

Soft Tissue Tumors

Adipocytic

Lipoma

Benign adipocytic tumor

Most are mature “white fat” with a single large lipid droplet.

Common. Usually superficial/subcutaneous.

May recur.

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

Molecular: Various chromosomal aberrations

Specific types:

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

Spindle Cell Lipoma—Fat + bland spindle cells with 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.

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

Chondroid Lipoma—Fat + round cells in a myxochondroid background.

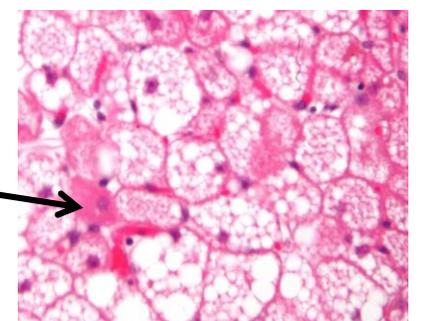
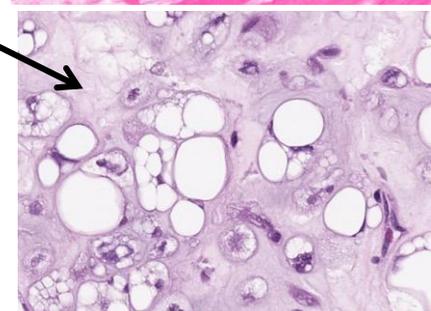
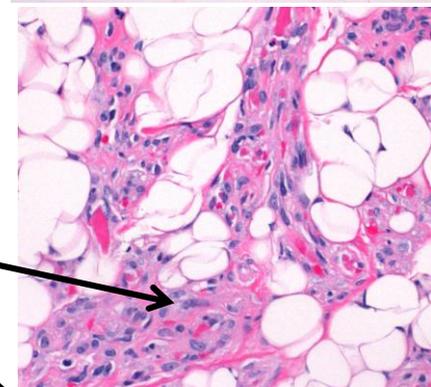
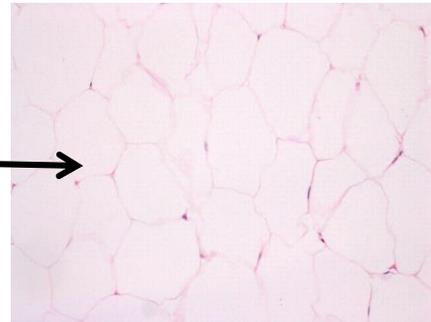
Neural fibrolipoma—Fat+ fibrous tissue growing in nerves. Usu. in arms.

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

Lipoblastoma—Occurs in infants and resembles fetal adipose tissue. Lobules of immature fat cells separated by connective tissue septa with a loose myxoid appearance.

Myolipoma—Fat + smooth muscle bundles

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



Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma

Most common adult sarcoma. Usually elderly.
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, use WDL term, harder to excise, basically incurable.

Variable amount of lipoblasts (cytoplasmic lipid-rich droplets with a hyperchromatic, indented/scalloped nucleus).

Can be lipoma-like (resembling mature fat), sclerotic (fibrous areas, often with scattered hyperchromatic atypical cells), 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, MDM2 FISH for gene amplification. P16 is a sensitive (but not specific) marker as it is downstream from CDK4, so it is overexpressed.

Can De-differentiate (see below).

Fatty Tumors to FISH for MDM2

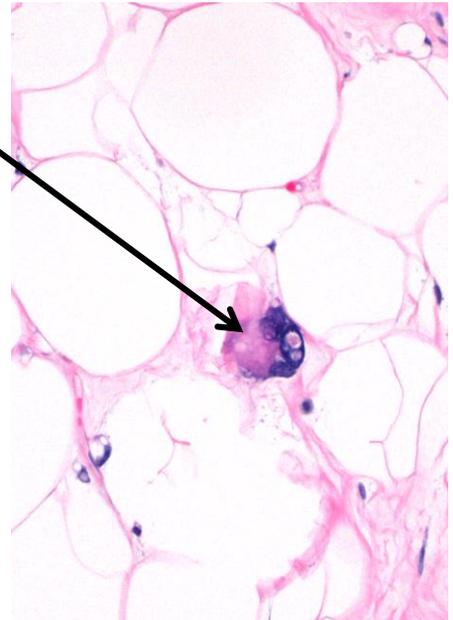
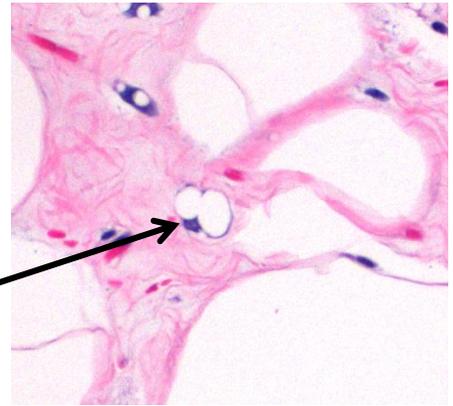
Lipomatous tumors with equivocal cytologic atypia

Recurrent lipomas

Deep lipomas 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*)

(No need to FISH classic cases with lipoblasts and/or atypia)



Dedifferentiated Liposarcoma

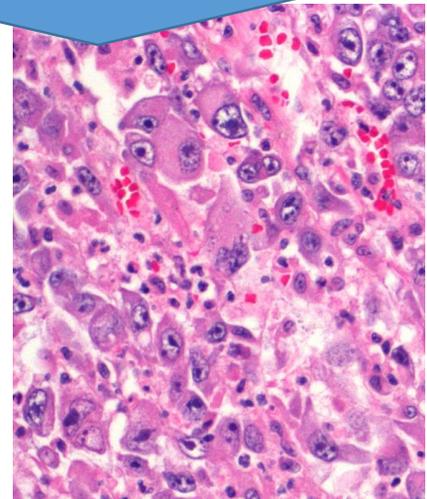
Contain an ALT/WDL component, with an abrupt transition to another component, which is usually an undifferentiated pleomorphic sarcoma (sometimes fibrosarcoma, or lower grade sarcoma).

Some say de-differentiated area should have a mitotic count of at least 5 mitotic figures per 10 high-power fields.

Molecular: Same 12q amplifications as in ALT/WDL (but with more superimposed), so can use same FISH.

Has Metastatic potential in addition to being more locally aggressive.

Can
Dedifferentiate



Myxoid Liposarcoma

Usu. younger and on the lower extremity

Resemble developing fat:

Multinodular proliferation of round cells

Abundant myxoid matrix,

Chicken-wire vasculature,

multivacuolar and univacuolar lipoblasts

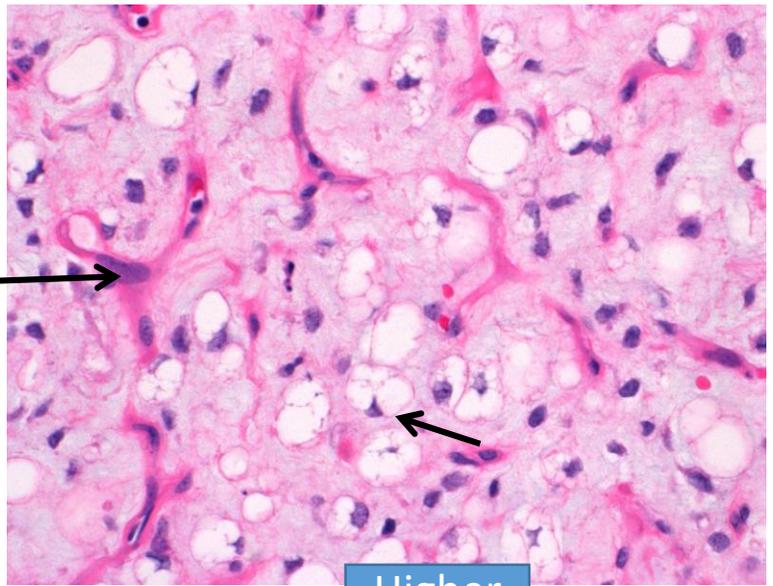
As get higher grade → lose myxoid component → composed of primarily round cells → "Round cell liposarcoma"

Molecular: FUS-DDIT3 fusions

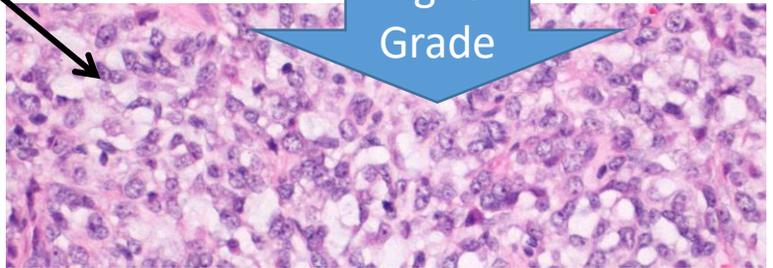
(do FUS break apart FISH)

Outcome: Higher round cell component → worse outcome.

Can metastasize.



Higher
Grade



Pleomorphic Liposarcoma

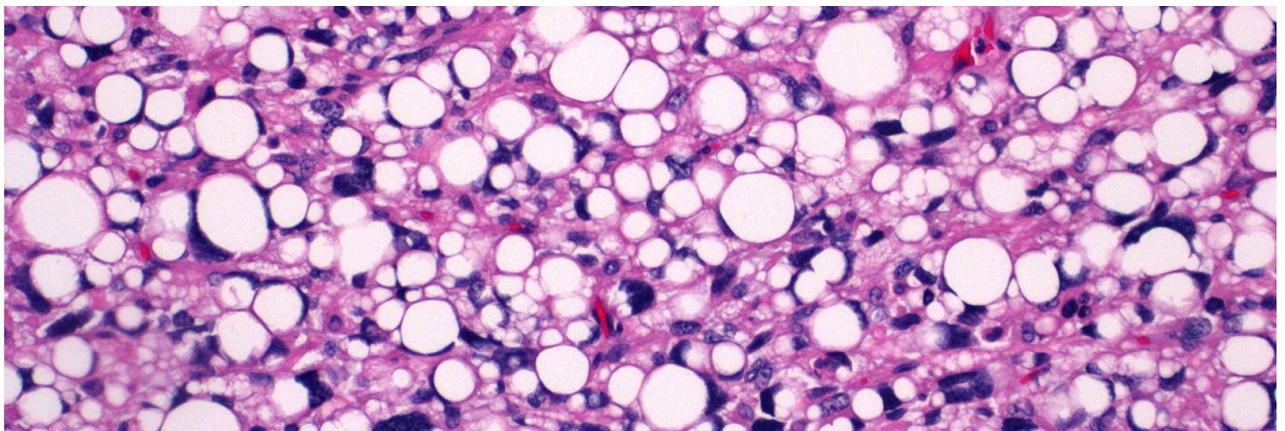
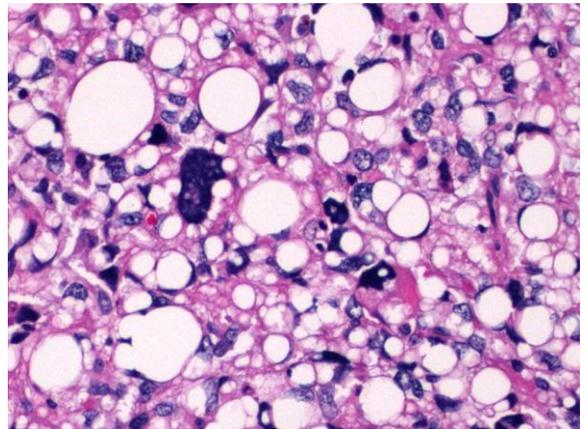
Least common liposarcoma.

Essentially, an undifferentiated pleomorphic sarcoma, but with scattered lipoblasts.

Extreme pleomorphism including bizarre giant cells.

Malignant with frequent metastases.

Molecular: Complex structural chromosomal rearrangements.



Fibroblastic/Myofibroblastic

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.

“Torn stroma” resembling “S” and “C” shapes.

Extravasated RBCs.

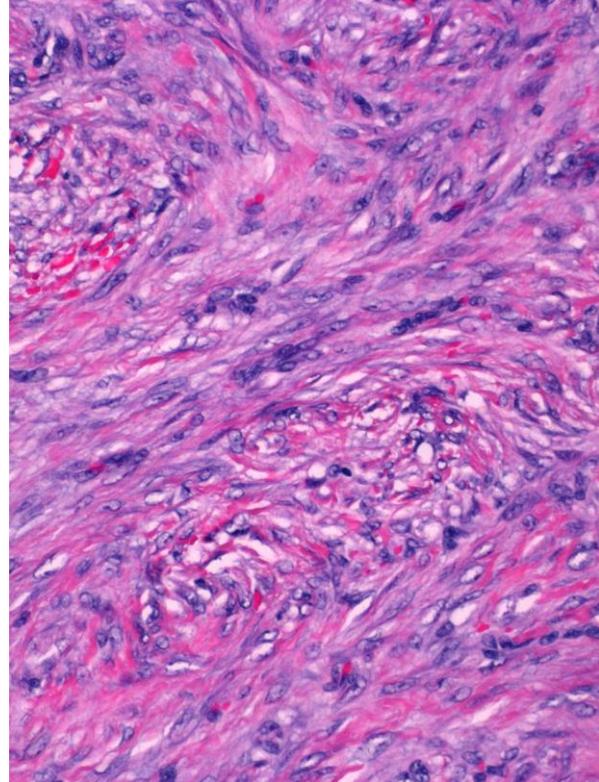
Pale nuclei with prominent nucleoli.

Older lesions may be scarred/collagenous.

Molecular: MYH9-USP6 gene fusions (do USP6 break apart FISH).

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

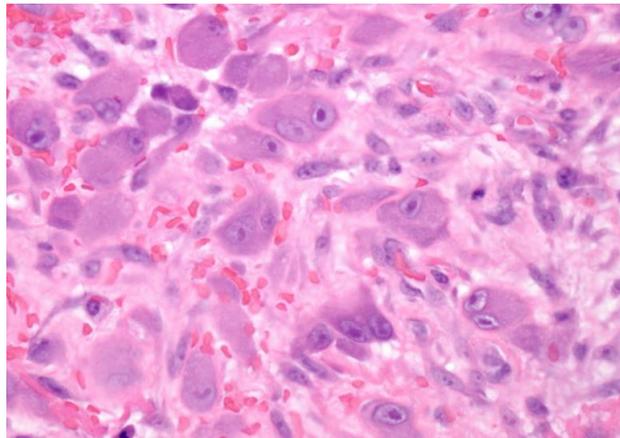
Benign. Subcutaneous soft tissue of adults usu. on arm.

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...)

If in muscle, use “Proliferative myositis.”



Ischemic Fasciitis

“Pseudosarcomatous” (Benign/reactive) proliferation overlying bony prominences of elderly and/or immobile patients.

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

Zonal growth with central necrosis surrounded by proliferating blood vessels and fibroblasts/myofibroblasts.

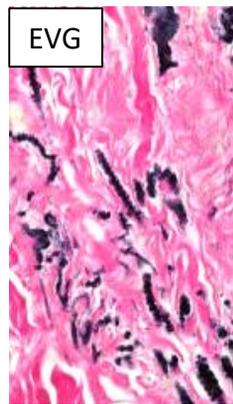
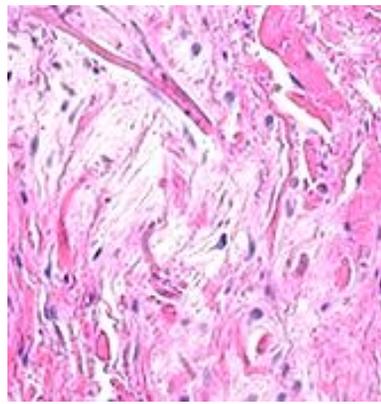
Can see scattered hyperchromatic atypical cells and mitoses, but no atypical mitoses.

Elastofibroma

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

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**.

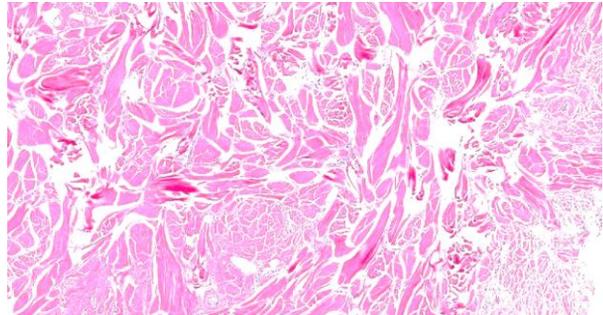


Nuchal-type Fibroma

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

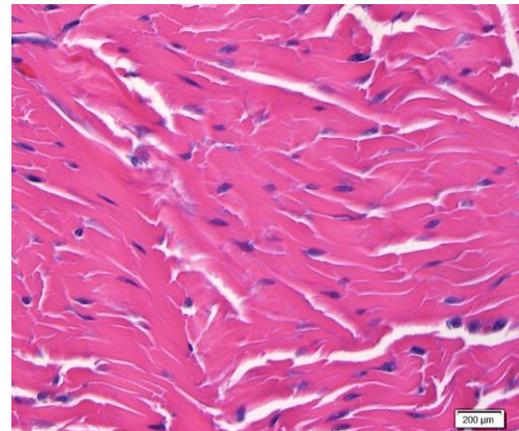
Benign. Usually back of younger patient.
Strong association with FAP and desmoid tumors (Gardner syndrome).

Histologic overlap with nuchal-type fibroma.

Densely collagenized with sparse spindled cells with interspersed lobules of fat.

Can entrap other structures at periphery.

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



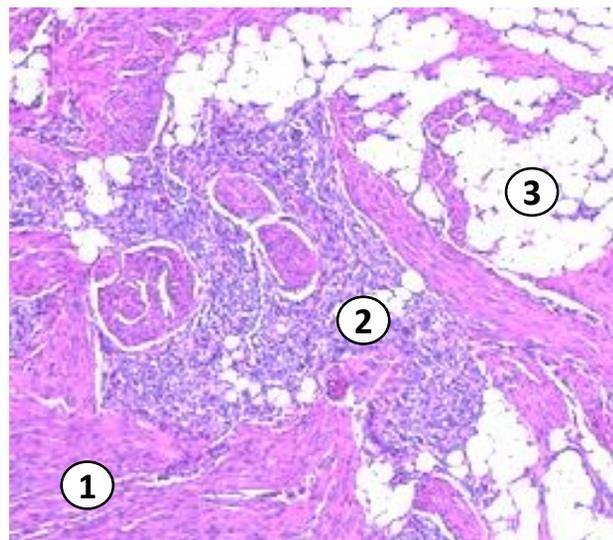
Fibrous Hamartoma of Infancy

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



Fibroma of Tendon Sheath

Benign. Slowly growing mass on tendon sheath or aponeuroses.

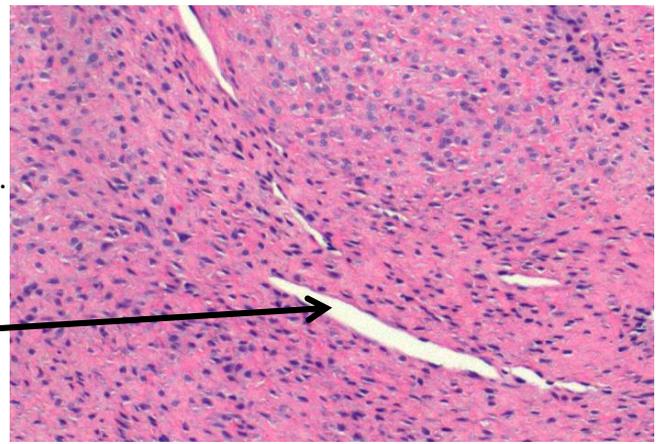
Usu. adults, under 2 cm, and on extremities, often hand.

Well-circumscribed, lobulated.

Mostly hypocellular with spindled cells in densely collagenized stroma.

Characteristic cleft-like areas spaces, possibly vascular.

IHC: variable actin and CD68



Calcifying Aponeurotic Fibroma

Benign. Primarily in Children. Can recur.

Slow-growing, painless mass on hands or feet attached to aponeurosis, tendons, or fascia

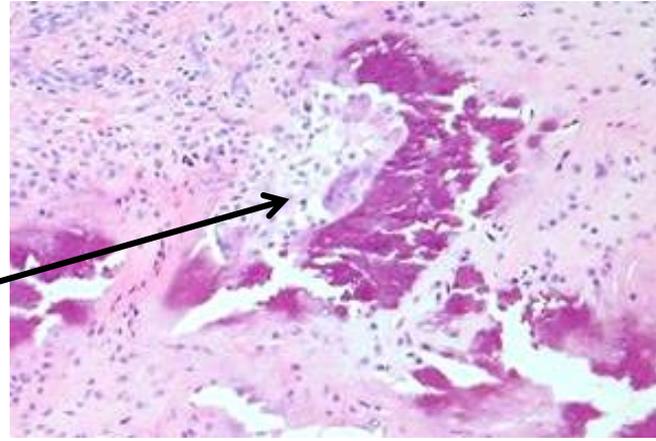
Variable cellularity throughout lesion.

Plump, bland fibroblasts with dense collagen.

Distinct areas of calcification and cartilage formation.

Infiltrative growth.

Molecular: FN1-EGF fusions



Fibromatosis

Benign (never metastasize), but infiltrative with strong tendency to recur.

2 Major Divisions:

Superficial: E.g., Palmar, plantar, penile. Small. Slowly-growing. Usu. older.

Deep (“Desmoid-type”): E.g., Abdominal, mesenteric. More aggressive. High-recurrence rate (>50%). Involve deep structures.

Usu. younger. Interestingly, microscopic margins do NOT predict recurrence.

Infiltrative growth into surrounding structures (esp. skeletal muscle).

Broad, sweeping fascicles.

Uniform spindled cells with small, pale nuclei with pinpoint nucleoli. Moderate amounts of collagen, surrounding cells, in slightly myxoid background.

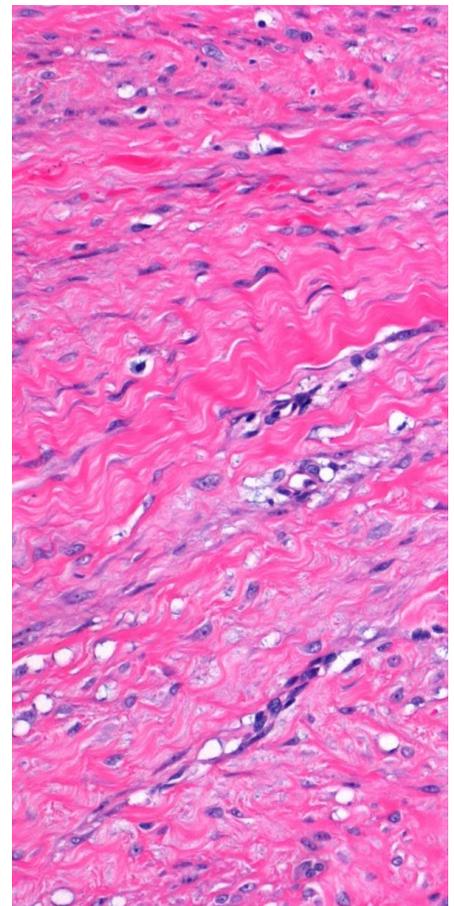
With age, less cellular and more collagen.

Microhemorrhages and scattered chronic inflammation.

IHC: Nuclear β -catenin (more cells with deep than superficial).

Some actin (+)

Molecular: Deep fibromatosis is associated with FAP and mutations in the APC/ β -catenin (CTNNB1) pathway



Inflammatory Myofibroblastic Tumor

Borderline malignancy (tend to recur, rarely metastasize).

Most common sites: Lung, mesentery, omentum.

Any age, but more common in children.

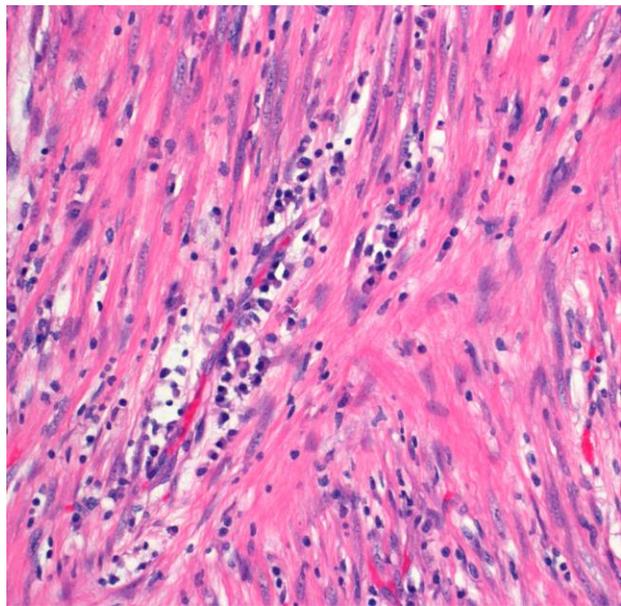
Bland spindled to stellate cells in myxoid to hyalinize stroma. Can have loose, fascicular, or storiform growth.

Prominent lymphoplasmacytic infiltrate.

Most cells bland, but sometimes large cells with prominent nucleoli.

IHC: Variable staining with actin/desmin. ALK (+) in ~50%

Molecular: ~50% have ALK gene rearrangements.



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)*

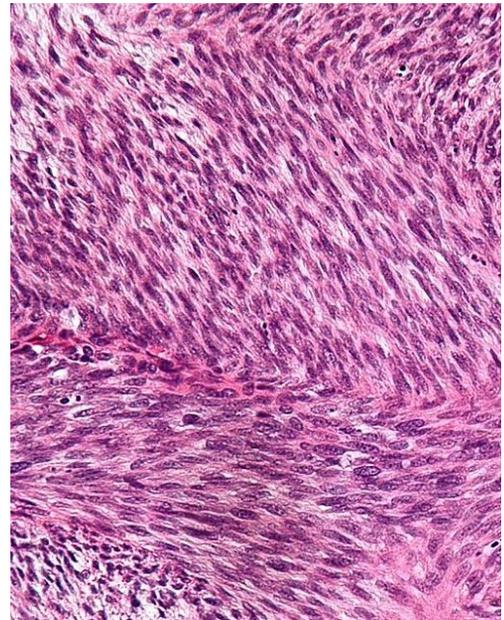
Now a diagnosis of exclusion! Must do work up to exclude other diagnoses (IHC and FISH).

Uniform spindled cells with fascicular to herringbone growth. Interwoven collagen fibers.



No specific IHC of molecular.

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

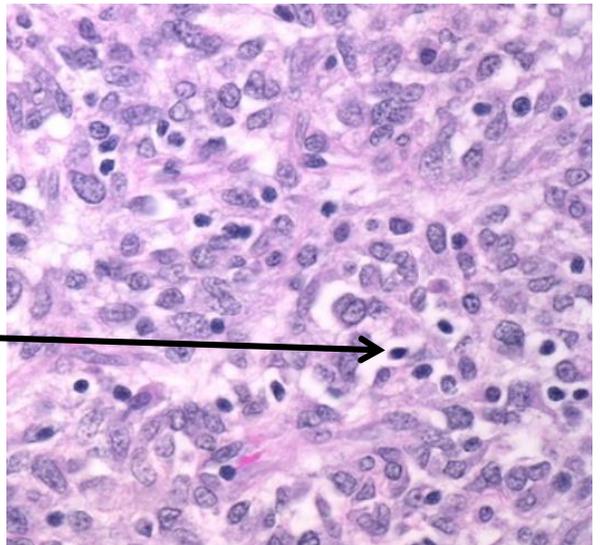


Infantile Fibrosarcoma

Malignant. Newborns (congenital) or infants. Usu. extremities.

Sheets of tightly packed spindle cells with herringbone appearance. Little pleomorphism. Mitoses present. Often lymphocytic infiltrate.

Molecular: ETV6-NTRK3 fusions (also seen in cellular mesoblastic nephroma)



Myxofibrosarcoma

Old name: Myxoid Malignant Fibrous Histiocytoma (MFH)

Malignant. Slow-growing mass on extremity of elderly.

Multinodular growth.

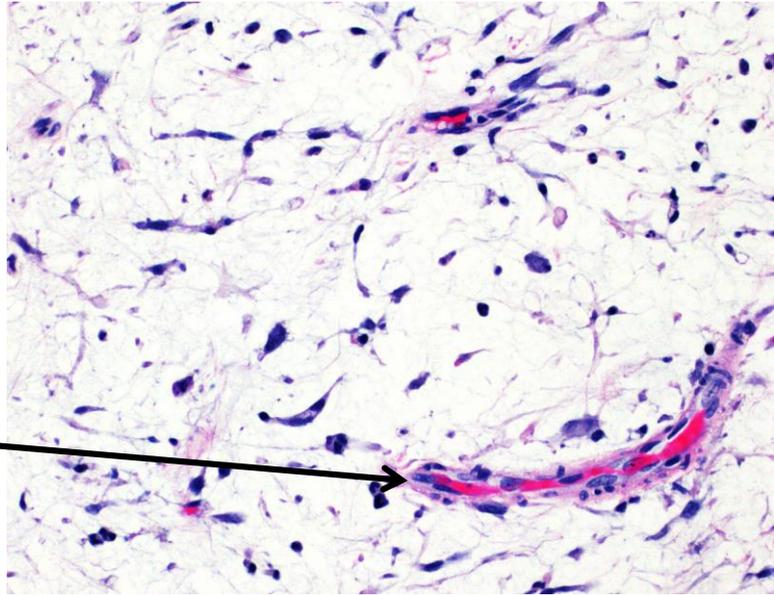
Myxoid background with varying cellularity (usually low).

Stellate to spindled cells with hyperchromatic, pleomorphic nuclei with indistinct pink cytoplasm.

Characteristic curvilinear vessels that the tumor cells attach to like “melting wax.”

IHC: focal actin

Molecular: Complex karyotype



Low-grade Fibromyxoid Sarcoma

Old/alternative 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.

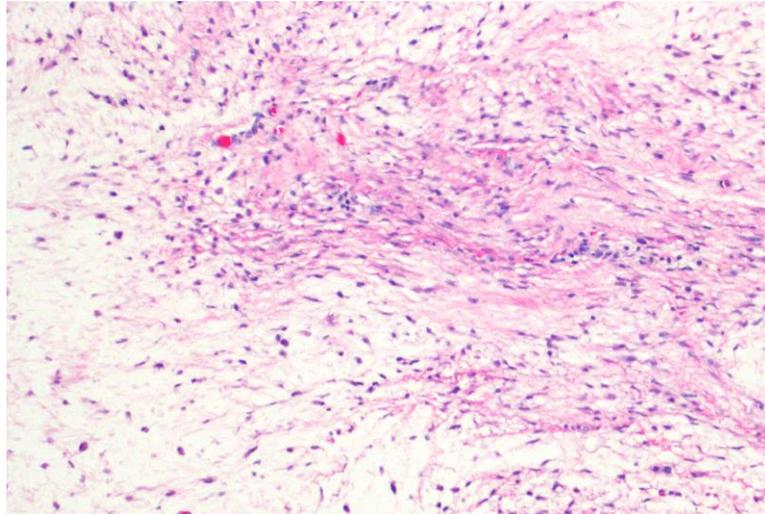
Bland spindled cells with small hyperchromatic nuclei.

Myxoid areas have curvilinear, branching capillaries.

Can have large collagenous rosettes.

IHC: (+) MUC4, often EMA

Molecular: FUS-CREB3L2 fusions (do FUS FISH)



Sclerosing Epithelioid Fibrosarcoma

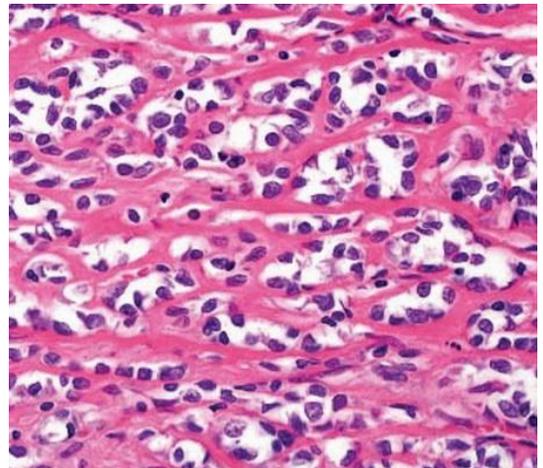
Malignant. Deep soft tissue of limbs.

Densely hyalinized stroma with epithelioid cells arranged in cords and nests.

Cells have scant clear cytoplasm and angulated nuclei.

IHC: (+) MUC4, often EMA

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



Nerve Sheath Tumors

Schwannoma

Benign. Often associated with nerve. Usu. adults. Composed entirely of well-differentiated Schwann cells. Very low risk of transformation.

Usually solitary and sporadic. NF2 associated with bilateral vestibular schwannomas.

Typically encapsulated.

Alternating compact spindle cells (Antoni A) and hypocellular less orderly areas (Antoni B)

Rows of nuclear palisading → Verocay bodies.

Axons not present in lesion → pushed to periphery.

Hyalinized blood vessels and lymphoid aggregates common.

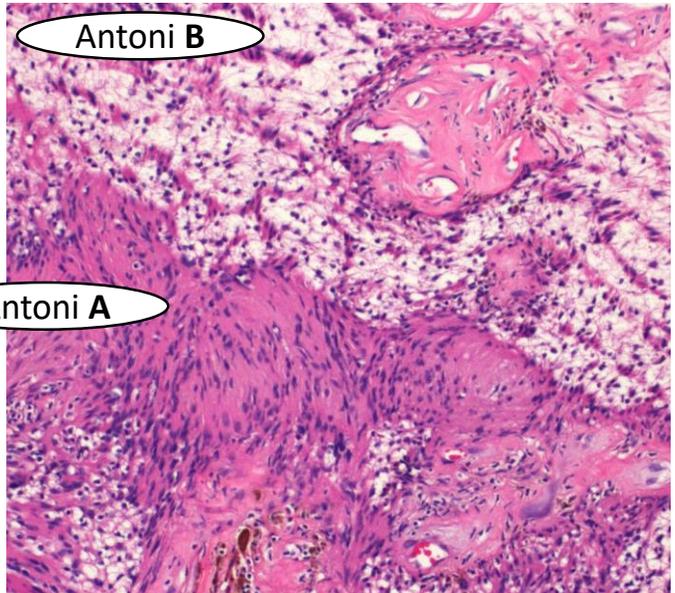
IHC: Strong, diffuse S100, scattered CD34, moderate calretinin. Neurofilament highlights displaced axons at periphery.

Subtypes:

“Ancient change” - Degenerative atypia with large, hyperchromatic nuclei, but no mitoses

Cellular – Exclusively Antoni A areas.

Melanotic – contain melanosomes, so stain with melanocytic markers. Often epithelioid. Higher risk of transformation.



Neurofibroma

Benign. Most commonly solitary and sporadic.

Multiple NF is a hallmark of neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease.

Higher, but still low, risk of transformation.

Can be cutaneous (most common), intraneural, or diffuse.

Plexiform NF → almost exclusively in NF1; higher risk of MPNST.

Mixture of Schwann cells, perineurial-like cells, fibroblastic cells, and entrapped axons.

Randomly oriented spindled cells with wavy, hyperchromatic nuclei.

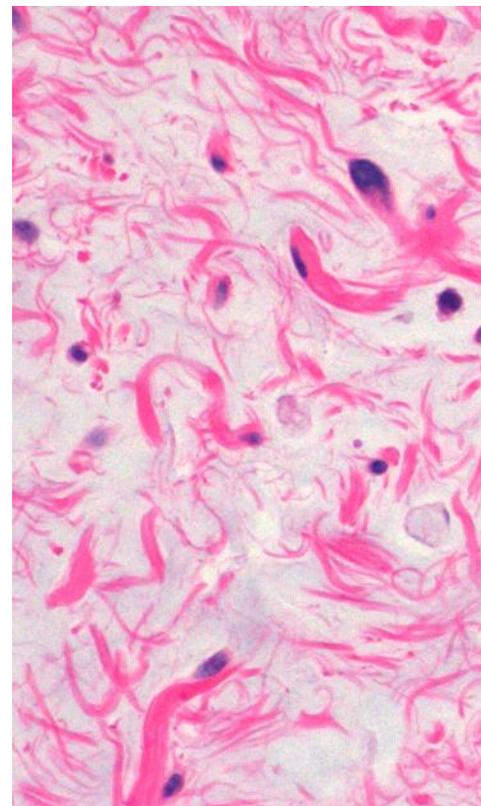
Often hypocellular and variably myxoid

Thin and thick collagen strands (“shredded carrot collagen”)

Entrapped axons are overrun by lesion and scattered throughout.

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

Types: Can be pigmented or show ancient change.



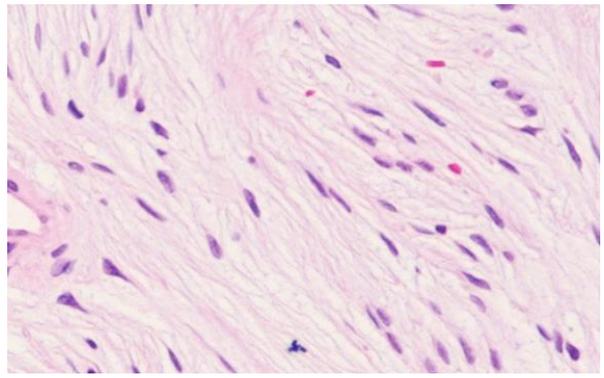
Perineurioma

Benign. Can be intraneural or soft tissue. Sporadic.

Spindle cell proliferation with characteristic long, thin, delicate, bipolar processes.

Wavy/tapering nuclei. Perivascular whorls.

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



Granular Cell Tumor

Benign neoplasm with neuroectodermal differentiation.

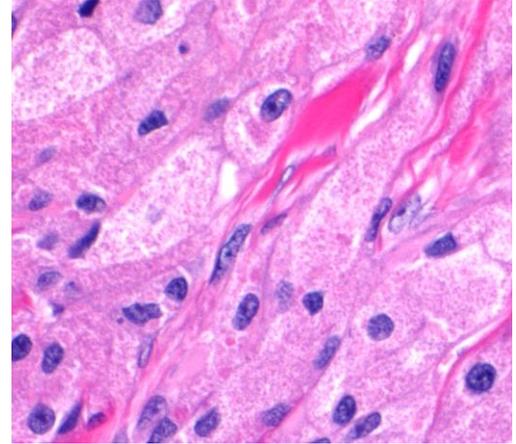
Epithelioid to spindled cells with abundant eosinophilic granular cytoplasm highlighted by PASd

Full of lysosomes due to inactivating mutations in ATP6AP1 or 2 (makes it so can't break down lysosomes) → granular appearance

Stains: (+) S100, CD68, Inhibin, Calretinin

Congenital (Gingival) Granular Cell Tumor (Congenital Epulis):

Although looks similar, S-100 (-), located on gingiva at birth.



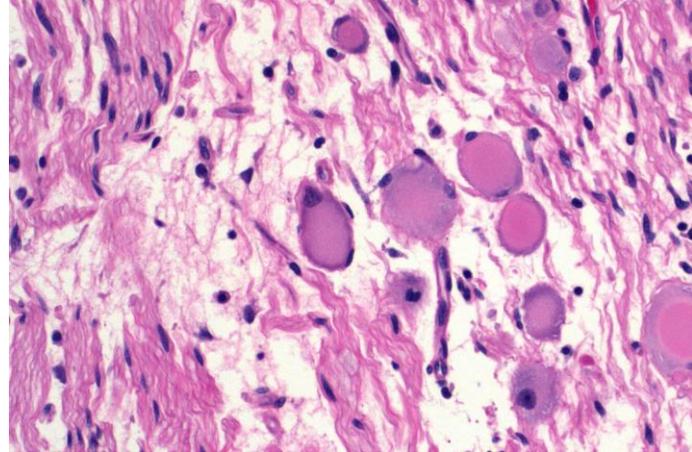
Ganglioneuroma

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

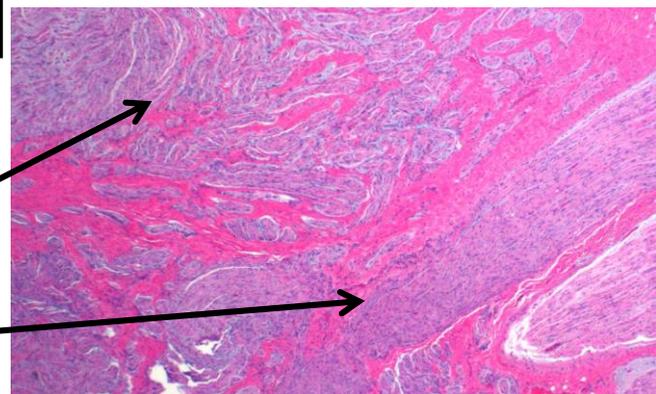


Traumatic (Amputation) Neuroma

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.



Malignant Peripheral Nerve Sheath Tumor (MPNST)

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

Must arise from a peripheral nerve or pre-existing peripheral nerve sheath tumor or display histologic/IHC evidence of nerve sheath differentiation.

Variable appearance, can resemble undifferentiated pleomorphic sarcoma or fibrosarcoma.

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. Geographic necrosis and/or mitotic activity (often greater than 10/10 HPFs)

IHC: **Patchy S100 and SOX10**.

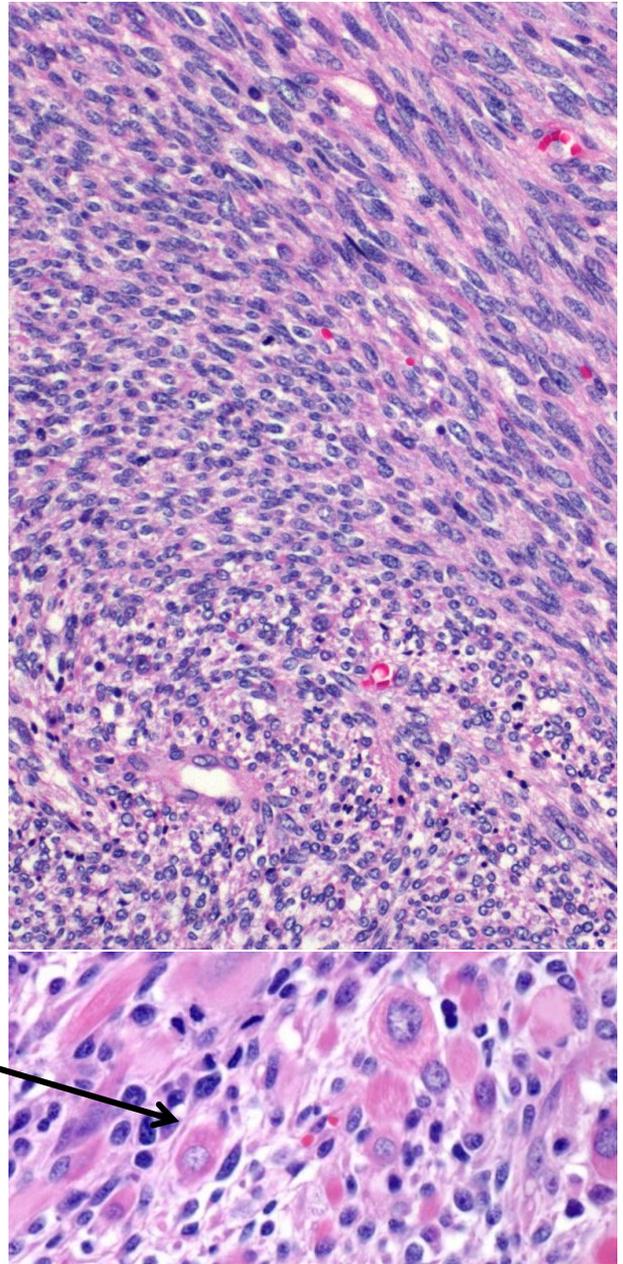
Loss of H3K27me3 expression (associated with worse prognosis. Not entirely specific—see with SUZ12 and EED gene inactivation)

Subtypes:

MPNST with rhabdomyoblastic differentiation (“Malignant triton tumor”)

MPNST with glandular differentiation

Epithelioid MPNST—composed of polygonal, epithelioid cells. Unique strong, diffuse S100 staining



Other Nerve Sheath Tumors

Nerve Sheath Myxoma: Benign. Superficial, myxoid. Irregular, slow-growing nodules separated by fibrous bands containing spindled cells in myxoid matrix. S100 (+)

Ectopic Meningioma: Benign. Essentially a meningioma in soft tissue. Whorled architecture. Oval nuclei. Occasional nuclear pseudoinclusions. IHC: EMA, PR, and SSTR2A (+)

Palisaded encapsulated neuroma (Solitary circumscribed neuroma): Benign. Dermal tumor, often on head/neck. Lobular with sharply demarcated borders. Composed of axons, Schwann cells, and perineural fibroblasts.

Perivascular Tumors

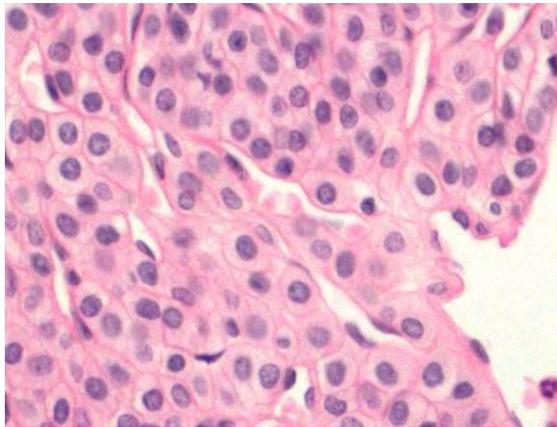
Glomus

Benign. Tumor derived from glomus body (specialized AV anastomosis that regulates heat).

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

Very richly vascular network separating tumor cell nests. Distinctive cells with round nuclei and eosinophilic cytoplasm.

IHC: Actin (+) other smooth muscle markers variable.



Myopericytoma/Myofibroma

Benign. Exist on a spectrum.

Myofibroma: Usu. Head/neck in first year of life.

Multinodular, well-circumscribed.

Biphasic: 1) immature-appearing plump spindled cells with staghorn vessels, 2) areas of more mature spindled cells in bundles and whorls.

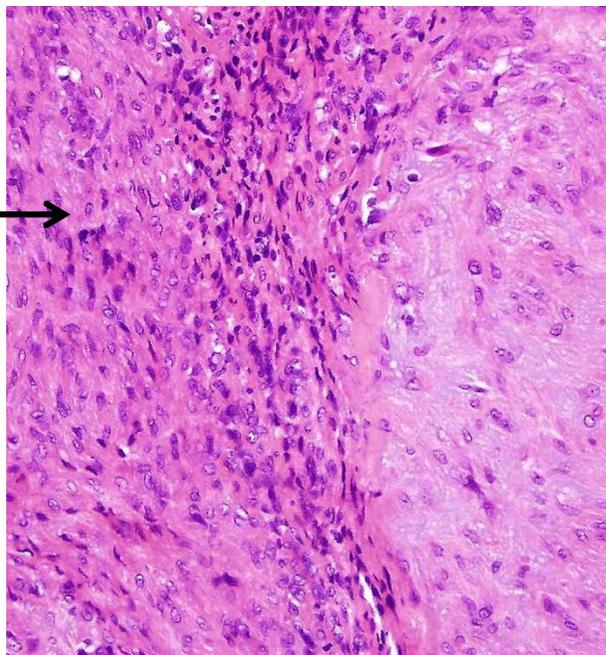
Myopericytoma: Superficial mass in adults.

Nodular, well-circumscribed.

Concentric, multilayered growth of spindled cells around vessels.

Very richly vascular

IHC: Actin (+) other smooth muscle markers variable.



Perivascular Epithelioid Cell Tumor (PEComa)

Benign.

Often areas of epithelioid tumor cells with abundant granular eosinophilic to clear cytoplasm with round nuclei.

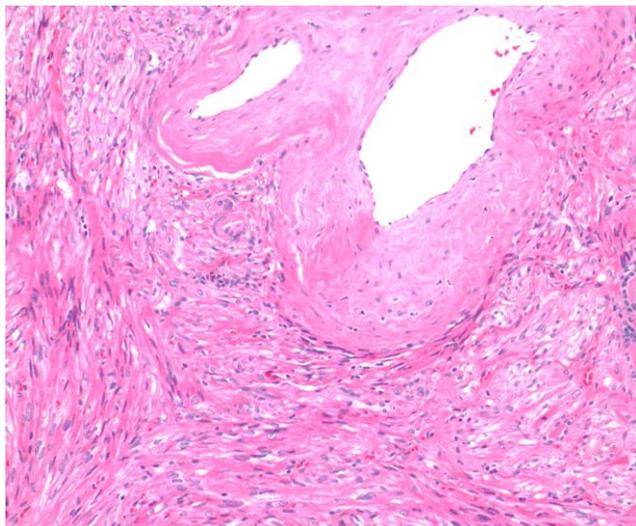
Associated with vessel walls in radial arrangement.

IHC: Express melanocytic (usu. HMB45, variable MelanA), and smooth muscle (Actins, desmin, etc..) markers.

A subset of cases are associated with Tuberous Sclerosis.

Can see in many sites/organs.

Includes Angiomyolipoma, Clear cell "sugar" tumor, and lymphangiomyomatosis.

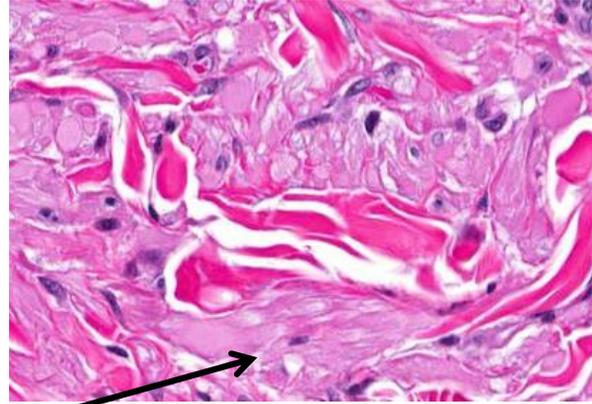


Smooth Muscle

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

Leiomyoma

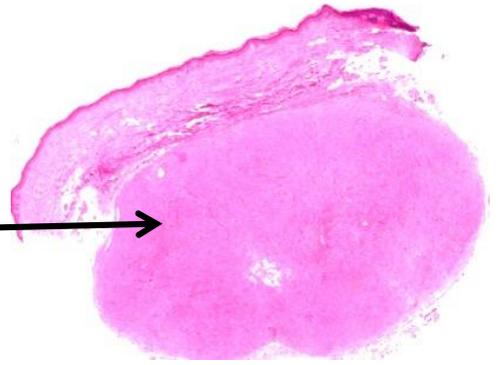
Benign.
Can see commonly in dermis (derived from pilar muscles and vessels).
Very uncommon in deep soft tissue.



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

Pilar Leiomyoma

Ill-defined, dermal nodule composed of haphazardly arranged smooth muscle bundles/fascicles
Fascicles often dissect between dermal collagen
Often painful.

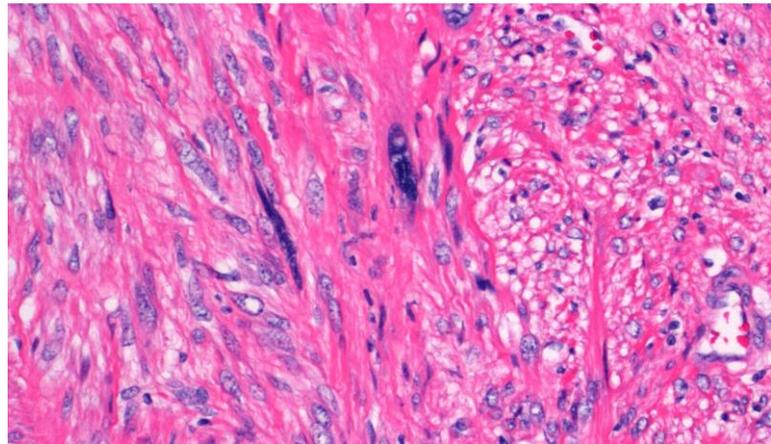


Angioleiomyoma

Well-circumscribed neoplasm composed of mature smooth muscle cells arranged around prominent blood vessels

Leiomyosarcoma

Malignant. Poor prognosis.
Often in retroperitoneum of adults.
Often arise from veins.
Similar appearance to leiomyoma (fascicular architecture)
But often notable pleomorphism.
Mitotic activity, often atypical mitoses.
Necrosis.

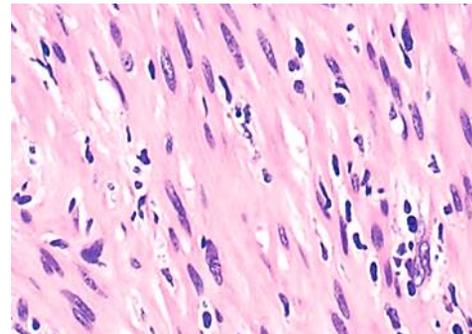


Molecular: Complex karyotype

EBV-associated Smooth Muscle Tumor

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 smooth muscle markers (e.g., Desmin, Actin)

Rhabdomyoma

Benign. But location/growth may cause problems (especially in heart)

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. Some spider cells

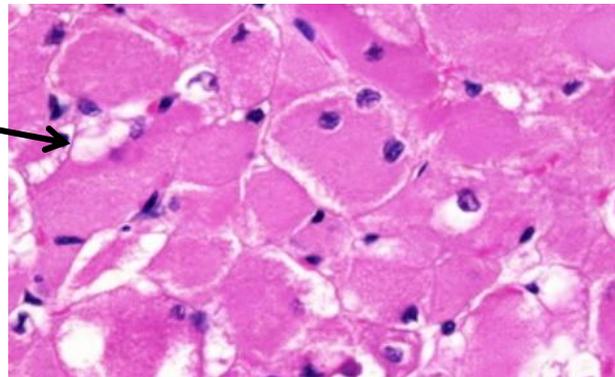
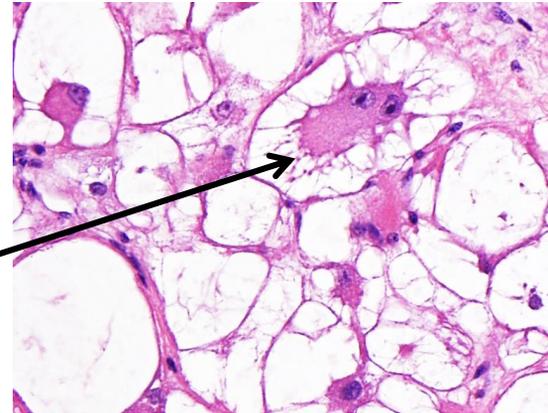
Unencapsulated, lobular growth.

Fetal-type Rhabdomyoma:

Usu. Head and neck. Any age.

Irregular bundles of immature skeletal muscle.

Myxoid background.



Embryonal Rhabdomyosarcoma

Malignant.

Most common soft tissue sarcoma in kids.

Occasional adult.

Usu. Head/Neck (e.g., nasal, tongue, etc..) or Genitourinary (e.g., bladder, prostate, etc...)

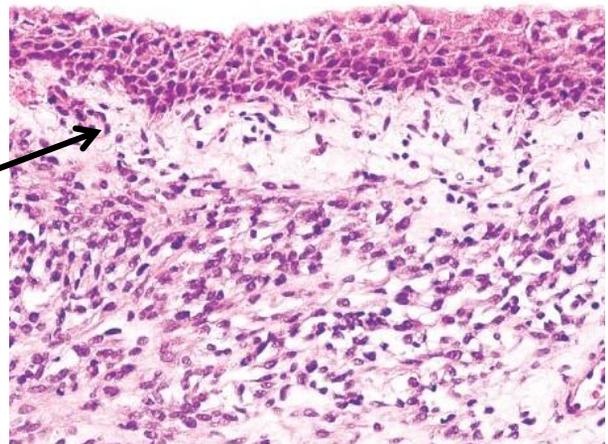
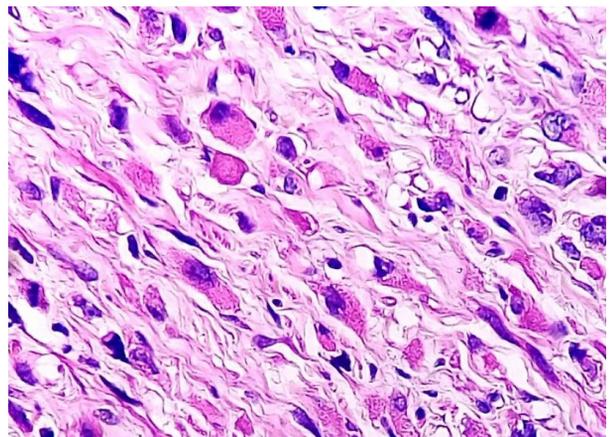
Resembles embryonic skeletal muscle cells.

Some areas are hypercellular "small round blue cells."

Other areas maturing with rhabdoid cells with abundant, eccentric eosinophilic cytoplasm, "tadpole cells," and "strap cells" (with cross striations)

Set in myxoid stroma

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)



Alveolar Rhabdomyosarcoma

Malignant. More aggressive than Embryonal Rhabdo.

Often adolescents and young adults in deep soft tissue of extremities and sinuses.

Highly cellular “small round blue cell” tumor.

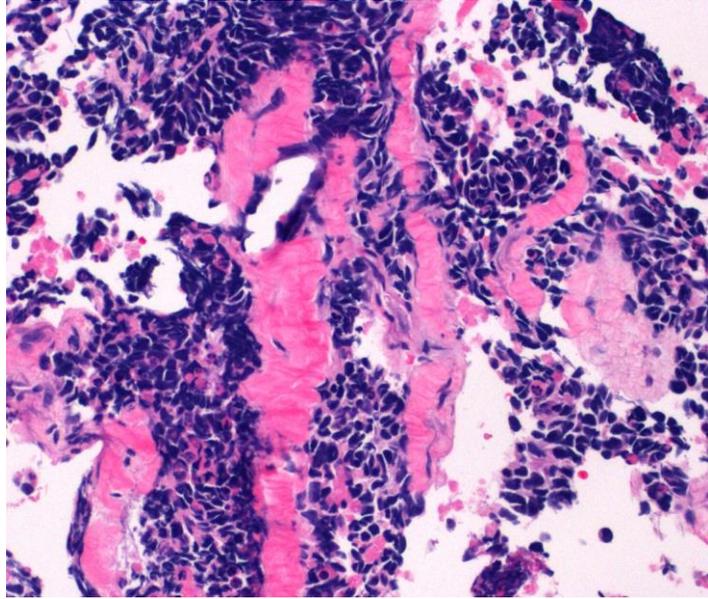
Monomorphous round nuclei.

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.



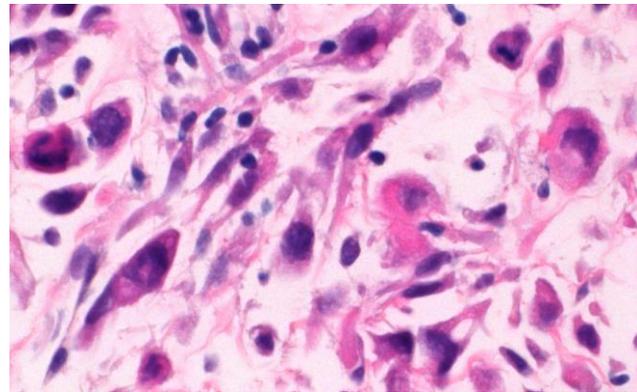
Pleomorphic Rhabdomyosarcoma

Malignant. Adults. Deep soft tissue.

High-grade cytologically: sheets of large, atypical cells.

Eosinophilic polygonal cells to tadpole-like.

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



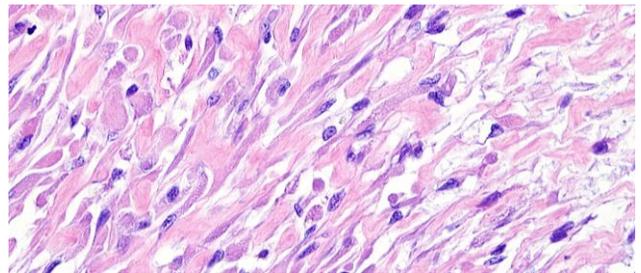
Spindle Cell Rhabdomyosarcoma

Malignant. Likely a variant of embryonal.

Usu. Young boys, esp. paratesticular.

Exclusively spindled cells with cigar-shaped nuclei.

Better prognosis than other Rhabdomyosarcomas.



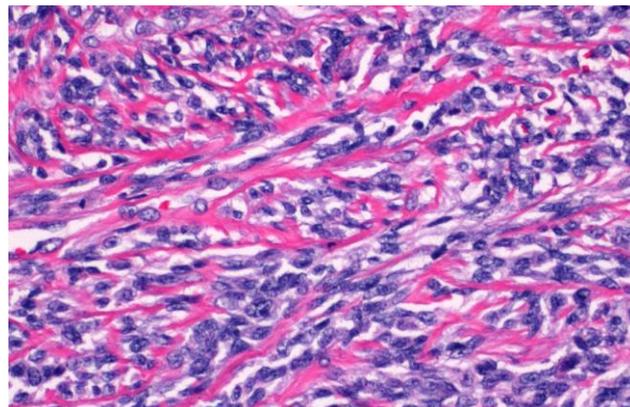
Sclerosing Rhabdomyosarcoma

Malignant. Usually adults in soft tissue.

Nests of small round blue cells in nests and single file.

Abundantly hyalinized, eosinophilic to basophilic matrix.

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



Fibrohistiocytic Tumors

Tenosynovial Giant Cell Tumor

Benign, but can be locally destructive.

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.

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

Localized-type:

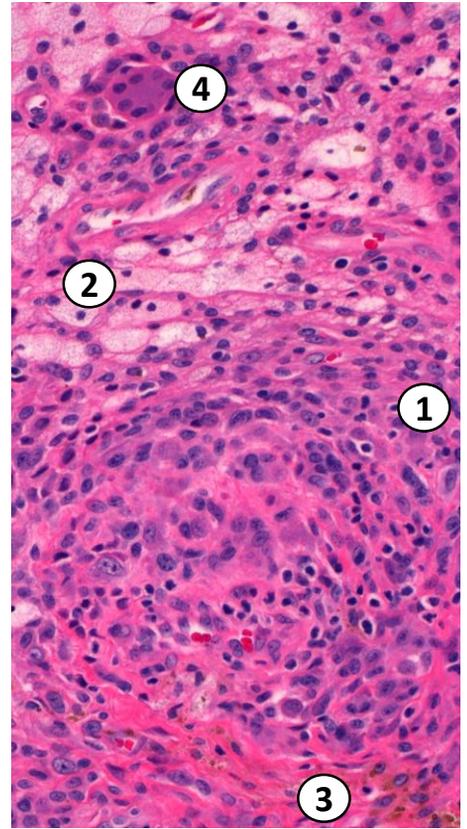
Discrete, rounded proliferation. Usually occurs in digits. Less aggressive. Often cure with excision.

Diffuse-type:

Grows in expansive sheets. Often in or around knee. Often intraarticular. Large. Destructive.

Aka "Pigmented Villonodular Synovitis" (PVNS)

Need to treat more aggressively.



Fibrous Histiocytoma

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

Fibroblastic and histiocytic cells arranged in short fascicles.

Dermatofibroma

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

Overlying epithelial basilar induction with hyperpigmentation (may mimic BCC)

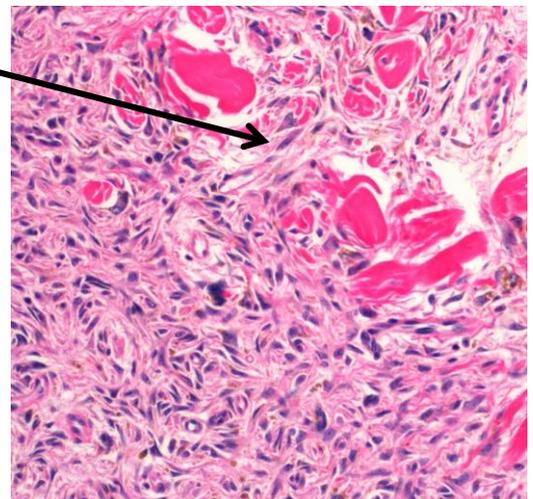
Lots of variants: Epithelioid, Cellular, Aneurysmal, etc...

IHC: FXIIIa(+), CD163(+), CD68(+), CD34(-)

"Deep Benign Fibrous Histiocytoma:" If in deep soft tissue.

Very rare.

Plexiform Fibrohistiocytic tumor: Plexiform architecture in deep soft tissue/dermis



Vascular Tumors

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

Vascular Malformations

Developmental abnormalities (occur during embryogenesis in utero), that grow *with* the host. Static. Do not regress.

Arteriovenous Malformation (AVM)

Large, tortuous arteries with fragmented elastic lamina and associated with thick-walled veins. Variable small vessel component.

Most common in head/neck and brain.

Venous Malformations (Venous Hemangiomas)

Poorly-circumscribed collection of abnormal veins

Vary in size/proportion.

Often abnormally thick or thin walls for size.

Includes: **Cavernous hemangiomas** (collection of large, dilated veins with thin walls)

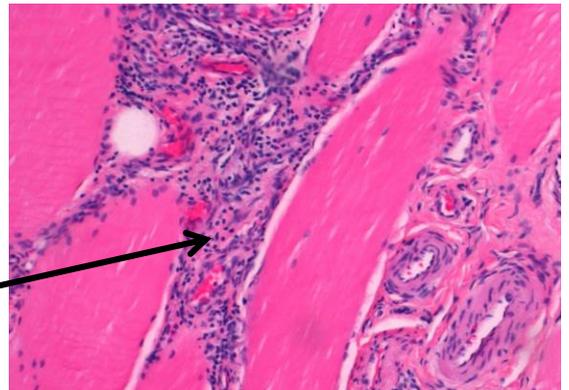
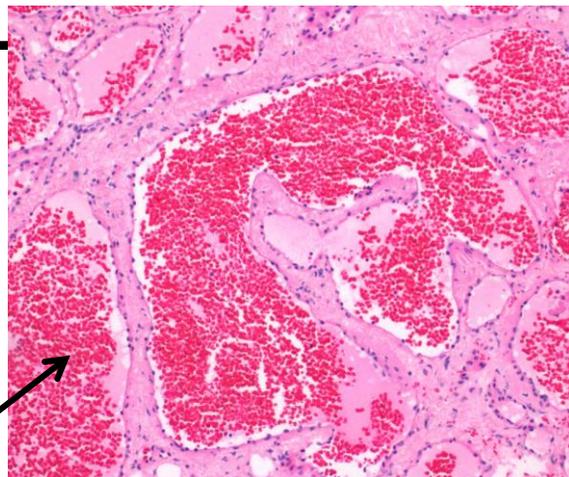
Cutaneous Capillovenous Malformation

E.g. Telangiectasia. Often diagnosed clinically.

Associated with a variety of conditions (e.g., Osler-Weber-Rendu)

Intramuscular hemangioma

Small vessels within muscle. Often parallel.



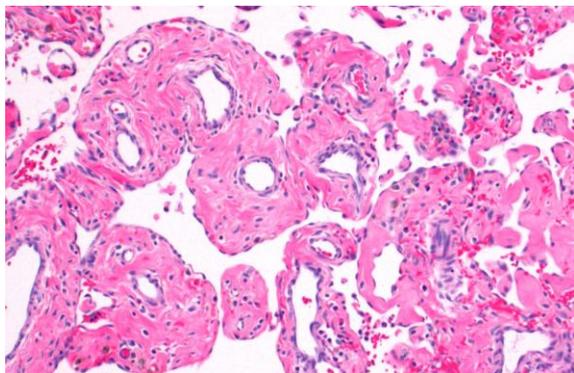
Papillary Endothelial Hyperplasia

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.

aka Mason's Tumor



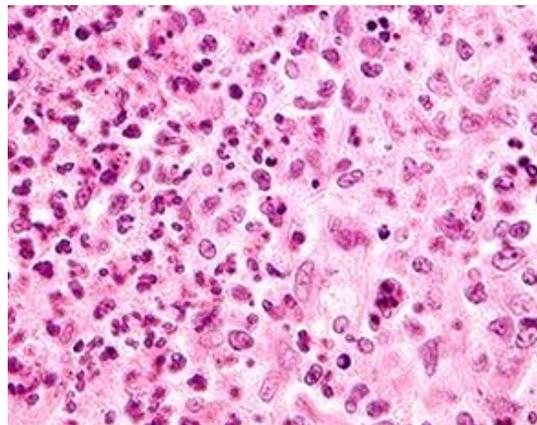
Bacillary Angiomatosis

Pseudo-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.

Lobules of capillary-sized vessels with plump endothelium with clear cytoplasm. Associated neutrophilic infiltrate.

Stains: Warthin-starry highlights organisms



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.

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.

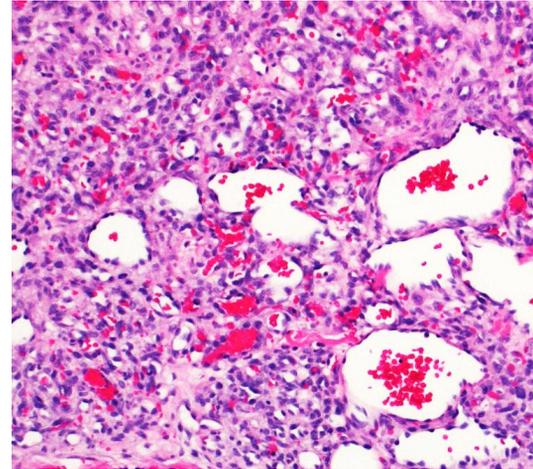
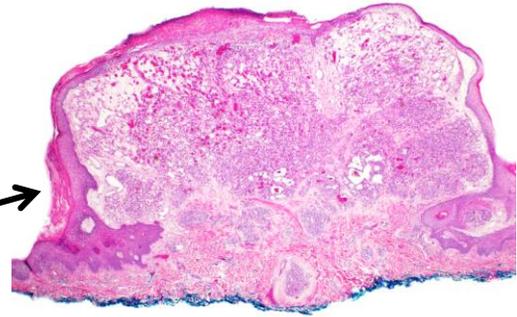
IHC: Unique expression of GLUT1 (not in other hemangiomas)

Rarer subtypes

Hobnail hemangioma

Anastomosing hemangioma

Spindle cell hemangioma



Epithelioid Hemangioma

aka Angiolymphoid hyperplasia with eosinophils

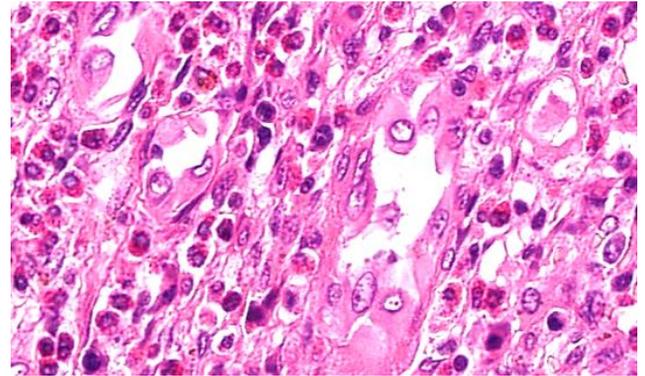
Benign.

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. Associated inflammatory infiltrate rich in eosinophils.



Lymphangioma

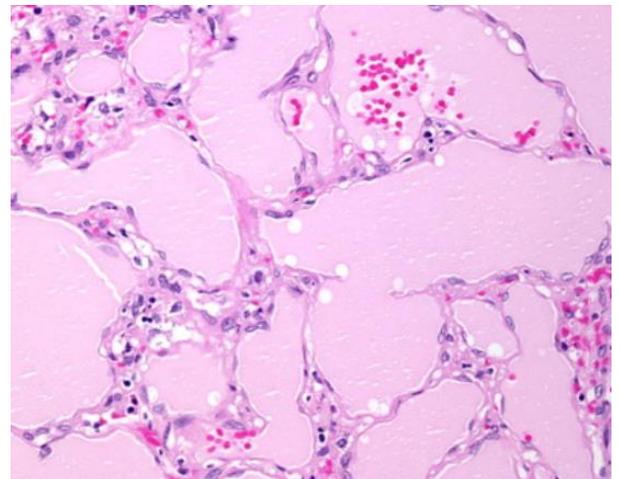
Benign. Often in kids during the first year of life.

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.



Kaposiform Hemangioendothelioma

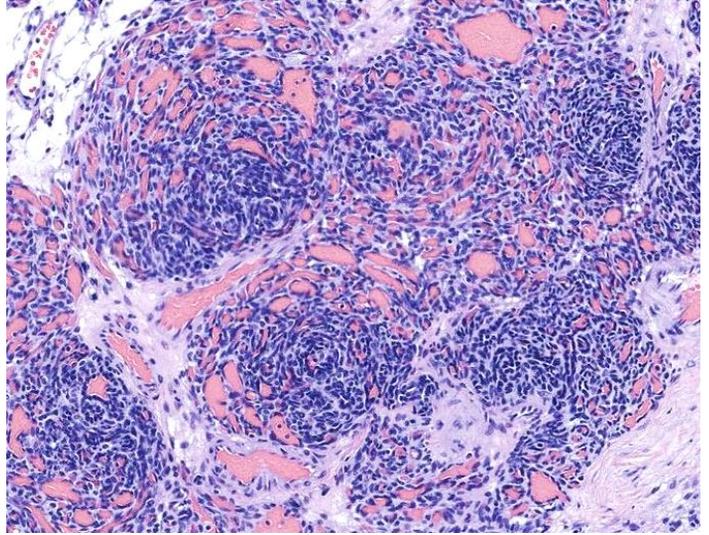
Locally aggressive vascular tumor.

Exclusively in children.

Often associated with Kasabach-Merrit phenomenon (consumption of platelets → thrombocytopenia)

Infiltrate soft tissue in “cannon-ball fashion.” Different areas have features of both capillary hemangioma and Kaposi sarcoma (spindled cells).

Tightly coiled glomeruloid-like areas.



Epithelioid Hemangioendothelioma

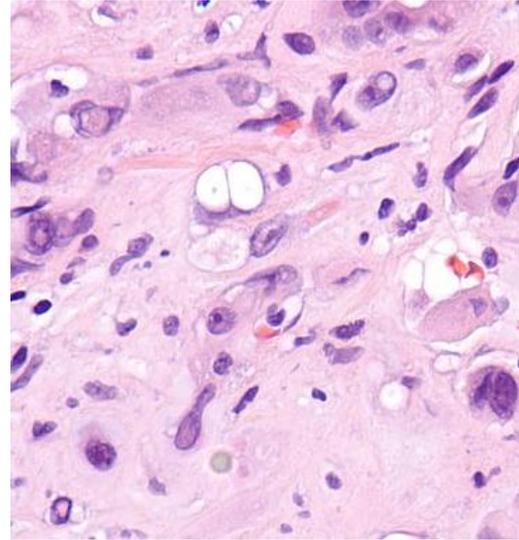
Malignant (but less aggressive than angiosarcoma).

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

Cords of epithelioid endothelial cells in myxohyaline stroma.
Eosinophilic cells with vacuoles containing erythrocytes (“Blister cells”).

IHC: CAMTA1 stain specific

Molecular: recurrent CAMTA1-WWTR1 fusions



Kaposi Sarcoma

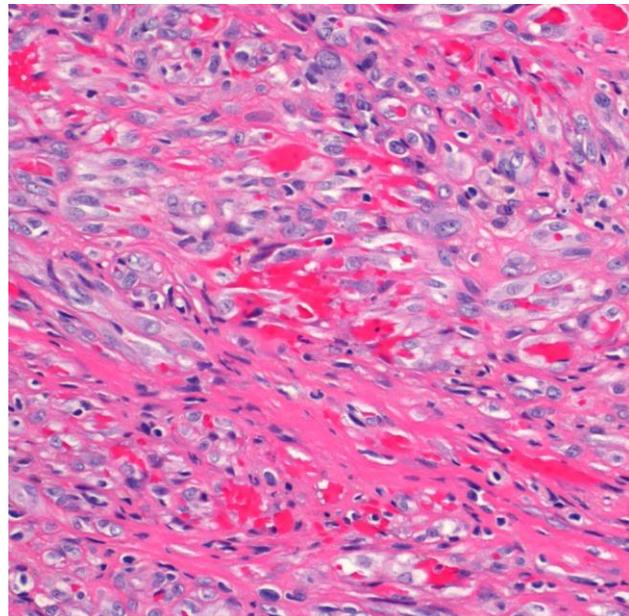
Locally aggressive. Often multiple cutaneous lesions
Caused by Human Herpes Virus 8 (HHV8) in all cases.

Can be Classic/Endemic, which are usually indolent, or associated with immunosuppression (either iatrogenically for organ transplantation or by AIDs), which is more aggressive often.

Proliferation of bland spindled cells with slit-like vascular spaces containing erythrocytes.

Often associated inflammatory infiltrate and hyaline globules.

IHC: HHV8



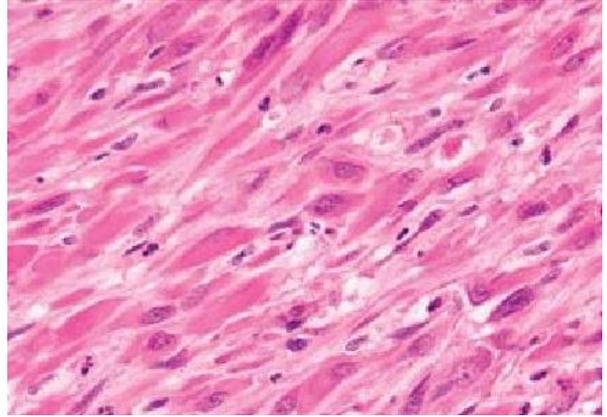
Pseudomyogenic Hemangioendothelioma

Rarely metastasize. Often develop additional nodules in same anatomic region. Often young men on leg.

Infiltrative sheets and fascicles of plump spindled cells. Abundant brightly eosinophilic cytoplasm (resembling rhabdomyoblasts, hence the name!). Vesicular nuclei.

IHC: CK AE1/AE3 (+), ERG(+), FOSB (+). CD31 (+/-), INI1 intact.

Molecular: SERPINE1 and FOSB genes fusion



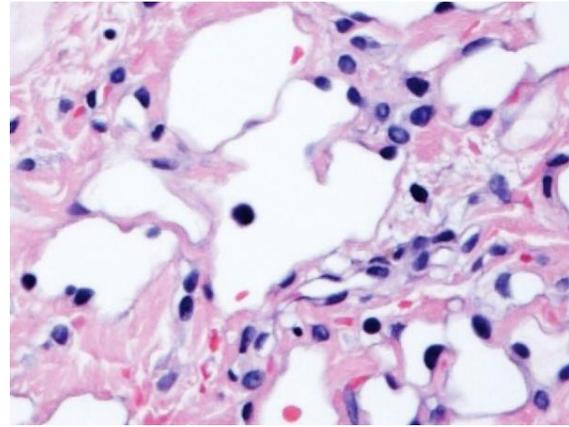
Atypical Vascular Lesion

Benign. Occur in irradiated skin (often of breast). Often small/multiple.

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 or true cytologic atypia

IHC/Molecular: No MYC overexpression/amplification.



Angiosarcoma

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.

Can be epithelioid or spindled.

Often extensive hemorrhage.

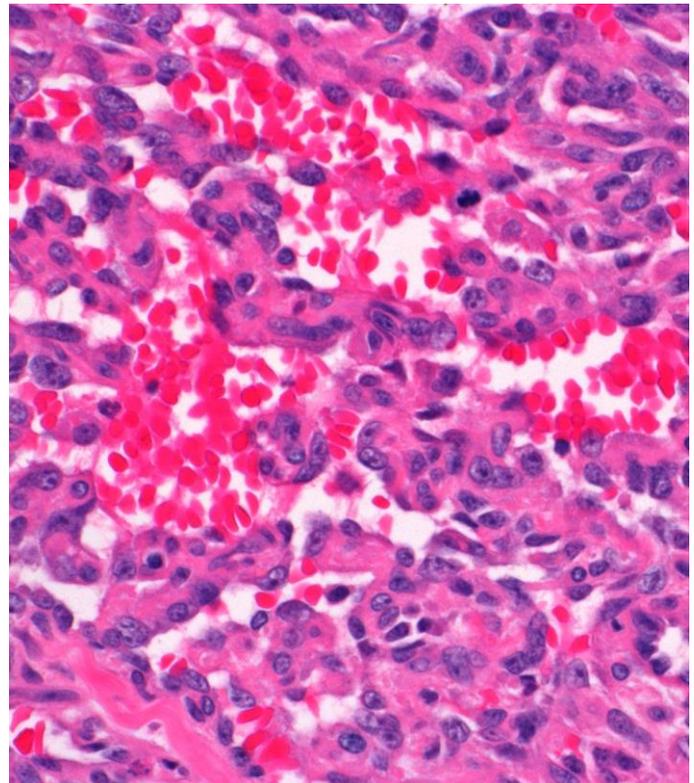
Unlike benign lesions: significant cytologic atypia, necrosis, endothelial cells piling up, and mitotic figures (although mitoses can be seen in some benign tumors)

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.



Tumors of Uncertain Differentiation

Myxoma

Benign. Adults.

Uniform, cytologically bland, small spindled to stellate cells in abundant myxoid stroma.

Can show cystic change and/or have more slightly more cellular areas. Grossly look like jelly.

Notably: No atypia or mitoses (otherwise consider myxofibrosarcoma)

Intramuscular:

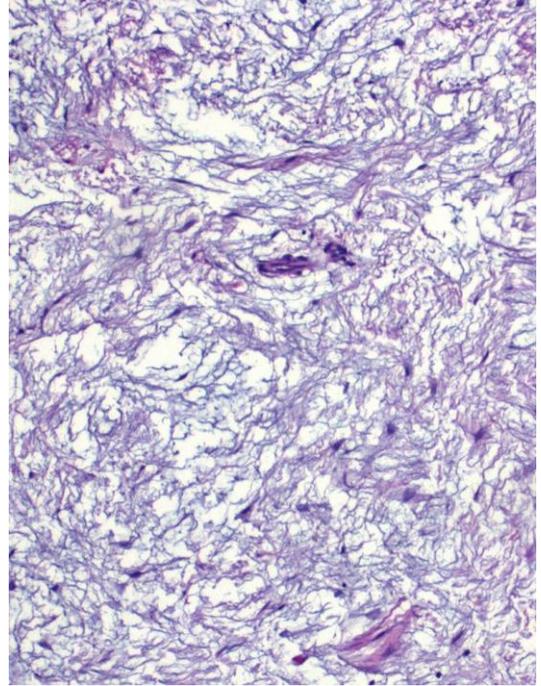
Within muscle. Frequent GNAS mutations.

Intramuscular myxoma + fibrous dysplasia = Mazabraud syndrome (both have GNAS mutations)

Juxta-articular:

Vicinity of a large joint (usu. Knee)

Lacks GNAS mutations.



Deep (“Aggressive”) Angiomyxoma

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

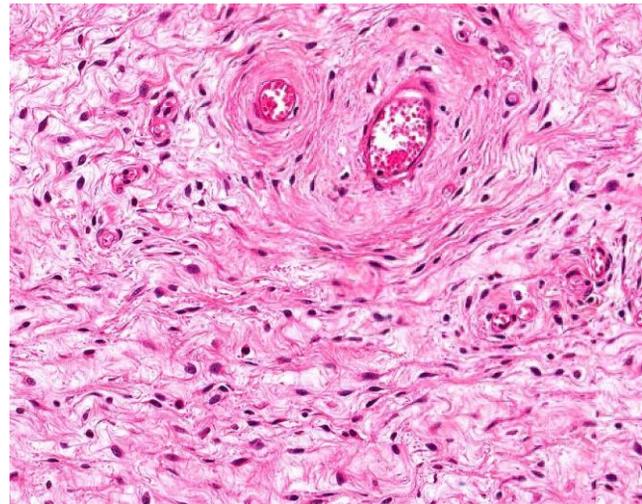
Small spindled to stellate cells in a loosely collagenized, myxoid stroma. Scattered vessels of varying size.

Scant eosinophilic cytoplasm.

Larger spindled myoid cells congregate around larger vessels and nerves.

IHC: ER, PR (+), Variable desmin and actin.

Molecular: HMGA2 rearrangements frequently.



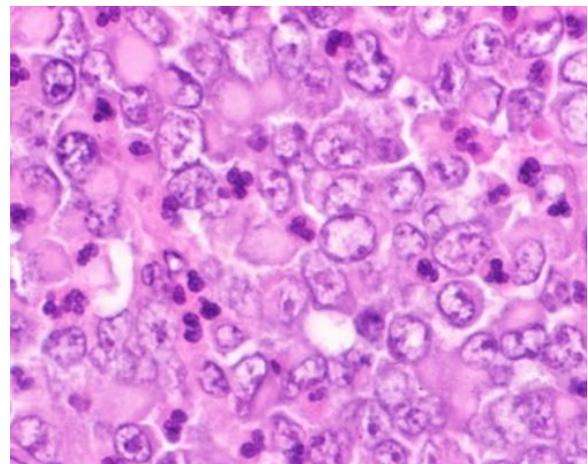
Extrarenal Rhabdoid Tumor

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)

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

IHC/Molecular: SMARCB1 (INI1) loss/inactivation
CAM5.2 (+) in inclusions.



Ossifying Fibromyxoid Tumor

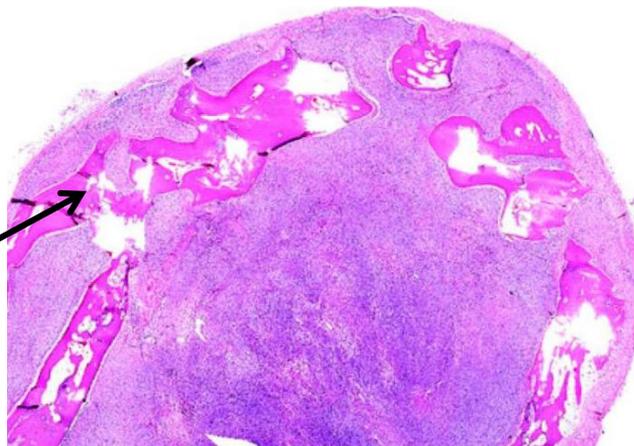
Usually benign with potential with recurrence.

Lobules of uniform, monomorphous round to spindled cells arranged in cords surrounded by fibromyxoid stroma.

Circumscribed mass with peripheral zones of metaplastic bone.

IHC: S100 (+), Desmin (+/-)

Molecular: PHF1 rearrangements



Angiomatoid Fibrous Histiocytoma

Indolent with very rare recurrence. Most commonly young.

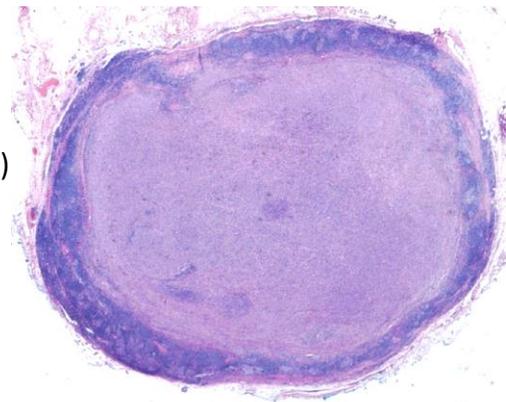
Often pericapsular cuffing of lymphocytes (mimicking a lymph node)

Nodules of spindled/histiocytoid cells with syncytial growth.

Pseudoangiomatoid spaces full of blood. Thick fibrous capsule.

IHC: Variable desmin and EMA.

Molecular: EWSR1-CREB1 fusions.



Ectopic Hamartomatous Thymoma

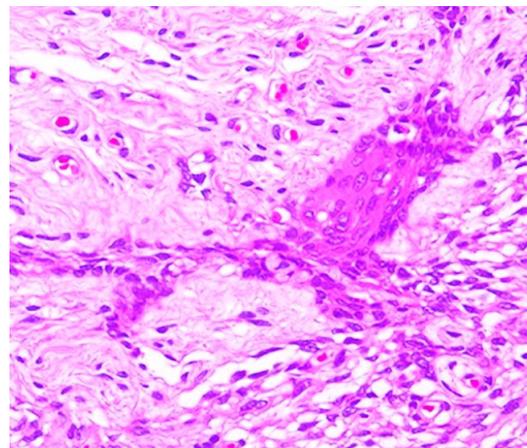
Benign. Exclusively in the lower neck region. Often adults.

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.



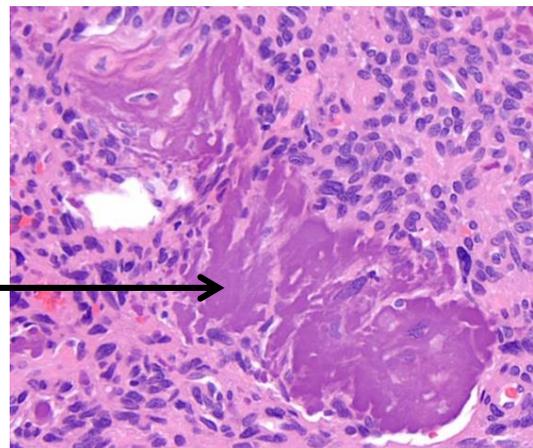
Phosphaturic Mesenchymal Tumor

Most tumors are benign (but cause significant side-effects!).

Produce FGF23 → causes tumor-induced osteomalacia by inhibiting renal proximal tubule phosphate reuptake.

Bland spindled to stellate cells with produce unusual hyalinized "smudgy" matrix with "grungy" or flocculent calcifications.

FGF23 can be demonstrated by testing blood or by IHC.



Clear Cell Sarcoma of Soft Tissue

aka Malignant Melanoma of Soft Parts

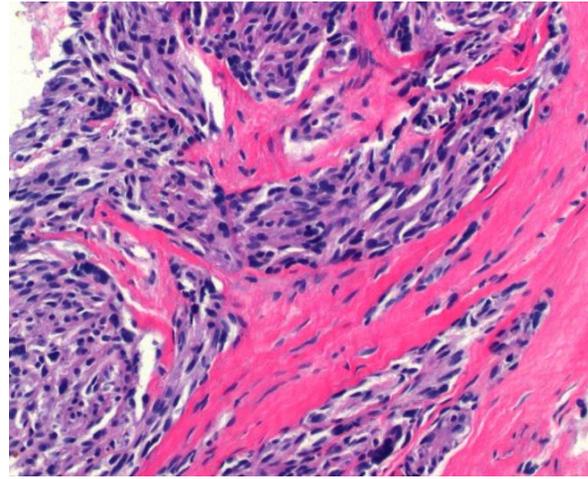
Malignant. Typically young adults.

Characteristic nested growth with dividing collagenous bands.

Epithelioid (mostly) to spindled cells with pale/eosinophilic to amphophilic (despite name) with vesicular nuclei and prominent nucleoli. Scattered multinucleated giant cells.

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

Molecular: EWSR1-ATF1 fusions



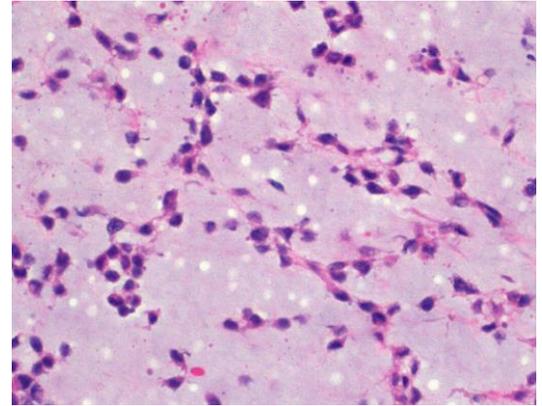
Extraskeletal Myxoid Chondrosarcoma

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 nuclei.

“AT&T tumor” → “reach out and touch someone” → cells are often reaching out to touch each other.

Molecular: NR4A3 fusions, often with EWSR1 or TAF15



Pleomorphic Hyalinizing Angiectatic Tumor/ Hemosiderotic Fibrolipomatous Tumor

Think: PHAT

Malignant. Usually adults in soft tissue. Often on foot.

PHAT:

Prominent thin-walled ectatic blood vessels lined by fibrin. Embedded in spindled to pleomorphic cells with intranuclear inclusions and fine hemosiderin granules.

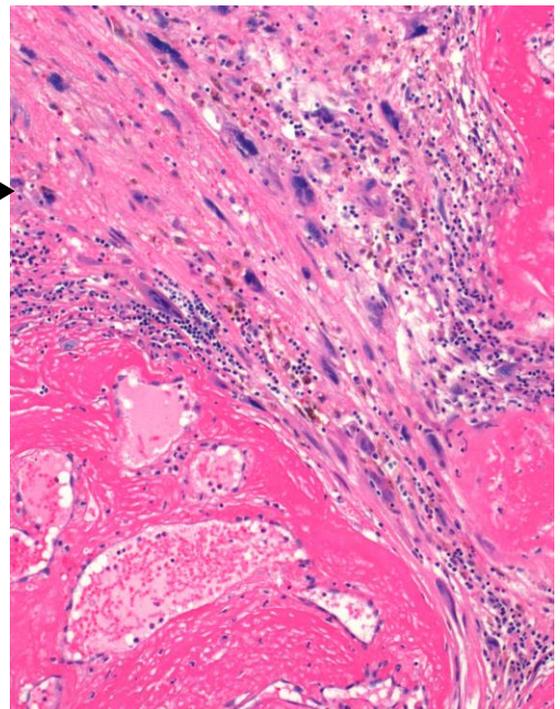
Hemosiderotic Fibrolipomatous Tumor:

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 MGEA5 rearrangements



Synovial Sarcoma

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

Monophasic SS → Just spindled component.

Biphasic SS → Spindled and epithelioid component.

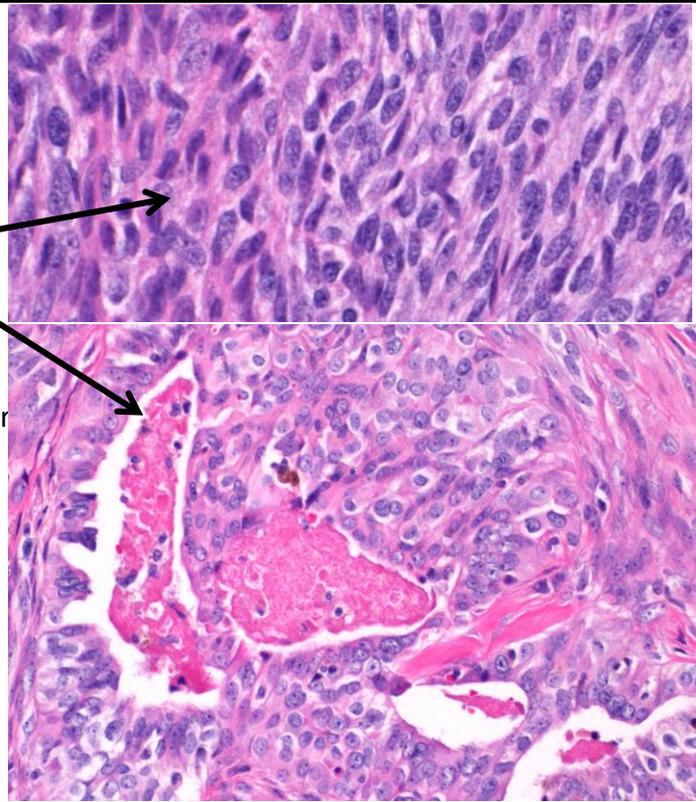
Fairly uniform spindled cells with relatively little cytoplasm.

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 young adults.

Classic/conventional type:

Cellular nodules of epithelioid to spindled cells with central degeneration/necrosis → looks vaguely granulomatous.

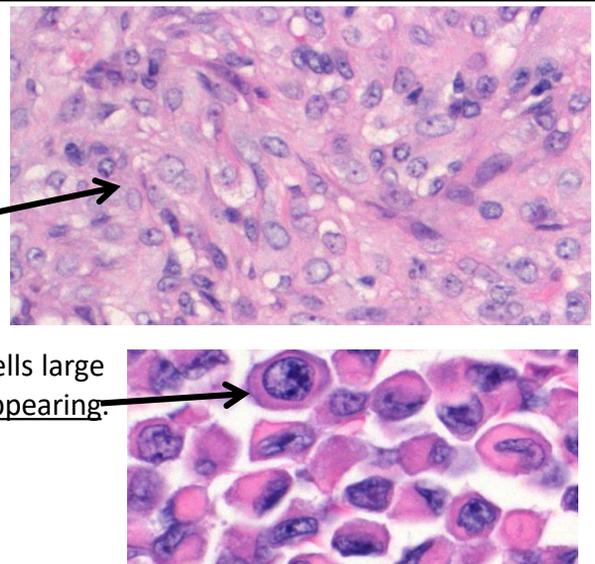
Vesicular chromatin and eosinophilic cytoplasm.

Proximal type:

Multinodular and sheet-like growth of large pleomorphic cells large vesicular nuclei and prominent nucleoli. Often Rhabdoid-appearing.

IHC: INI1 loss; Cytokeratin/EMA and CD34 (+)

Molecular: Complex, but SMARCB1 (INI1) deletions/loss.



Alveolar Soft Part Sarcoma

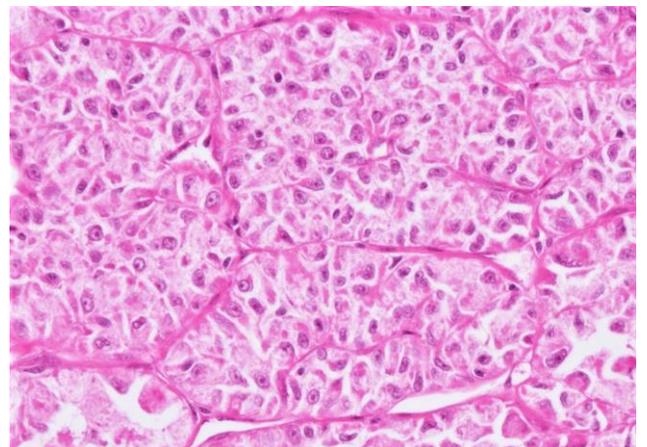
Malignant. Often young adults.

Organoid nests of large, uniform, epithelioid cells with abundant, eosinophilic, granular cytoplasm. Round nuclei with prominent nucleoli.

PAS demonstrates rhomboid or rod-shaped intracytoplasmic inclusions.

IHC: TFE3 (+), S100 and Desmin (-/+)

Molecular: ASPCR1-TFE3 Fusion



Ewing Sarcoma

Malignant. Variable neuroectodermal differentiation.
Often arises in the bone of young (but can see in many organs; Chest wall = *Askin tumor*).

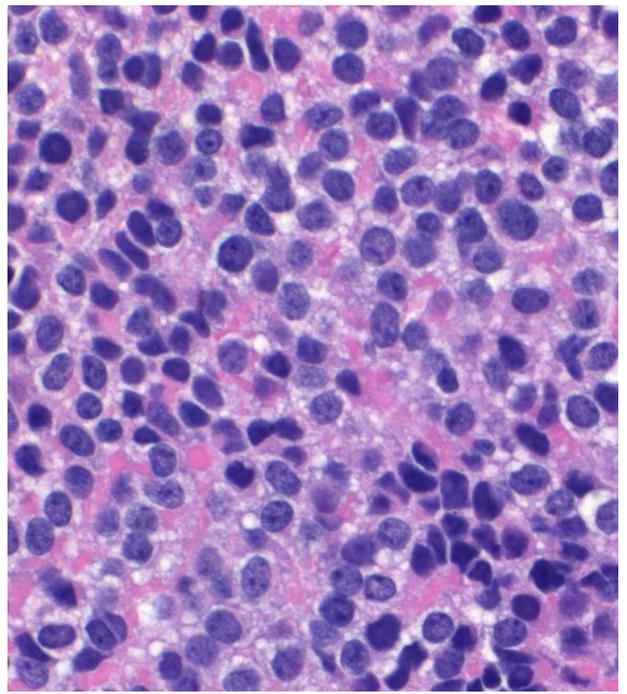
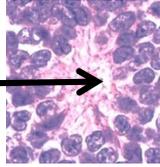
Usually uniform, small, round, blue cells with sheet-like to lobular, growth pattern with variable necrosis

IHC: Strong, membranous CD99 staining (Sensitive, but not specific staining)

Cytoplasmic glycogen stains with PAS

Molecular: EWSR1 fusion (with FLI-1 or ERG) t(11;22)

Can see pseudorosettes



CIC-rearranged Sarcomas

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

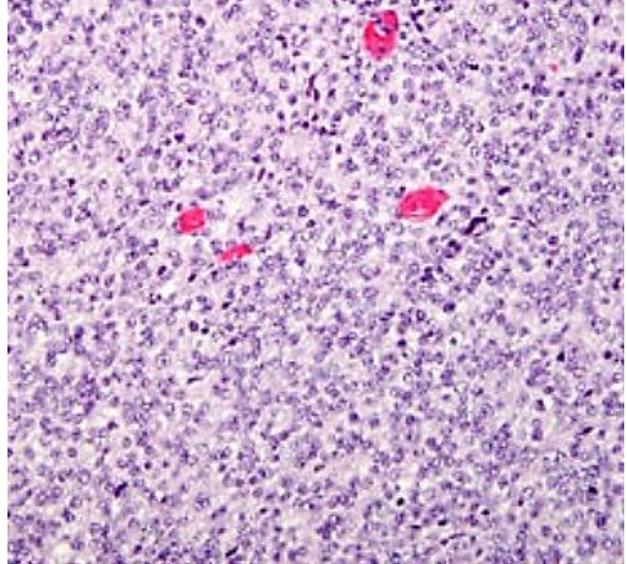
Solid proliferation of small round cells (like Ewing sarcoma).

Scant eosinophilic to clear cytoplasm.

Geographic necrosis usually present.

IHC: WT1 (+), variable CD99

Molecular: CIC-DUX4 fusions



BCOR-rearranged Sarcomas

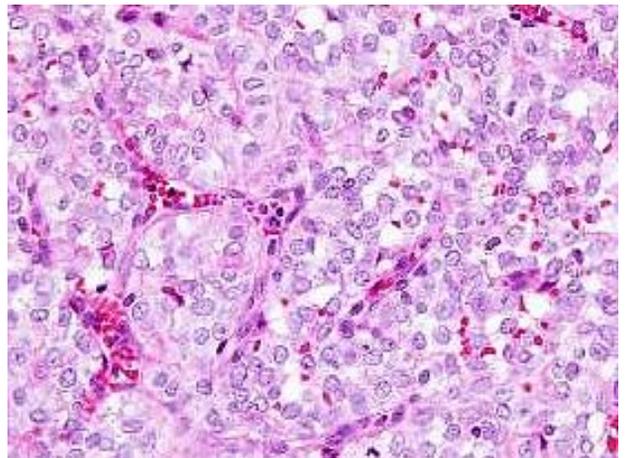
Malignant. Outcome similar to Ewing.
Often in bone or soft tissue of young.

Solid proliferation of mostly small round cells with monomorphic round nuclei, fine chromatin, and delicate capillary network.

Sometimes partially spindled.

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

IHC: SATB2



Solitary Fibrous Tumor (“SFT”)

Old name: *Hemangiopericytoma*

(referred to cellular tumors on a spectrum with SFT)

Usually benign.

Adults in deep soft tissue or serosal surfaces (classically lung/pleura).

“Patternless pattern” of varying cellularity of bland spindled cells with varying amounts of collagenized stroma.

Prominent “Staghorn vessels” (dilated, thin-walled, branching vessels).

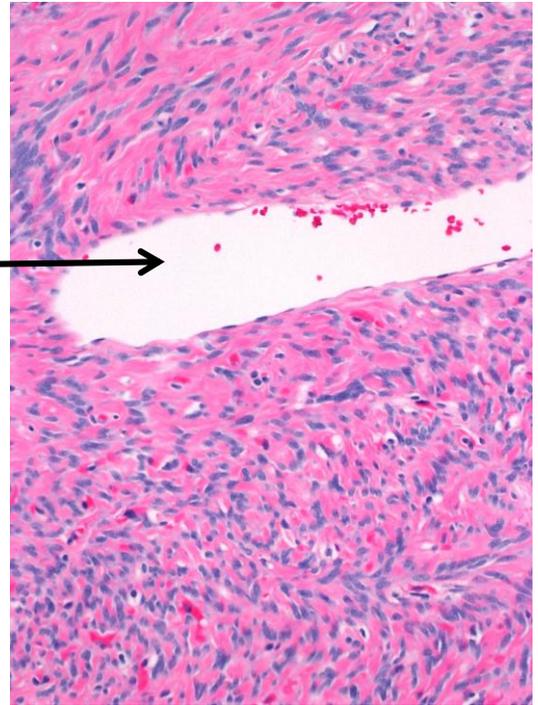
Can be hyalinized or myxoid.

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

Molecular: NAB2/STAT6 gene fusion

Factors associated with malignant behavior:

Numerous mitoses (esp. >4/10 HPF), Large size (esp. >15 cm), and tumor necrosis.



Intimal Sarcoma

Malignant.

Arises in large blood vessels of systemic and pulmonary circulation. Characteristic predominantly intraluminal growth with obstruction of blood flow and seeding tumor emboli.

Mild to severely pleomorphic spindled cells with necrosis, nuclear pleomorphism, and mitoses. Can have myxoid or fascicular areas.

IHC: MDM2 (+)

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

Undifferentiated Sarcoma

A sarcoma with no identifiable line of differentiation.

Heterogeneous group and diagnosis of exclusion.

Subclassify based on histologic appearance.

Undifferentiated Pleomorphic Sarcoma

(aka **Malignant Fibrous Histiocytoma (MFH)**)

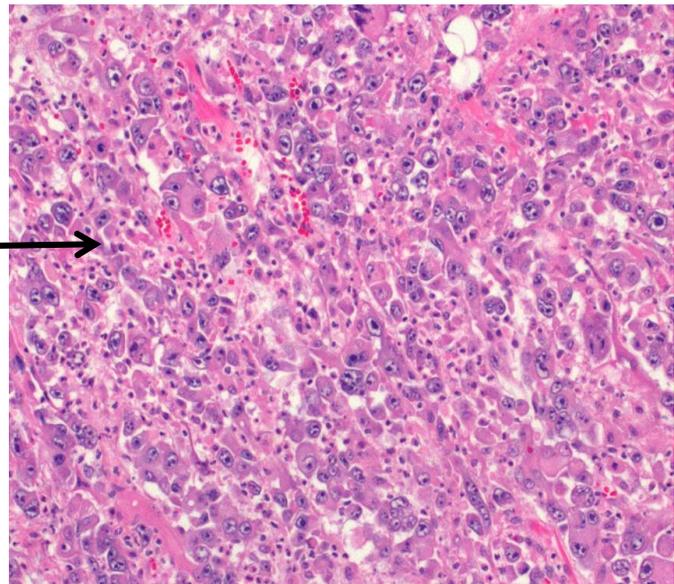
Wildly pleomorphic cells.

Complex karyotypes

Undifferentiated Spindle Cell Sarcoma

Undifferentiated Round Cell Sarcoma

Undifferentiated Epithelioid Sarcoma



Pattern-Based Approach

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

General Comments: Although a pattern-based approach is very useful, in many cases you might have a good idea of the Dx via "instant pattern recognition." Nevertheless, it can be helpful to judiciously consider mimickers and other diagnoses based on a pattern-based approach.

Myxoid

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

Myxoma	Low-grad fibromyxoid sarcoma
Neurofibroma	Myoepithelioma
Perineurioma	Myoepithelial carcinoma
Neurothekeoma	Myxoinflammatory fibroblastic sarcoma
Spindle cell lipoma	Aggressive angiomyxoma
Nodular fasciitis	Chordoma
Ossifying fibromyxoid tumor	
Myxoid liposarcoma	
Myxofibrosarcoma	
Extraskelatal myxoid chondrosarcoma	

Note: Some people prefer SOX10 over S100

Pleomorphic

IHC to consider: S100, Desmin, CD45, CK AE1/AE3, MDM2, ERG

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

Round cell

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

Ewing sarcoma	BCOR-rearranged sarcomas
Alveolar rhabdomyosarcoma	Lymphoma/Leukemia
Round cell liposarcoma	Wilm's tumor
Desmoplastic small round cell tumor	Neuroblastoma
Synovial sarcoma	
Mesenchymal chondrosarcoma	
CIC-rearranged sarcomas	

Spindled Cells

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

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

Epithelioid

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

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

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

Tumor Behavior

“Beyond Benign and Malignant”

Soft tissue tumors can have varied behavior that often exists more on a spectrum than carcinomas making specific subtyping (if possible) of considerable clinical importance. While some tumors (e.g., fibromatosis) are benign (meaning that they do not metastasize), they can nevertheless be locally destructive and recurrent.

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.

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% N

+

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

Histologic Type	Score
ALT/WDL	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrosarcoma	2
Myxofibrosarcoma	2
Undifferentiated Pleomorphic Sarcoma	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly-differentiated leiomyosarcoma	3
Low-grade fibromyxoid sarcoma	3
Sclerosing epithelioid sarcoma	2
Synovial sarcoma	3
DFSP	1
Pleomorphic rhabdomyosarcoma	3
Mesenchymal chondrosarcoma	3
Extra-skeletal osteosarcoma	3
Ewing sarcoma	3
Malignant rhabdoid tumor	3
Undifferentiated sarcoma, NOS	3

The following tumors are not graded: GIST, alveolar and embryonal rhabdomyosarcoma, MPNST, angiosarcoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma, alveolar soft part sarcoma, and epithelioid sarcoma.