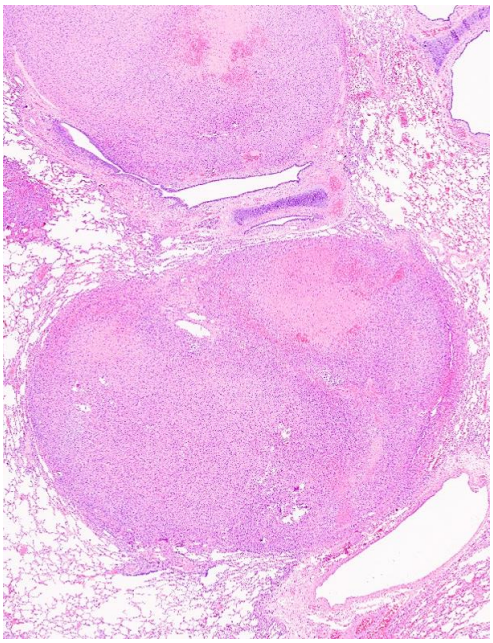
Primarily **children and young adults**.
Usually **abdominal cavity**, including retroperitoneum, pelvis, omentum, mesentery.

Nests of small round cells. Dispersed chromatin.
Set in **desmoplastic stroma** with sharp outlines.
Frequent necrosis and mitoses.

IHC: **(+)Cytokeratin, Desmin** (dot-like), and WT-1 (C-terminus) (multiphenotypic differentiation)

Molecular: **EWSR1-WT1 fusion**

Intimal Sarcoma



Malignant.
Arises in large blood vessels of systemic and pulmonary circulation or within heart cavities.
Characteristic predominantly **intraluminal growth** with obstruction of blood flow and seeding tumor emboli.

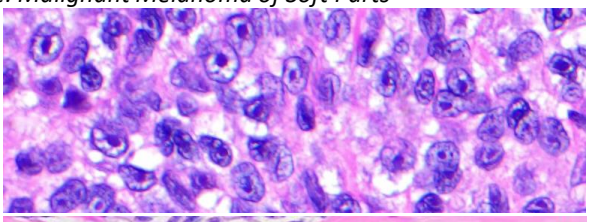
Morphologically non-distinct and poorly differentiated. Mild to severely pleomorphic spindled cells with necrosis, nuclear pleomorphism, and mitoses. Can have myxoid or fascicular areas. Sometimes heterologous differentiation.

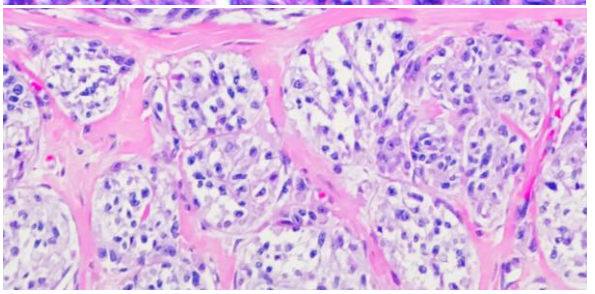
IHC: MDM2 (+)

Molecular: Amplification of MDM2/CDK4 (like in ALT/WDL)

Clear Cell Sarcoma of Soft Tissue

Old name: Malignant Melanoma of Soft Parts





Malignant, aggressive. Typically young adults.

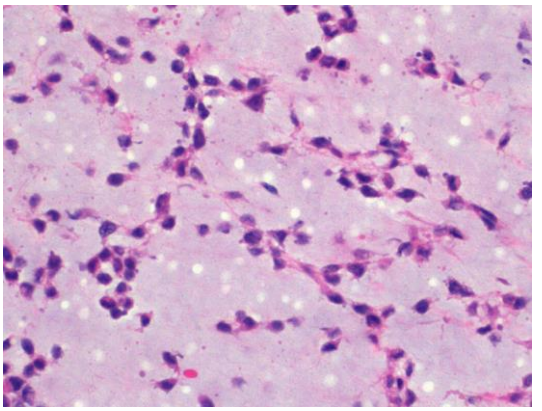
Characteristic **nested growth with dividing collagenous bands**. Scattered wreath-like multinucleated giant cells.

Plump epithelioid to spindled cells with palely eosinophilic cytoplasm (despite name) with vesicular nuclei and **prominent nucleoli**.

IHC: Expresses **melanocytic markers** (S100, HMB45, MITF, etc..)

Molecular: EWSR1-ATF1 fusions

Extraskeletal Myxoid Chondrosarcoma

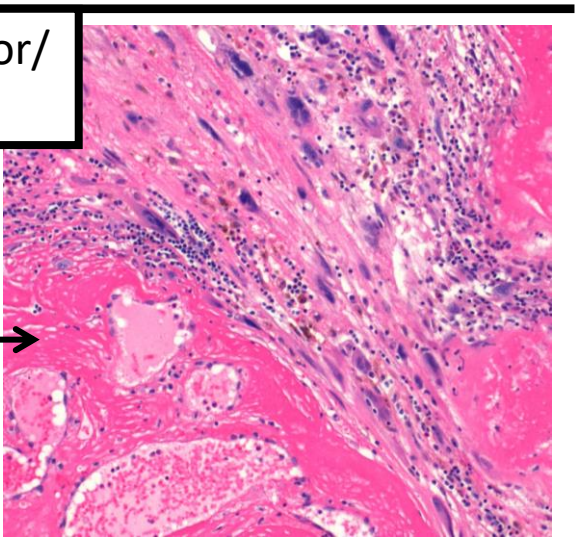


Malignant. Prolonged survival, but frequent, metastases.

Despite name, *no* overt cartilaginous differentiation!
Abundant myxoid matrix with cords, clusters, networks, and nests of cells with modest amounts of eosinophilic cytoplasm and round/oval, bland nuclei.
"AT&T tumor" → old ad "reach out and touch someone" → cells are often reaching out to touch each other.

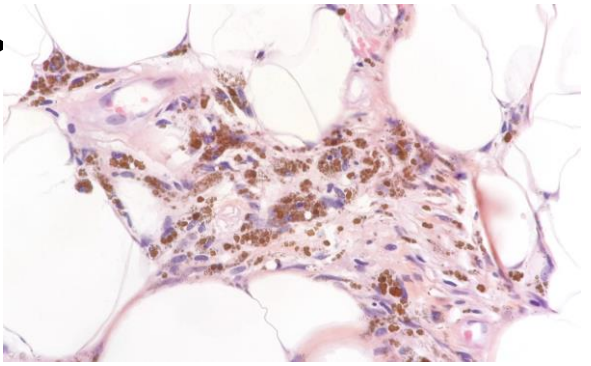
Molecular: **NR4A3 fusions**, often with EWSR1 or TAF15
IHC: (+) ISNM1

Pleomorphic Hyalinizing Angiectatic Tumor/ Hemosiderotic Fibrolipomatous Tumor



Rare. Locally recurring, non-metastasizing.
Usually adults in soft tissue. Often on foot. Usually SubQ.

PHAT: ***Think: PHAT***
Clusters of ectatic thin-walled ectatic blood vessels lined by fibrin.
Embedded in spindled to pleomorphic cells with intranuclear inclusions and fine hemosiderin granules.
Very low to absent mitotic activity

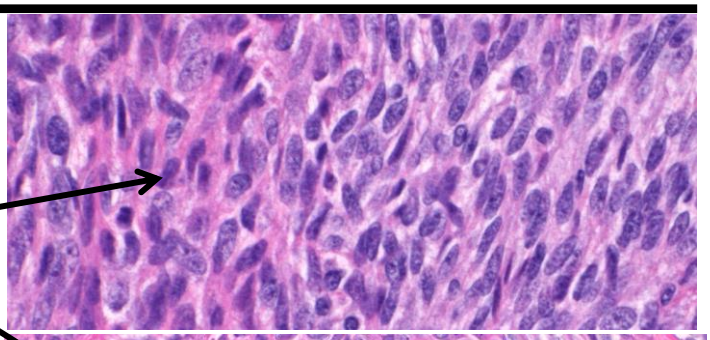


Hemosiderotic Fibrolipomatous Tumor: *(HFLT)*
Thought to represent early PHAT. Can be by itself or at periphery of PHAT.
Adipocytes with admixed hemosiderin-laden spindled cells, hemosiderin-laden macrophages, and scattered inflammation.

IHC: CD34 (+)

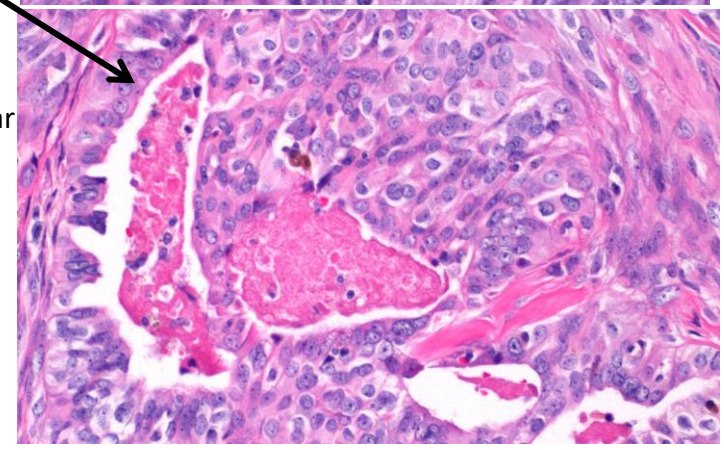
Molecular: Both have recurrent TGFBR3 and/or OGA (formerly MGEA5) rearrangements

Synovial Sarcoma



Malignant. Usually young adults.
Often deep extremity soft tissue, but also common in Thorax and Head/Neck.

Monophasic SS→ Just spindled component.
Biphasic SS→ Spindled and epithelioid component.
~2/3 are monophasic.

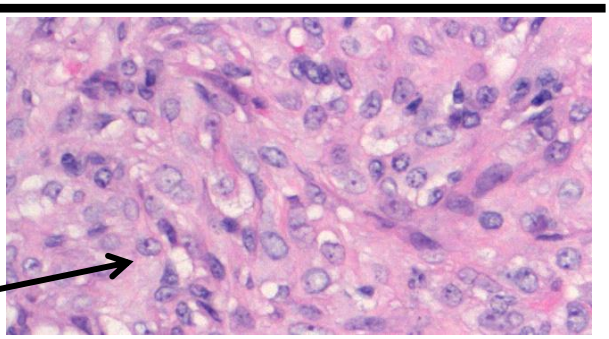


Fairly uniform spindled cells with relatively little cytoplasm. Variable epithelial differentiation.
Ovoid, "stubby," nuclei with hyperchromatic granular chromatin and small nucleoli.
Can see "Stag-horn" vessels.
Epithelial cells arranged in nests and glands with paler cytoplasm and vesicular nuclei.

IHC: Patchy EMA and CK (particularly strong in epithelial areas). Usu. CD99 (+). TLE-1 (+)

Molecular: **SS18-SSX gene fusions.** t(X;18)

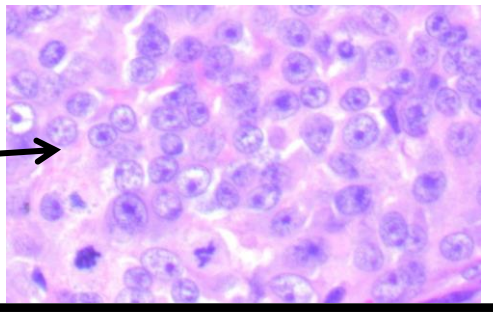
Epithelioid Sarcoma



Malignant. Often youngish adults.
Frequent **lymph node metastases**.

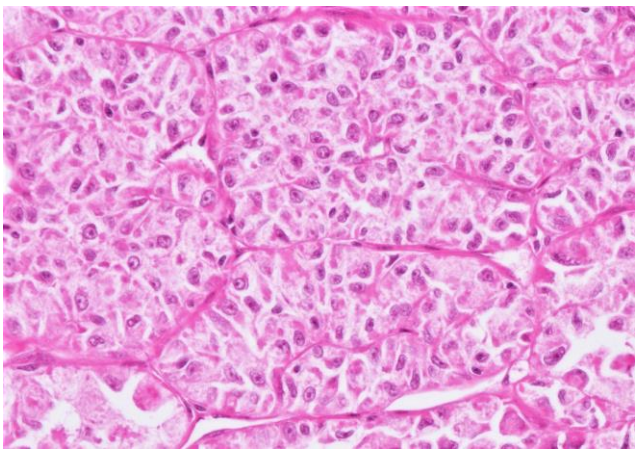
IHC: **INI1 loss; (+)Cytokeratin/EMA**, (±) CD34, ERG
Molecular: Complex, but SMARCB1 (INI1) deletions/loss.

Classic (distal) type:
Cellular nodules of epithelioid to spindled cells with central degeneration/necrosis→ looks vaguely **granulomatous**.
Vesicular chromatin and eosinophilic cytoplasm.
Acral sites on fingers/hands.



Proximal (Large cell) type:
Multinodular and sheet-like growth of large pleomorphic cells large vesicular nuclei and prominent nucleoli. Often Rhabdoid-appearing.
Worse prognosis. Deep soft tissue of trunk/pelvis (+)GATA3

Alveolar Soft Part Sarcoma

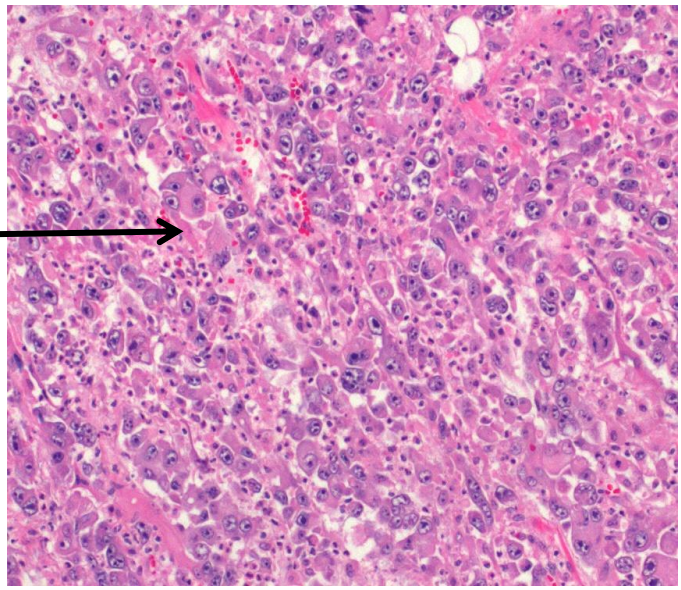


Malignant. Often young adults.

Organoid nests of large, uniform, polygonal, epithelioid cells with abundant, eosinophilic, granular cytoplasm. Round nuclei with prominent nucleoli.
PAS demonstrates rhomboid or rod-shaped intracytoplasmic inclusions.

IHC: (+)TFE3 (nuclear, strong, diffuse),
(-/+) S100 and Desmin
Molecular: ASPSCR1-TFE3 Fusion

Undifferentiated Sarcoma



A sarcoma with no identifiable line of differentiation.
Heterogeneous group and <u>diagnosis of exclusion</u>.
Subclassify based on histologic appearance.

<u>Undifferentiated Pleomorphic Sarcoma (UPS)</u>
old name: Malignant Fibrous Histiocytoma (MFH)
- Wildly pleomorphic cells.
- Complex karyotypes
- More common in older adults
- Aggressive with frequent metastases.

Undifferentiated Spindle Cell Sarcoma
Undifferentiated Round Cell Sarcoma
- More common in younger patients.

Undifferentiated Epithelioid Sarcoma

<u>Stains/studies to do before diagnosing an "Undifferentiated Pleomorphic Sarcoma":</u>

As this is a diagnosis of *<u>exclusion</u>*, special studies are required to exclude common alternative diagnoses. The specifics may depend on location/scenario, but consider the following:

Keratins (including high and low molecular weights), ±EMA, p63 → positive in metastatic carcinoma
Desmin→ positive in leiomyosarcoma or other muscular tumor (even worse prognosis)
S100 or SOX10 → positive in metastatic melanoma or MPNST
ERG/CD34→ positive in vascular tumors
MDM2→ exclude a dedifferentiated liposarcoma, particularly in the retroperitoneum
CD45, CD30, CD68, CD163 → positive in weird hematolymphoid/histiocytic things

Also, make sure that the tumor is well-sampled (a better-differentiated component could be hiding in there!).

<u>Remember</u>:
SMA → may show wispy (myofibroblastic-like) staining in UPS
CD68, CD163, CD31, MITF→ can stain intratumoral histiocytes
Keratins→ may stain rare/scattered cells in UPS

<u>vs AFX and PDS</u>

Atypical Fibroxanthoma (AFX) and Pleomorphic Dermal Sarcoma (PDS) are *similar histologically* (high-grade, undifferentiated mesenchymal tumors) and also show no significant differentiation by immunohistochemistry (with the same negative stains). However, these are usually found on <u>the sun exposed skin of the elderly</u> (and therefore have mutations with a "UV signature") and do *<u>not</u>* originate the deep soft tissue. These tumors also have a relatively good prognosis, with AFX being essentially benign if strictly defined and PDS having a low metastatic rate (~5%).

AFX: Strictly defined as a dermal mesenchymal neoplasm with no specific line of differentiation (negative for epithelial, melanocytic, vascular markers) with NO invasion into SubQ tissue, Necrosis, LVI, or PNI.

PDS: like AFX but with aggressive growth characteristics like SubQ invasion, necrosis, LVI, or PNI

Location-Based Differential Diagnoses

Distal Extremities

- Fibromatosis (plantar/palmar)
- Clear cell sarcoma
- Epithelioid sarcoma
- Atypical spindle cell/pleomorphic lipomatous tumor
- PHAT/HFT
- Desmoplastic Fibroelastoma

Fingers and Toes

- Rheumatoid nodule
- Ganglion cyst
- Glomus tumor
- Tenosynovial giant cell tumor
- Fibroma of tendon sheath
- Acral fibromyxoma
- Dermal nerve sheath myxoma
- Epithelioid hemangioma
- Inclusion body fibromatosis
- Myxoinflammatory fibroblastic sarcoma
- Soft tissue chondroma
- Atypical spindle cell/Pleomorphic lipomatous tumor
- Fibro-osseous pseudotumor of digits
- Calcifying aponeurotic fibroma

Genital/Groin

- Epithelioid sarcoma
- Angiomyofibroblastoma
- Cellular angiofibroma
- Deep (aggressive) angiomyxoma
- Genital rhabdomyoma
- Intranodal Palisaded Myofibroblastoma
- Mammary-type Myofibroblastoma
- Spindle cell rhabdomyosarcoma
- Superficial Myofibroblastoma
- Massive edema

Mesentery/Omentum/ Peritoneum

- Desmoid fibromatosis
- Desmoplastic small round cell tumor
- GIST
- Inflammatory myofibroblastic tumor
- Calcifying fibrous tumor
- Mesothelioma
- Sclerosing mesenteritis

Head and Neck

- Nodular fasciitis
- Desmoid fibromatosis
- Embryonal rhabdomyosarcoma
- Paraganglioma
- Alveolar soft part sarcoma
- Atypical fibroxanthoma
- Cellular neurothekeoma
- Ectopic meningioma
- Epithelioid hemangioma
- Rhabdomyoma
- Solitary circumscribed neuroma
- Spindle cell rhabdomyosarcoma
- Ectopic thymoma

Retroperitoneum

- Well-differentiated liposarcoma
- Dedifferentiated liposarcoma
- Desmoid fibromatosis
- Schwannoma
- Ganglioneuroma
- Extrarenal rhabdoid tumor
- Inflammatory myofibroblastic tumor
- Leiomyosarcoma
- PEComa

Trunk, Shoulders, Back

- Spindle cell/pleomorphic lipoma
- Desmoid fibromatosis
- DFSP
- Elastofibroma
- Lipoblastoma
- Proliferative myosititis

Based on: Diagnostic Pathology: Soft Tissue Tumors. Lindberg. Third edition. 2019.

Age-Based Differential Diagnoses

Infancy (< 3yrs)

- Fibrous hamartoma of infancy
- Infantile fibrosarcoma
- Inclusion body fibromatosis
- Lipoblastoma
- Lipoblastomatosis
- Myofibroma
- Fibromatosis coli

Infants, Children, Adolescents (<20rs)

- Nodular fasciitis
- Embryonal rhabdomyosarcoma
- Angiomatosis
- Calcifying aponeurotic fibroma
- Dabska tumor
- Extrarenal rhabdoid tumor
- Fibromatosis
- Gardner fibroma
- Giant cell fibroblastoma
- Kaposiform hemangioendothelioma

Adolescent to Young Adult (~10-35yrs)

- Alveolar rhabdomyosarcoma
- Synovial sarcoma
- Epithelioid sarcoma
- Fibromatosis
- Alveolar soft part sarcoma
- Angiomatoid fibrous histiocytoma
- Desmoplastic small round cell tumor
- Inflammatory myofibroblastic tumor
- Low-grade fibromyxoid sarcoma
- Myxoid liposarcoma
- Plexiform Fibrohistiocytic tumor

Young to Middle-Aged Adult (~20 to 50 yrs)

- Tenosynovial giant cell tumor
- Fibroma of tendon sheath
- Fibromatosis
- Leiomyosarcoma
- Clear cell sarcoma
- DFSP
- Epithelioid hemangioendothelioma
- Epithelioid sarcoma
- Hibernoma
- Low-grade myofibroblastic sarcoma
- Myositis ossificans
- Myxoinflammatory fibroblastic sarcoma
- Nodular fasciitis
- Pseudomyogenic hemangioendothelioma

Middle-aged to older adult (~40-60yrs)

- ALT/WD-liposarcoma
- Dedifferentiated liposarcoma
- Intramuscular myxoma
- Spindle cell/pleomorphic lipoma
- Desmoplastic fibroblastoma
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal osteosarcoma
- Hemosiderotic Fibrolipomatous tumor
- Mammary-type Myofibroblastoma
- Ossifying fibromyxoid tumor
- Proliferative fasciitis
- Sclerosing epithelioid fibrosarcoma

Old to elderly adult (>50rs)

- Undifferentiated pleomorphic sarcoma
- Well-diff & Dediff liposarcoma
- Atypical fibroxanthoma
- Elastofibroma
- Ischemic fasciitis
- Myxofibrosarcoma
- Pleomorphic liposarcoma
- Pleomorphic rhabdomyosarcoma

Based on: Diagnostic Pathology: Soft Tissue Tumors. Lindberg. Third edition. 2019.

Differential Diagnoses

CD34 IHC expression

Main utility: Rarely expressed in carcinomas

- Vascular tumors
- Peripheral nerve sheath tumors
- GIST
- SFT
- DFSP
- Spindle cell lipoma
- Epithelioid sarcoma
- Lymphoblastic leukemia
- Superficial CD34(+) fibroblastic tumor
- Atypical spindle cell lipomatous tumor
- Cellular angiofibroma
- Myxoma
- Deep benign fibrous histiocytoma
- Elastofibroma
- Fibrous hamartoma of infancy
- Hemosiderotic Fibrolipomatous tumor
- Giant cell fibroblastoma
- Mammary-type Myofibroblastoma
- Acral fibromyxoma

S100 IHC expression

- Nerve sheath tumors
- Melanoma/Melanocytes
- Adipocytes
- Chondrocytes
- Ossifying fibromyxoid tumor
- Myoepithelial cells
- Langerhans cells
- Rosai-Dorfman disease
- Some Breast cancers

Sarcomas that go to Lymph nodes

- Epithelioid sarcoma
- Clear cell sarcoma
- Rhabdomyosarcoma
- SDH-deficient GIST

Spindled tumors with Hyper and Hypo cellular areas

- Low-grade fibromyxoid sarcoma
- MPNST
- Schwannoma
- SFT
- Myofibroma
- Myopericytoma
- Botryoid-type rhabdomyosarcoma

Herringbone pattern

- Fibrosarcoma (Adult & Infant)
- DFSP (with fibrosarcomatous transformation)
- MPNST
- Spindle cell rhabdomyosarcoma
- Synovial sarcoma

Storiform/Whorled pattern

- DFSP
- Nodular fasciitis
- Perineurioma
- Hybrid nerve sheath tumors
- Follicular dendritic cell sarcoma
- Low-grade fibromyxoid sarcoma
- Low-grade myofibroblastic sarcoma
- Inclusion body fibromatosis
- Fibrous histiocytoma

Nuclear Palisading

- Schwannoma
- MPNST
- Synovial sarcoma
- Leiomyosarcoma
- Leiomyoma
- Fibrous histiocytoma

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Associated with atrophic skeletal muscle
- Desmoid fibromatosis

- Intramuscular hemangioma
- Intramuscular lipoma
- (any infiltrative tumor)

Skeletal muscle checkerboard
- Intramuscular hemangioma
- Intramuscular lipoma

- Intramuscular myxoma
- Low-grade myofibroblastic sarcoma
- Proliferative myositis

Clear cells
- Clear cell sarcoma
- PEComa

- Sclerosing epithelioid fibrosarcoma
- Myoepithelial tumors
- Ewing sarcoma
- Alveolar soft part sarcoma

Granular cells
- Granular cell tumor
- PEComa
- Hibernoma

- Extranodal Rosai-Dorfman disease
- Chondroid lipoma
- Rhabdomyoma
- Alveolar soft part sarcoma
- Congenital granular cell epulis

Rhabdoid cells
- Rhabdomyosarcoma
- MPNST (triton tumor)
- (Extrarenal) Rhabdoid tumor
- Epithelioid sarcoma, proximal-type

- Pseudomyogenic hemangioendothelioma
- Desmoplastic small round cell tumor
- Extraskeletal myxoid chondrosarcoma
- Myoepithelial carcinoma
- Dedifferentiated liposarcoma

Staghorn vessels
- SFT
- Synovial sarcoma
- Infantile fibrosarcoma

- Glomus tumor
- Myopericytoma/Myofibroma
- Leiomyosarcoma
- Deep benign fibrous histiocytoma

Prominent Eosinophils
- Epithelioid hemangioendothelioma
- Langerhans's cell histiocytosis
- Hodgkin lymphoma

- Inflammatory Myofibroblastic tumor
- Inflammatory fibroid polyp
- Myxoinflammatory fibroblastic sarcoma
- Solitary (Juvenile) xanthogranuloma

Prominent foamy histiocytes
- Schwannoma
- Tenosynovial giant cell tumor

- Dermatofibroma
- Juvenile xanthogranuloma
- Rosai-Dorfman disease

Prominent mixed inflammation
- Leiomyosarcoma (inflammatory variant)
- Dedifferentiated liposarcoma
- Myxoinflammatory fibroblastic sarcoma

- Well-differentiated liposarcoma (inflammatory variant)
- Superficial CD34(+) fibroblastic tumor
- Pseudomyogenic hemangioendothelioma
- Inflammatory fibroid polyp

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