

Soft Tissue FNA and Small Biopsy: Part 2

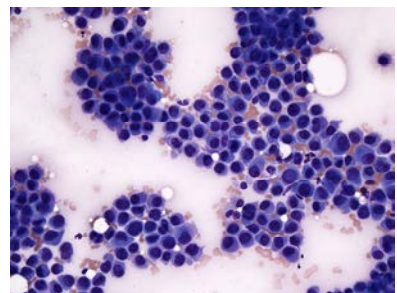
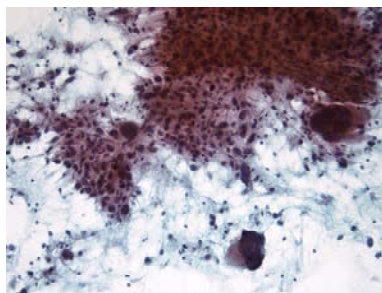
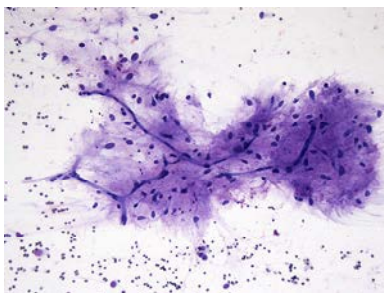
Vickie Jo, M.D.

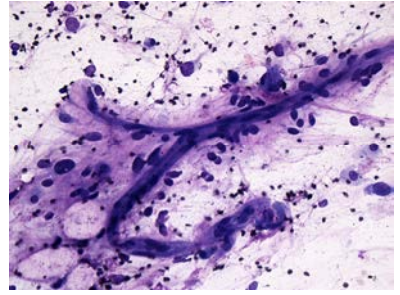
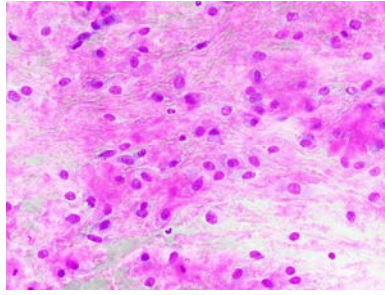
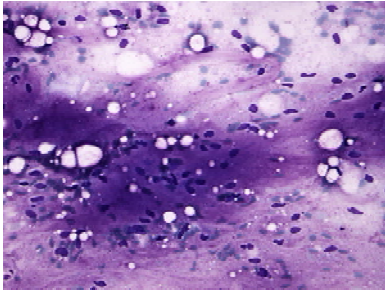
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Associate Professor of Pathology

Part 2: Practical Pattern-Based Approach

- Myxoid Tumors
- Pleomorphic Tumors
- Epithelioid Tumors





MYXOID TUMORS

Myxoid Soft Tissue Tumors: Common Scenarios

- Adipocytic tumors with prominent myxoid stroma
- Bland, hypocellular myxoid lesions
- Cellular myxoid tumors
 - Uniform cytomorphology
 - Pleomorphic cytomorphology → Pleomorphic DDX

Adipocytic tumors with myxoid stroma

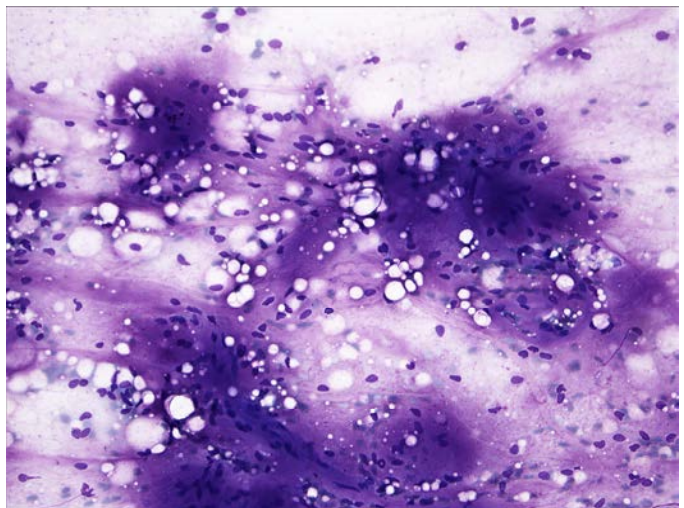
- Spindle cell/pleomorphic lipoma
- Myxoid liposarcoma

Can also enter this DDX:

- Pleomorphic liposarcoma (ST Part 1; Pleomorphic DDX)
- Dedifferentiated liposarcoma (ST Part 1; Pleomorphic DDX)

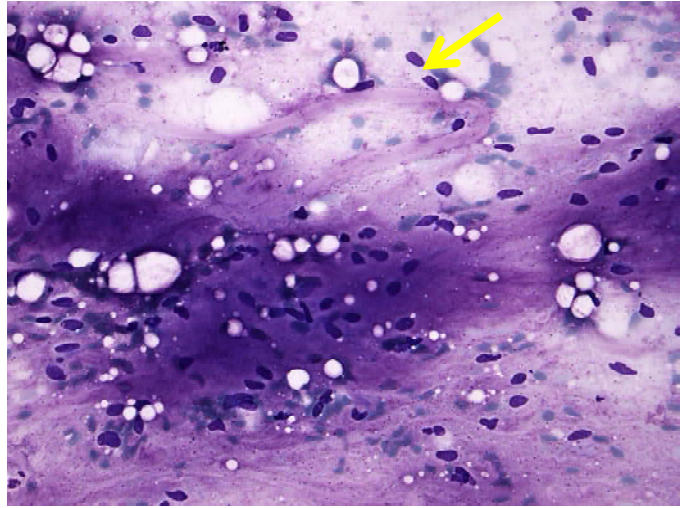
Spindle Cell/Pleomorphic Lipoma

- Adulthood, M>F
- Typical anatomic distribution: subcutaneous posterior neck, back, shoulder
- Alterations of chr 13q14 (*Retinoblastoma* (Rb) locus)
- IHC: CD34 +, Rb loss (not easy on cell blocks)

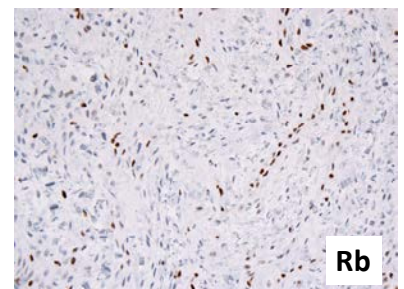
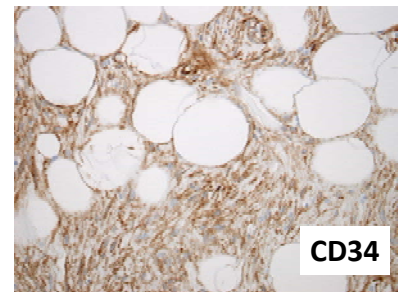
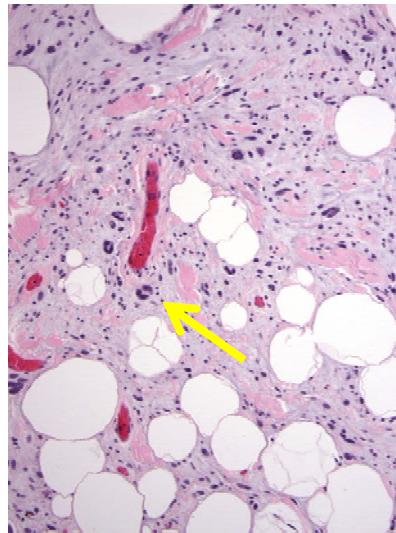
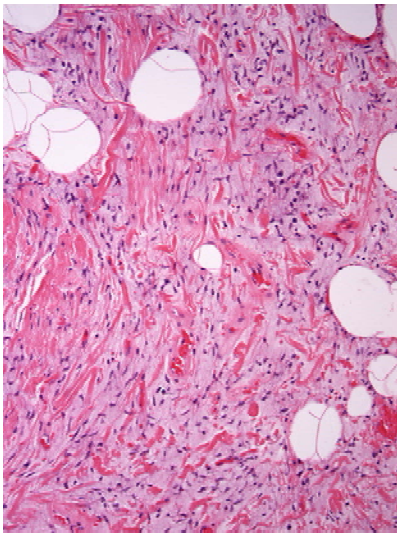


Spindle Cell/Pleomorphic Lipoma

- Large fragments of myxoid or collagenous stroma; mature adipocytes
- Bland, short stubby spindle cells
- Ropy collagen fibers (v long)
- Lipoblasts rare (not atypical)
- Lacks prominent vasculature
- Floret-like cells in “pleomorphic lipoma”

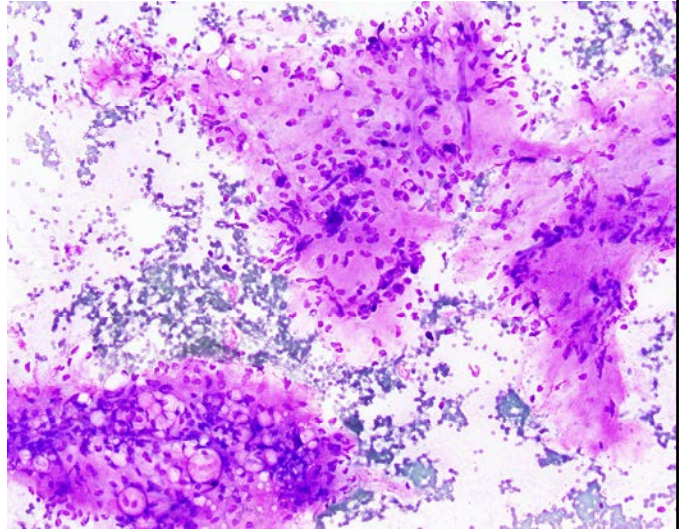


Spindle Cell Lipoma



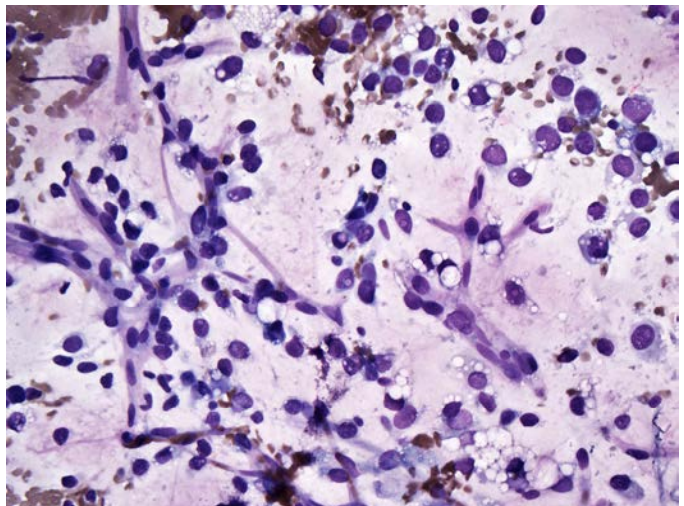
Myxoid Liposarcoma

- Adults (4-5th decade), M=F
- Deep soft tissue of limbs (thigh)
- Grade is most important prognostic factor
 - 3-tier system based on cellularity
 - High grade tumors enter round cell DDX
- *FUS::DDIT3*
 - *DDIT3* FISH
 - *DDIT3* IHC is a reliable surrogate

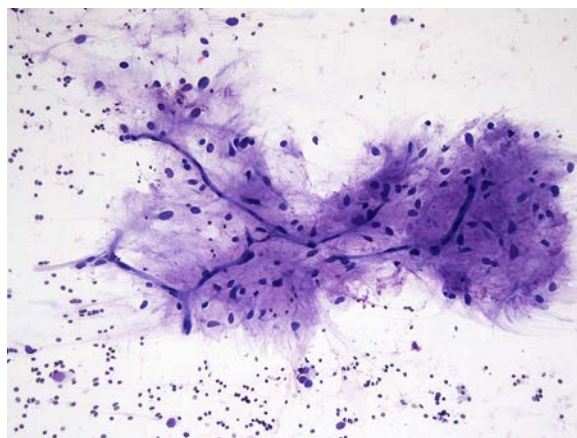
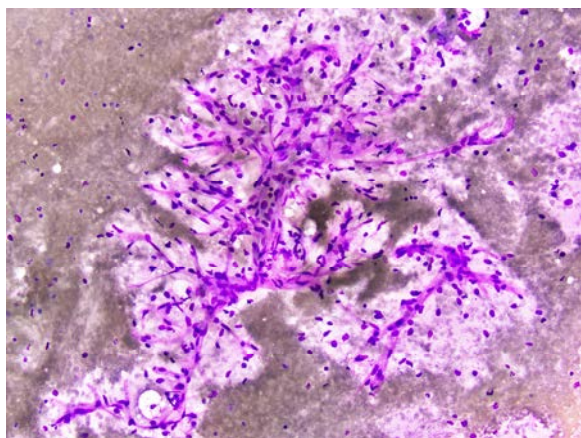


Myxoid Liposarcoma

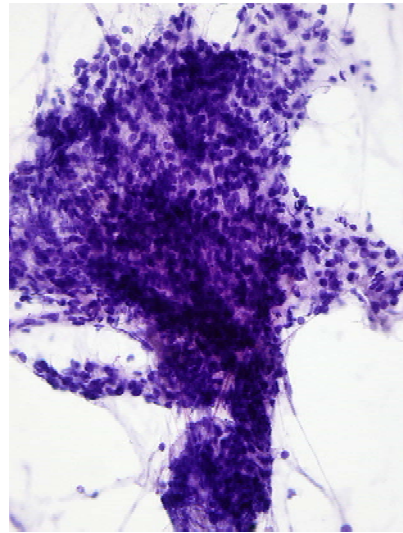
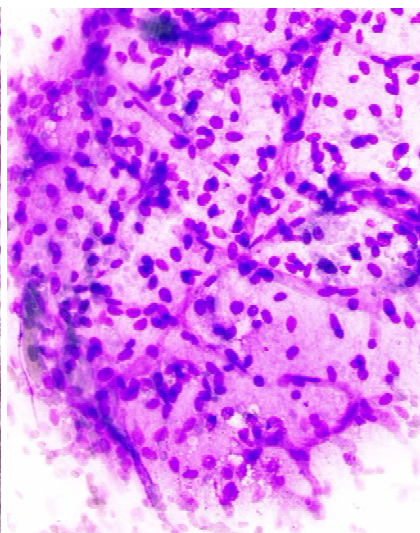
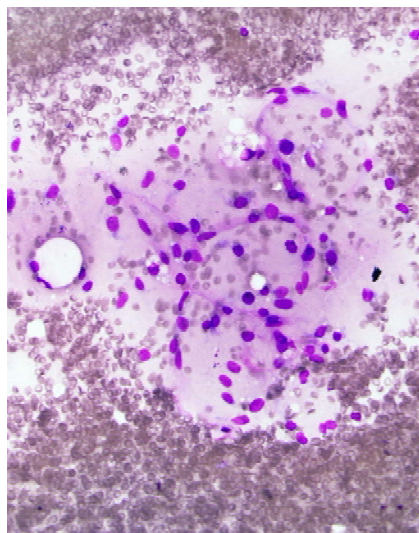
- Large myxoid stromal fragments
- Delicate branching capillaries (“chicken-wire” or “crow’s feet”)
- Uniform ovoid-to-round tumor cells
 - Increased cellularity and atypia with grade
- Small lipoblasts (often uni- or bivacuolated)
 - Presence are NOT required for diagnosis



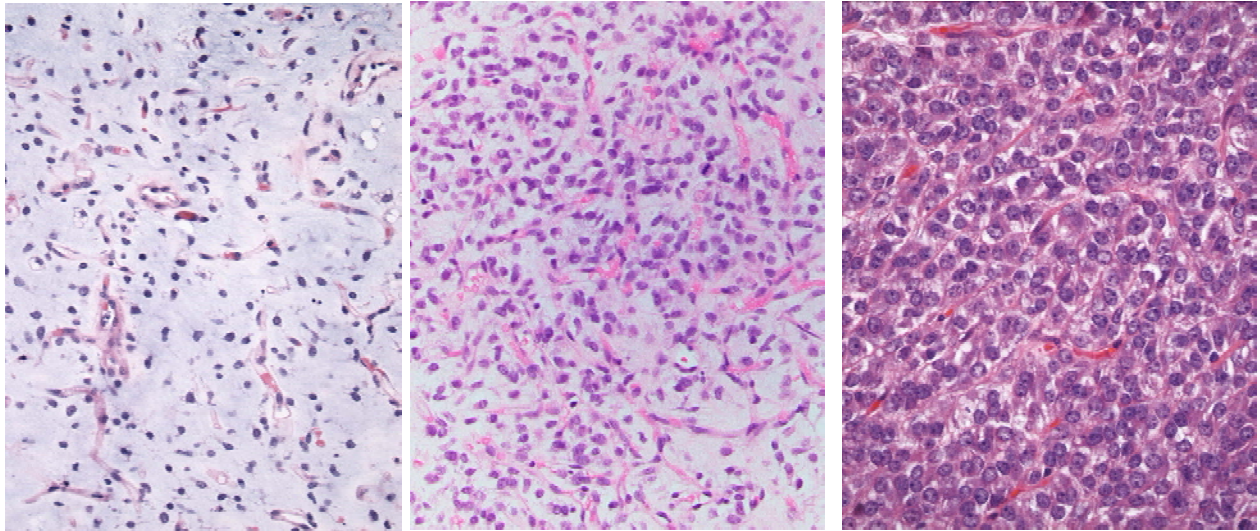
Myxoid Liposarcoma



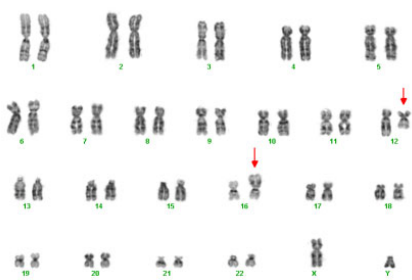
Myxoid Liposarcoma



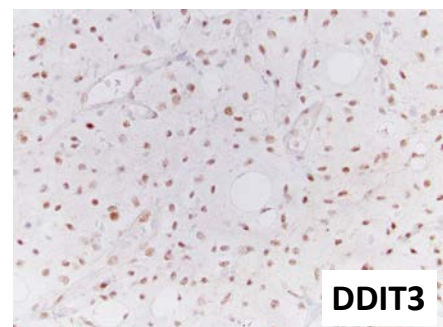
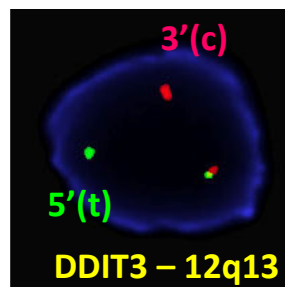
Myxoid Liposarcoma



Myxoid Liposarcoma



$t(12;16)(q13;p11)$



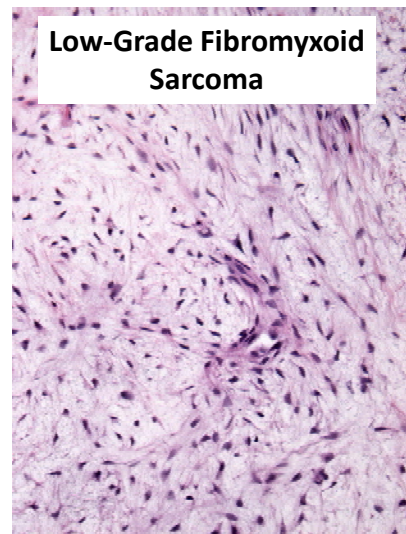
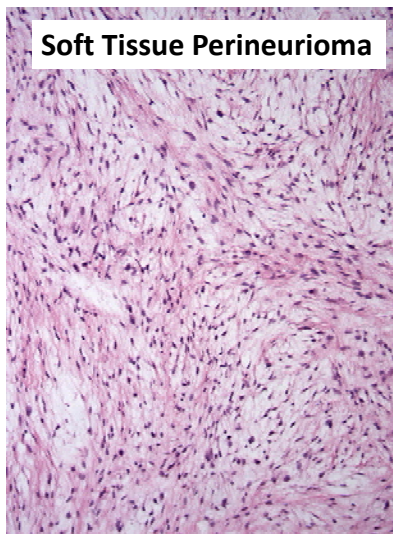
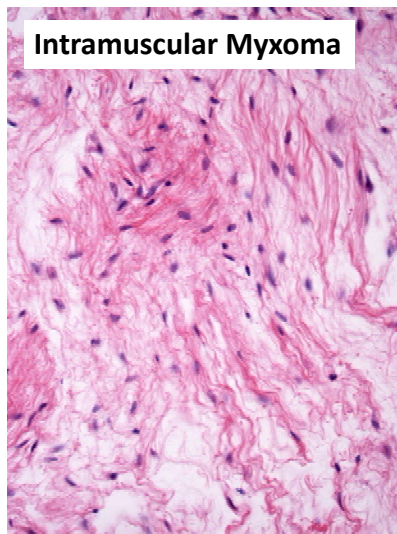
DDIT3 IHC is highly sensitive and specific

Myxoid Tumors: Bland, Hypocellular Pattern

- DDX is challenging because there is significant overlap between benign entities and some sarcomas
 - Descriptive diagnosis is reasonable after sarcoma is excluded
- IHC has limited value, but MUC4 is helpful to exclude low-grade fibromyxoid sarcoma

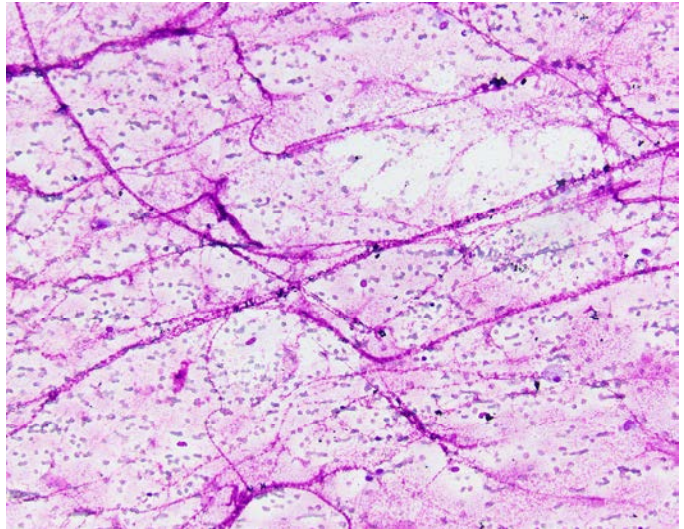
Tumor type	Cytology	MUC4 IHC
Ganglion cyst	Not cellular	-
Intramuscular myxoma	Abundant film of myxoid granular stroma	-
Soft tissue perineurioma	Tumor cells with long bipolar processes	-
Low-grade fibromyxoid sarcoma	Bland to mildly atypical tumor cell nuclei	+
Low-grade myxofibrosarcoma	Curvilinear vessels, appreciable cytologic atypia	-

Myxoid Tumors: Bland, Hypocellular Pattern

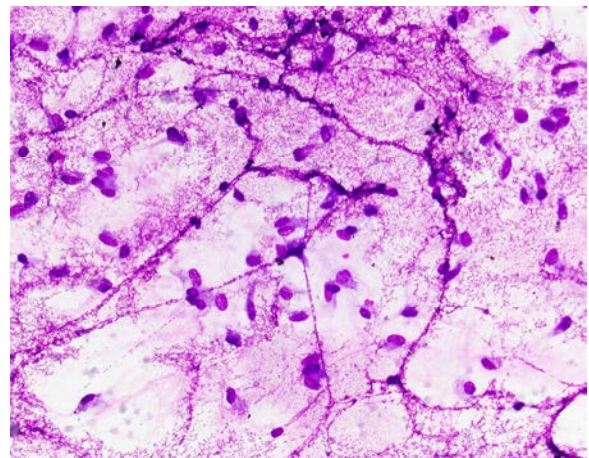
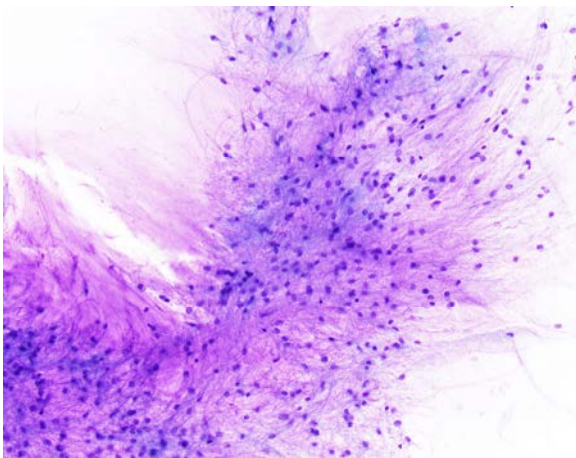


Intramuscular Myxoma

- Slow-growing deep-seated mass in thigh, hip/buttock, arm, can be large (up to 20 cm)
- Adults, F>M
- *GNAS1* mutations
- Mazabraud syndrome: multiple intramuscular myxomas and polyostotic fibrous dysplasia
- Abundant filmy granular myxoid matrix
- Bland spindle and ovoid tumor cells with long cytoplasmic processes
 - Stripped nuclei
- Entrapped atrophic skeletal muscle may be sampled



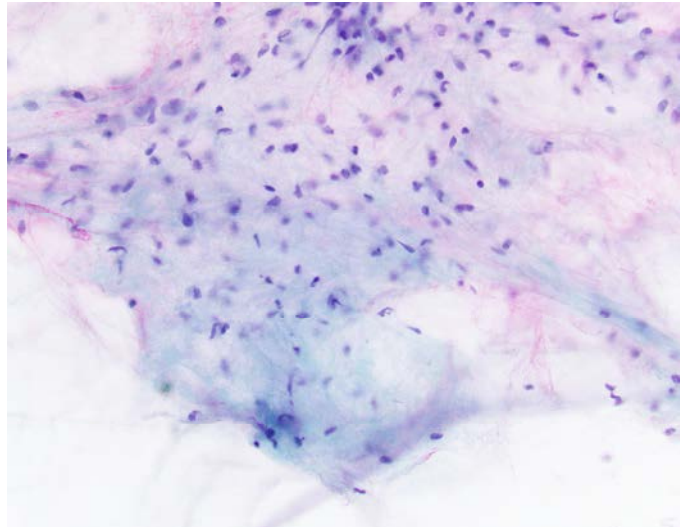
Intramuscular Myxoma



Cellular Variant

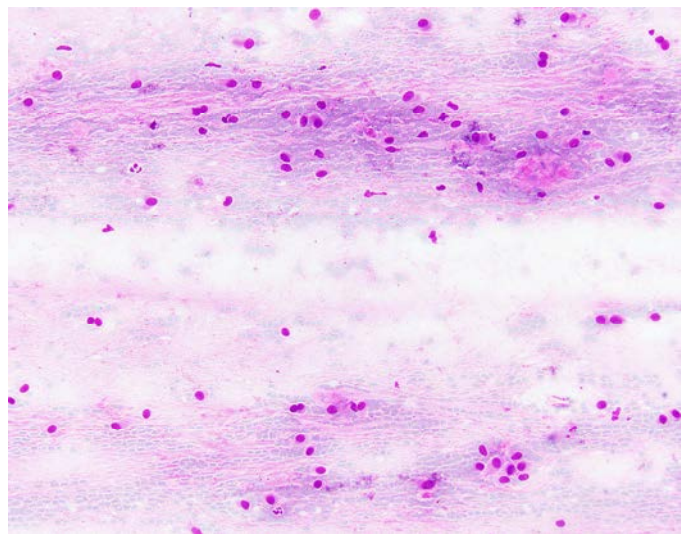
Low-Grade Fibromyxoid Sarcoma

- Young adults, slight M>F
- Deep-seated tumors in the lower extremity
- Low rates of recurrence/metastases in first 5 yrs, but common]decades later
- Occasional hybrid tumors with sclerosing epithelioid fibrosarcoma
- *FUS* fusions (most *FUS::CREB3L2*)
- MUC4 is highly sensitive and specific

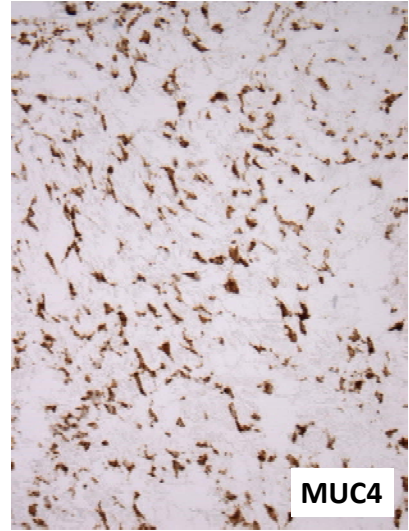
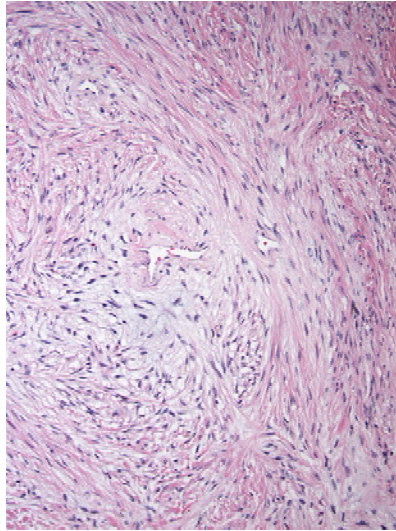
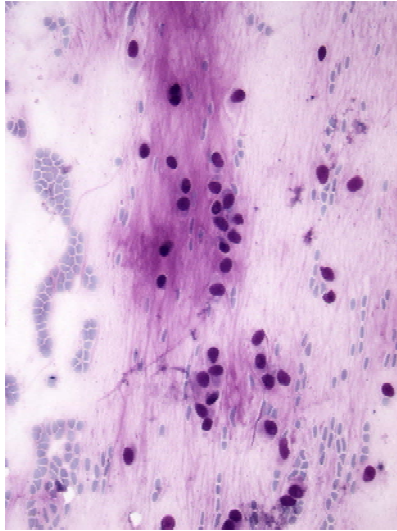


Low-Grade Fibromyxoid Sarcoma

- Appears deceptively bland
 - Often not recognized as a sarcoma on bx
 - Clinical correlation (young adult; hx of “benign tumor” decades ago)
- Abundant myxoid matrix
- Plump spindle cells ovoid-to-round nuclei with mild or no cytologic atypia
- No prominent vascular component



Low-Grade Fibromyxoid Sarcoma



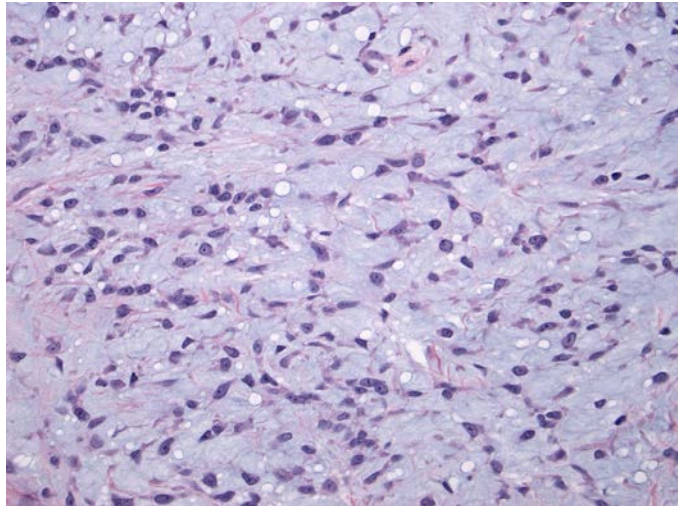
Myxoid Tumors: Cellular, Uniform Cell Population

- This group includes many translocation-associated sarcomas
- IHC and molecular testing is often necessary for diagnosis

Tumor Type	S-100	EMA	Keratin	Desmin	Other	FISH
Myxoid liposarcoma	-/+	-	-	-	DDIT3+	<i>DDIT3</i>
Extraskeletal myxoid chondrosarcoma	+ (20%)	-	-	-	INSM1+	<i>NR4A3</i>
Myoepithelial neoplasms of soft tissue	+	+	+	-	SOX10 (50-80%) p40 (60%)	<i>EWSR1</i>
Sclerosing epithelioid fibrosarcoma	-	-	-	-	MUC4+	<i>EWSR1</i>
Ossifying fibromyxoid tumor	Rare +	-	-	+ (50%)	Rare MUC4+	<i>PHF1</i>

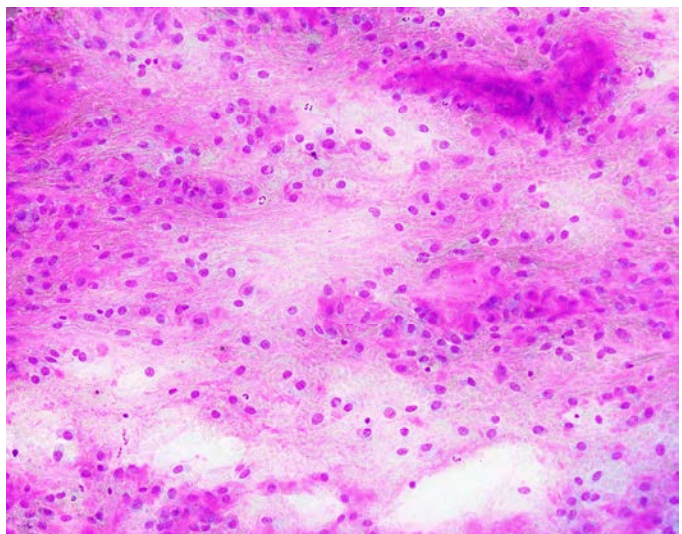
Extraskelatal Myxoid Chondrosarcoma

- NOT a true cartilaginous tumor
- M=F, middle age
- Deep soft tissue of limbs
- IHC features are nonspecific
 - 20% desmin +; INSM1 +
- *EWSR1::NR4A3*
 - *NR4A3* FISH is best diagnostic tool

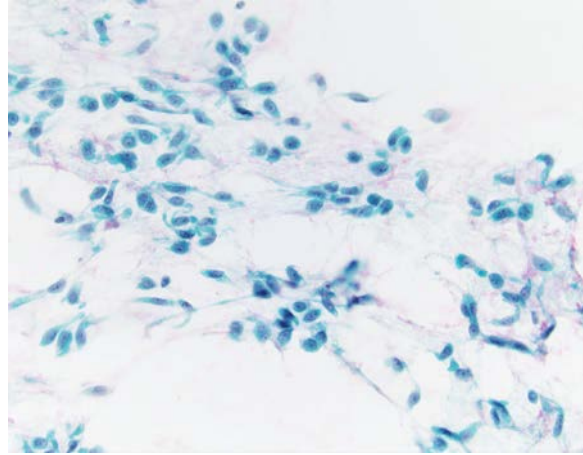
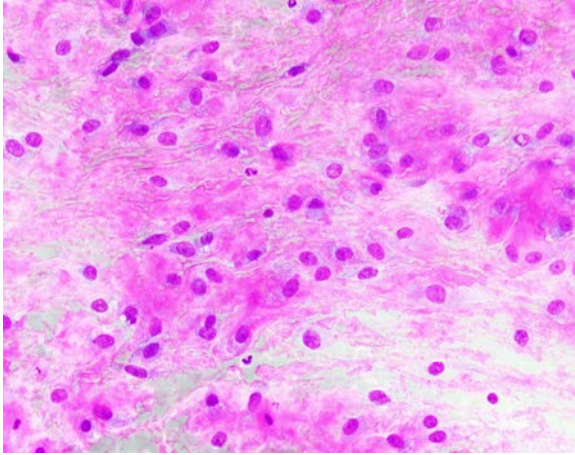


Extraskelatal Myxoid Chondrosarcoma

- Bright magenta fibrillary stroma
- Embedded bland, spindled-to-epithelioid cells
- Uniform round or oval nuclei
 - Small or inconspicuous nucleoli; nuclear grooves and clefts may be seen
- Cytoplasm varies: scant, wispy, tapered, abundant
- Can show interconnected, cordlike arrangements

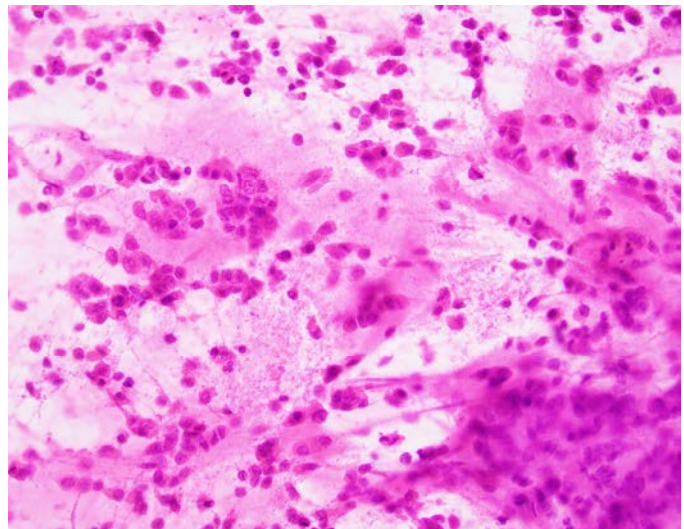


Extraskeletal Myxoid Chondrosarcoma

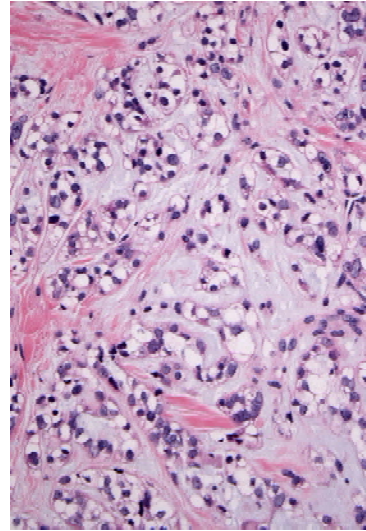
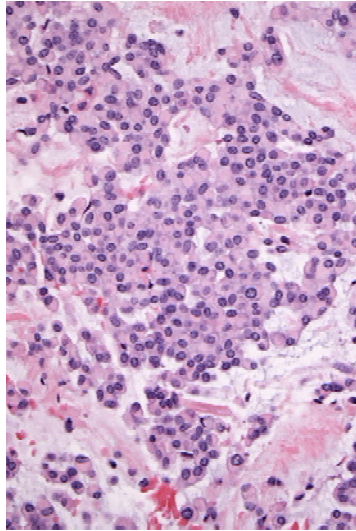
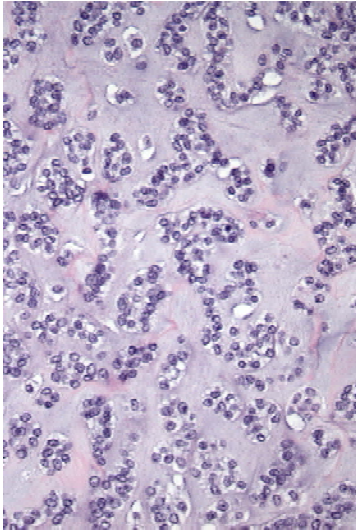


Myoepithelial Neoplasms of Soft Tissue

- Wide cytologic heterogeneity
 - Spindled, epithelioid, clear cell, round cell
- Clustered, reticular, single arrangements of cells within chondromyxoid stroma
- Immunophenotype also variable
 - Most are positive for keratin/EMA and S-100/GFAP
 - SOX10 and p40 often positive
- *EWSR1* fusions (multiple partners)
- Distinction between benign (myoepithelioma) and malignant (myoepithelial carcinoma) deferred to histology in most cases



Myoepithelial Neoplasms of Soft Tissue

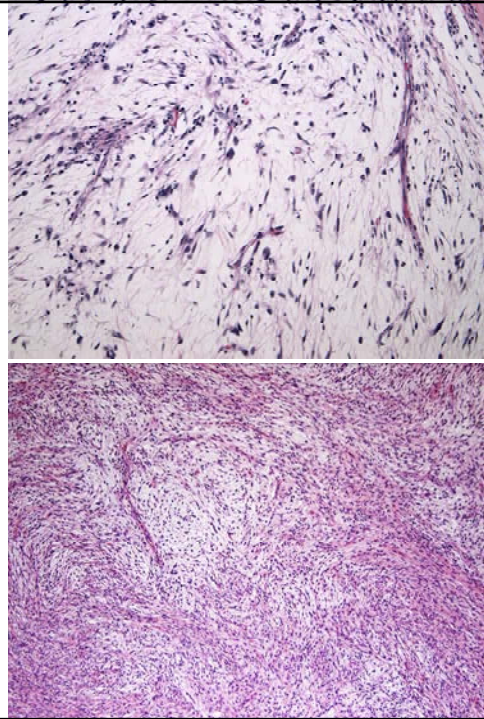


Myxoid Pleomorphic Tumors

- Myxofibrosarcoma
- Pleomorphic liposarcoma (ST Part 1)
- Dedifferentiated liposarcoma (ST Part 1)
- Undifferentiated pleomorphic sarcoma → Pleomorphic DDX

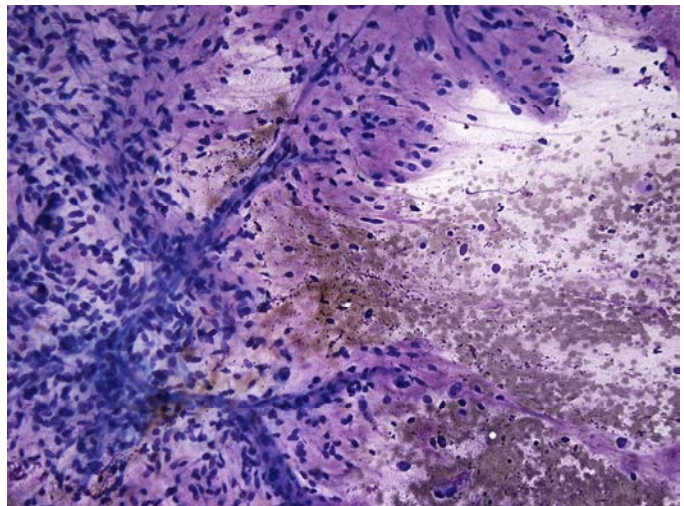
Myxofibrosarcoma

- Common sarcoma in elderly patients
- Slight M>F
- Limbs, dermal/subcutaneous or deep
- Grade is prognostic, based on cellularity (typically defer to resection)
- No specific IHC phenotype, complex genetics

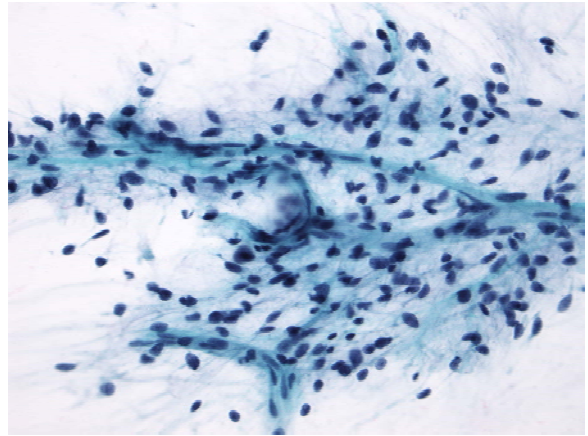
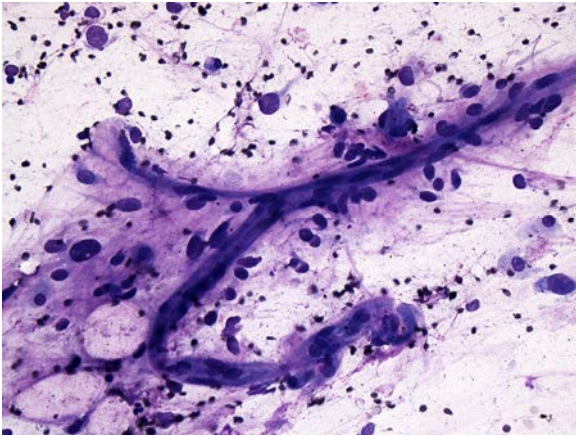


Myxofibrosarcoma

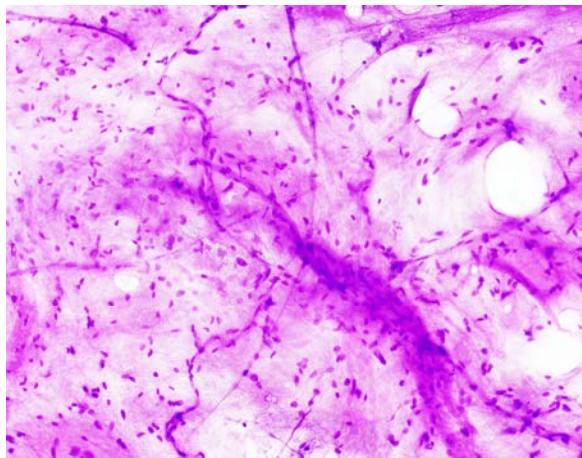
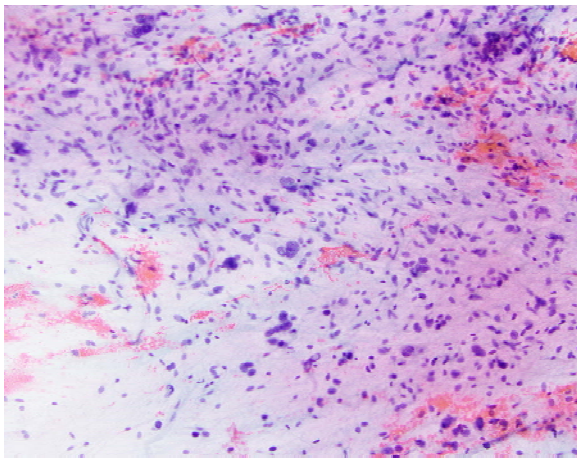
- Curvilinear vessels
- Atypia may be mild in low-grade tumors
- High grade tumors: increased cellularity, atypia, necrosis
- Pseudolipoblasts (tumor cells with mucin in cytoplasm)
- Pleomorphic spindle or epithelioid cells
 - May be indistinguishable from pleomorphic liposarcoma and unclassified pleomorphic sarcoma

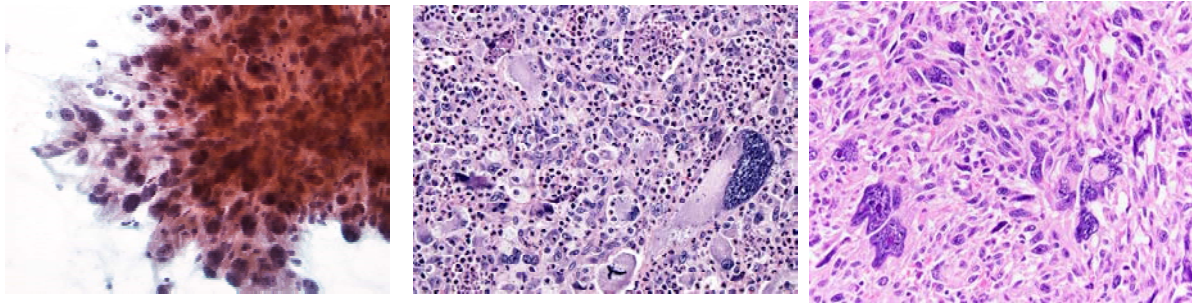


Myxofibrosarcoma



Dedifferentiated Liposarcoma (ST Pt 1)





PLEOMORPHIC TUMORS

Pleomorphic Soft Tissue Tumors

- Aggressive sarcomas in older adults; most have indistinct immunophenotypes and complex genetics
- These can be difficult to distinguish from one another on morphologic grounds
 - Highly cellular smears
 - Pleomorphic and anaplastic cells in groups and singly dispersed
 - Multinucleated giant tumor cells
 - Numerous mitoses, including atypical forms
 - Necrosis
- IHC is helpful for some entities, but most useful in excluding carcinoma and other non-mesenchymal malignancies

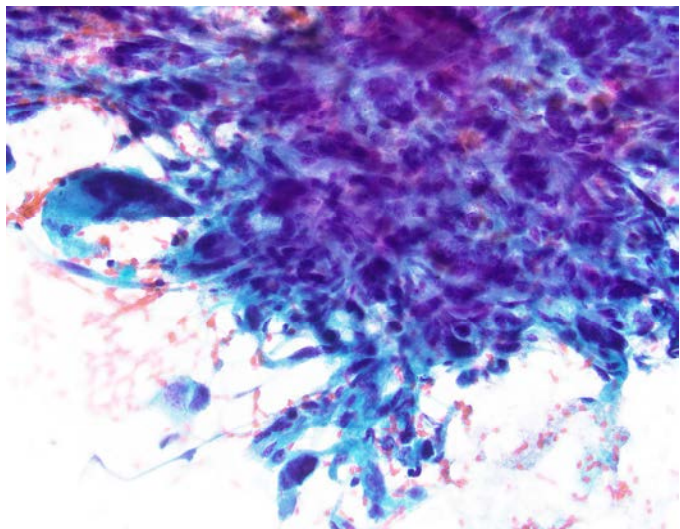
Pleomorphic Soft Tissue Tumors: DDX

Tumor Type	Metastatic Rate	IHC
Dedifferentiated liposarcoma	15-20%	MDM2, CDK4
Myxofibrosarcoma	25-30%	-
Pleomorphic liposarcoma	50%	-
Undifferentiated pleomorphic sarcoma	50%	-
Extraskeletal osteosarcoma	60%	SATB2
Pleomorphic leiomyosarcoma	70%	SMA, Desmin, Caldesmon
Pleomorphic rhabdomyosarcoma	90%	Desmin, Myogenin, MyoD1

Adapted from Hornick JL. Ann Diagn Pathol. 2018;37:118-124.

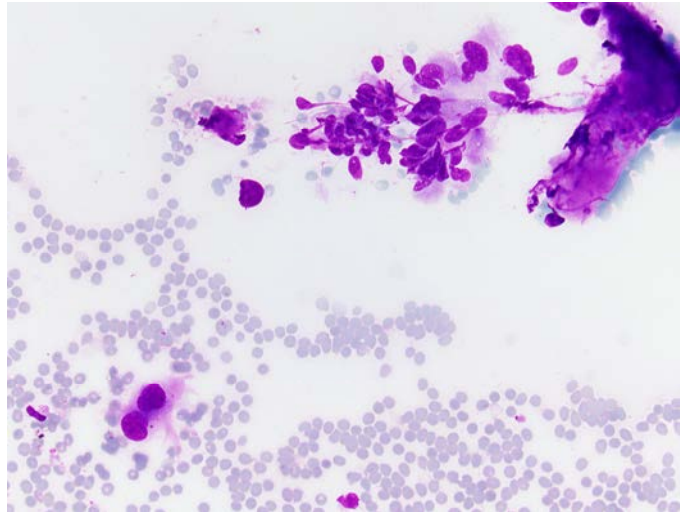
Dedifferentiated Liposarcoma (ST Pt 1)

- Clinical correlations:
retroperitoneal location, WDLPS component on imaging or FNA
- *MDM2* amplification is diagnostic
 - MDM2 IHC may be positive in other sarcomas, such as myxofibrosarcoma and MPNST
 - Also a feature of intimal sarcoma

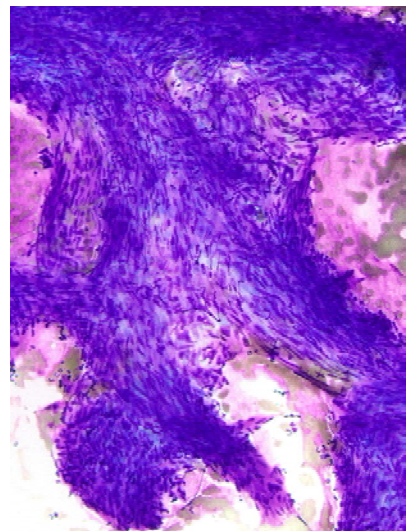
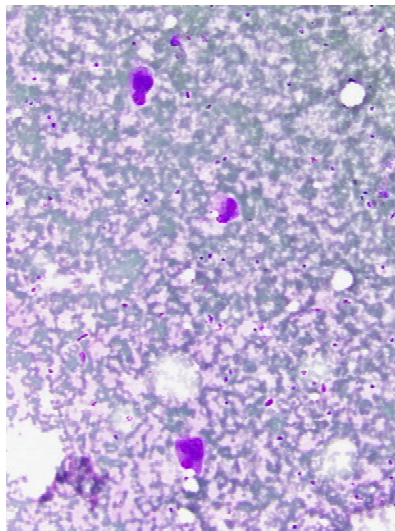
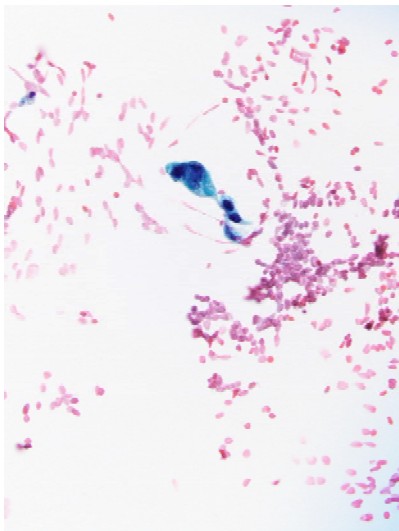


Pleomorphic Leiomyosarcoma

- Arises in deep soft tissues of extremities and retroperitoneum
 - Often in association with a large vessel
- Pleomorphic cells often singly dispersed and bi-/multinucleated
- Characteristic fascicular fragments of leiomyosarcoma helpful if present
- IHC identifies smooth muscle differentiation: SMA, desmin, caldesmon

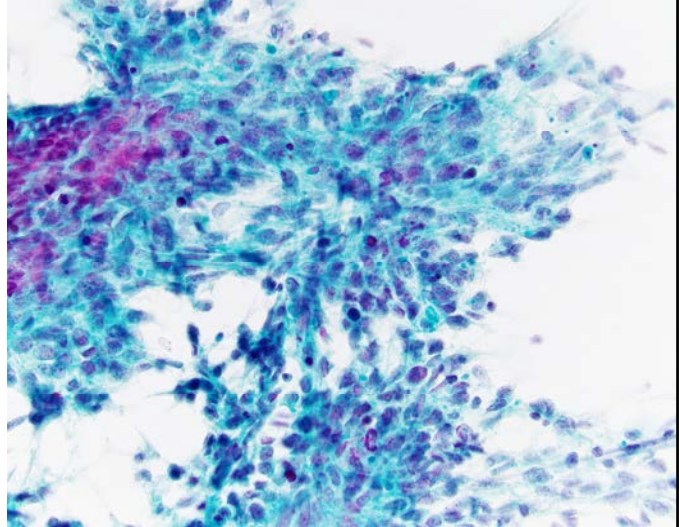


Pleomorphic Leiomyosarcoma

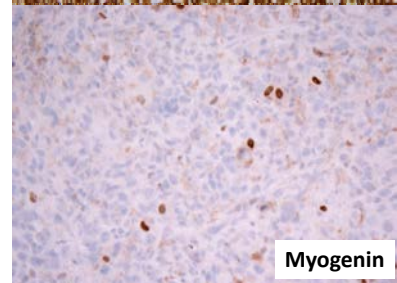
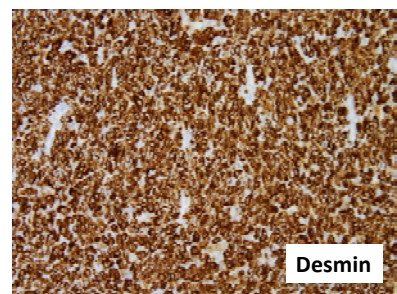
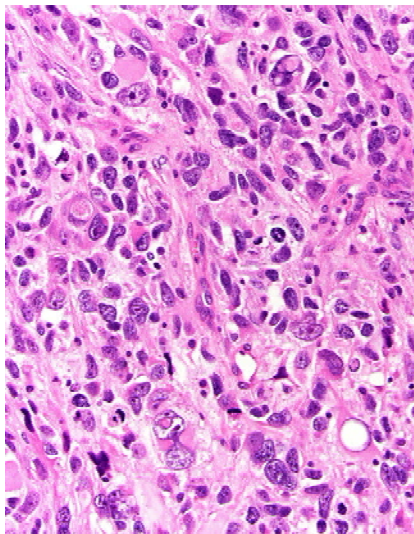
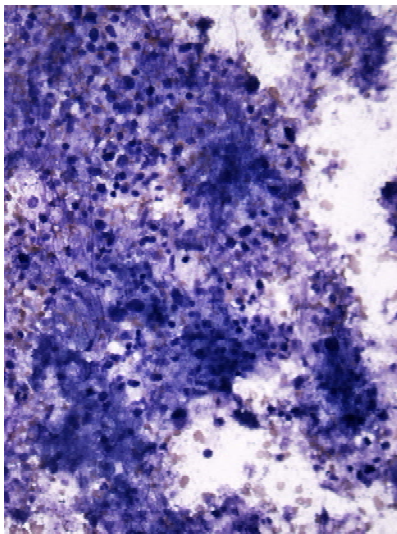


Pleomorphic Rhabdomyosarcoma

- Deep soft tissue sites most common
- Aggressive: rapid growth, frequent metastases, and median survival <8 months
- Frequent binucleation and multinucleation
- Necrosis, high mitotic activity
- May see rhabdoid forms
- IHC identifies skeletal muscle differentiation
 - Very strong desmin staining
 - Myogenin and MyoD1 multifocal

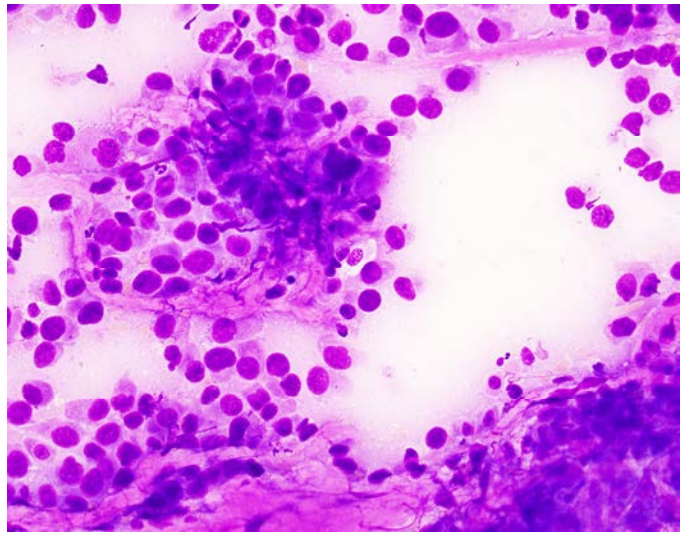


Pleomorphic Rhabdomyosarcoma



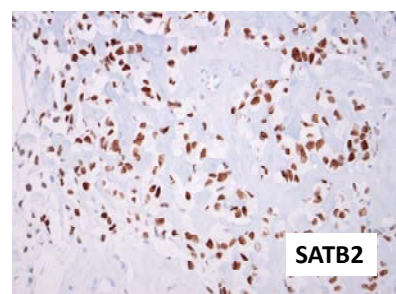
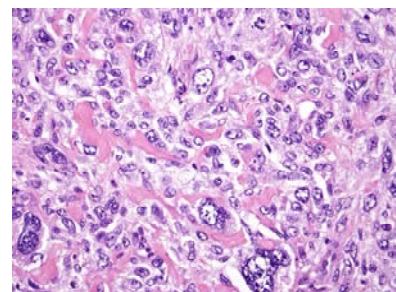
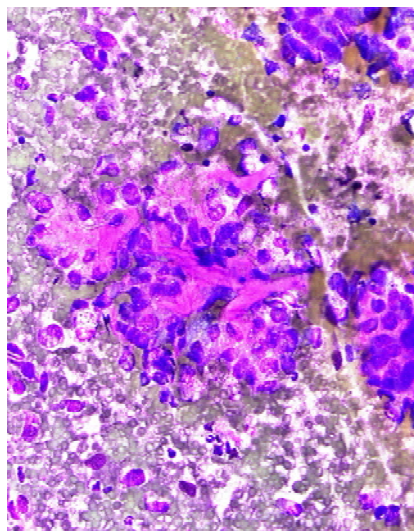
Extraskkeletal Osteosarcoma

- Very rare; 10% report prior history of trauma or radiation
- Older adults
- Typically arise in proximal extremities, most deep-seated
- Broad morphologic spectrum, most high-grade and pleomorphic
 - Osteoblastic is most common
- Clinical correlation to exclude heterologous osseous differentiation in other entities



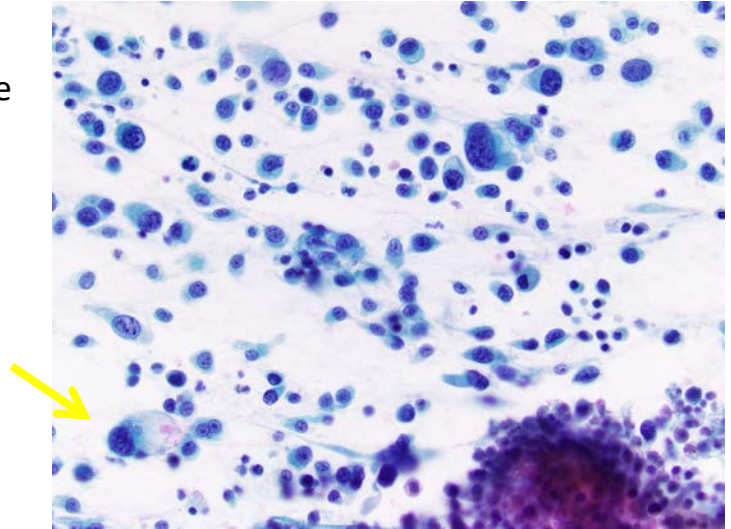
Extraskkeletal Osteosarcoma

- Diagnostic criterion is osteoid matrix deposition
 - Homogeneous dense or glassy texture, fibrillary or strand-like, sharp borders
- SATB2 is a marker of osteoblastic differentiation
 - But positivity does not distinguish malignant from benign
 - Can see SATB2 in other pleomorphic sarcomas (usually focal)

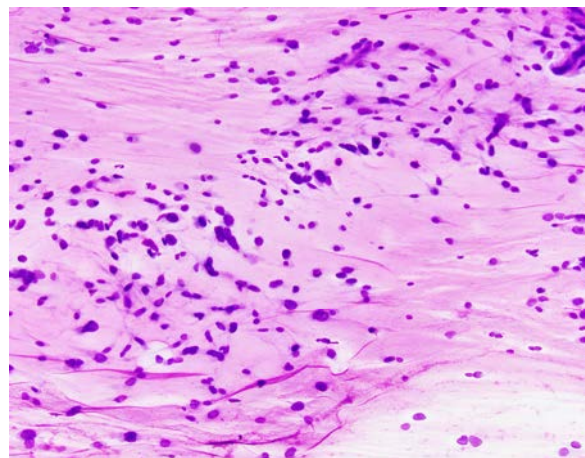
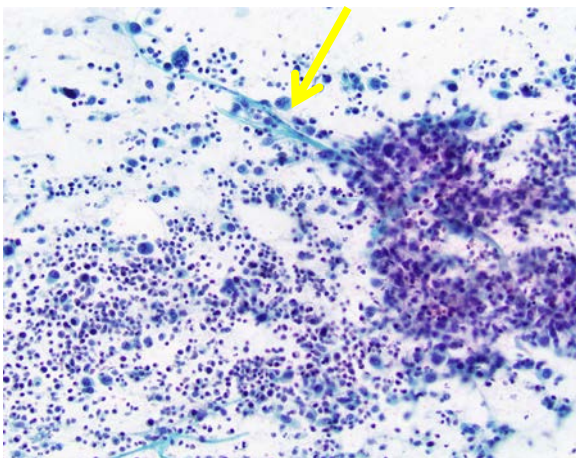


Myxofibrosarcoma

- Key features (myxoid stroma and curvilinear vessels) may be focal or not sampled on FNA
- Pseudolipoblasts may be mistaken for adipocytic differentiation

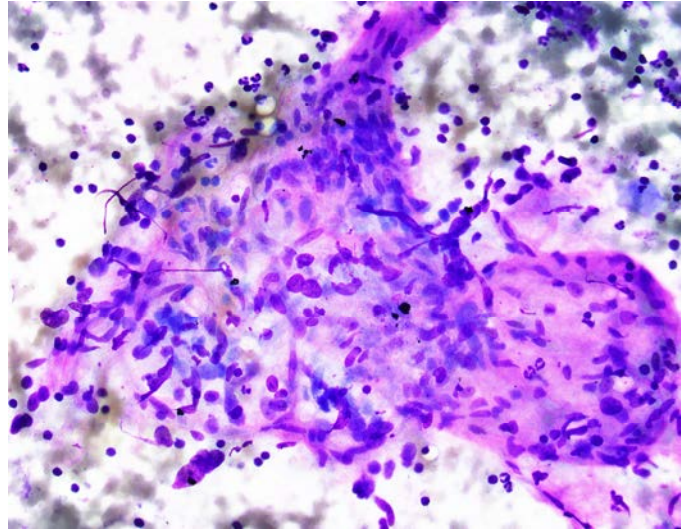


Myxofibrosarcoma

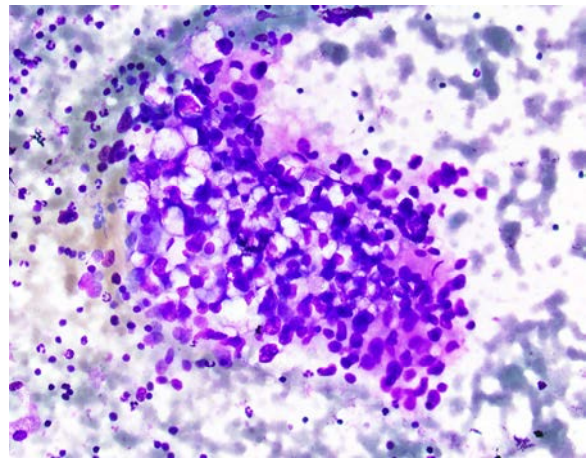
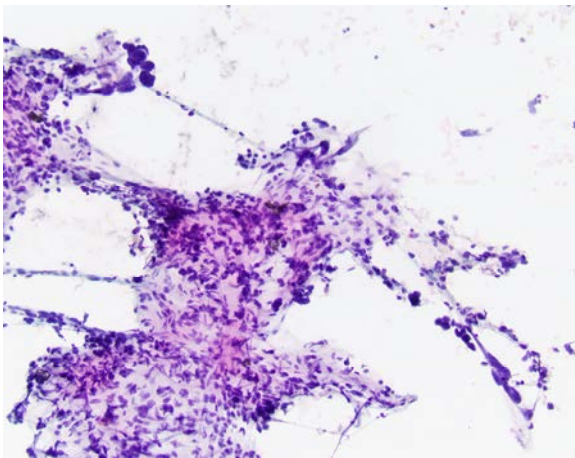


Pleomorphic Liposarcoma (ST Part 1)

- Diagnostic lipoblasts may not be sampled on FNA
- Can show myxoid stroma and curvilinear vessels

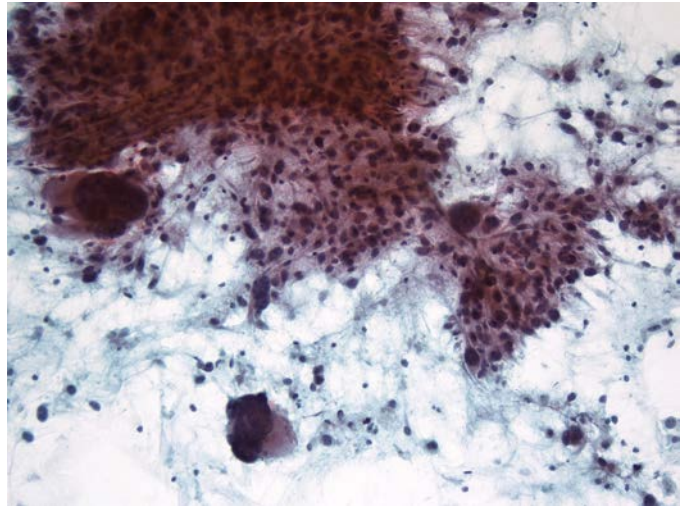


Pleomorphic Liposarcoma (ST Part 1)

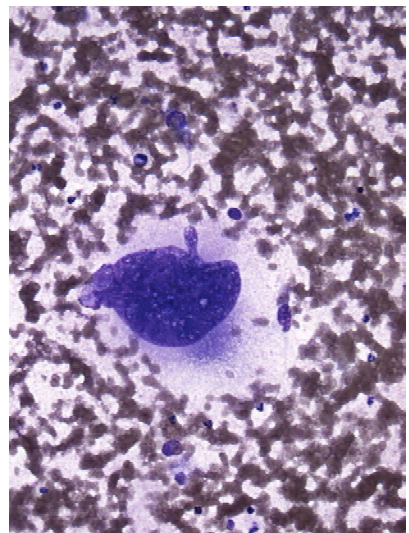
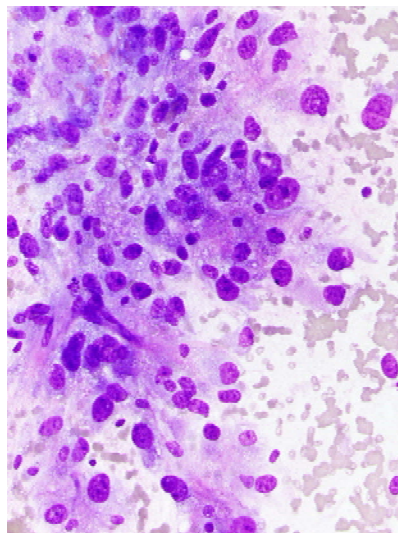
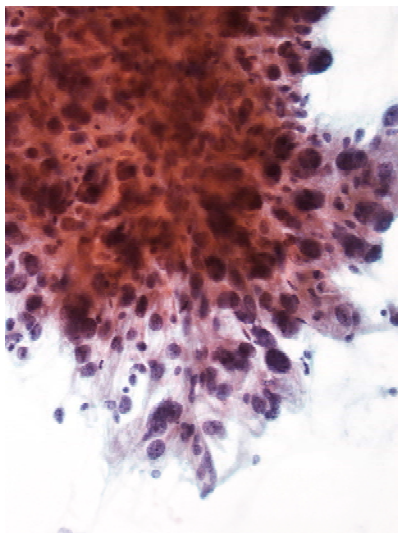


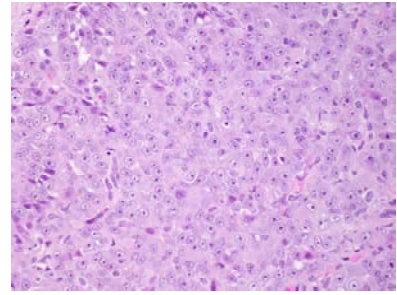
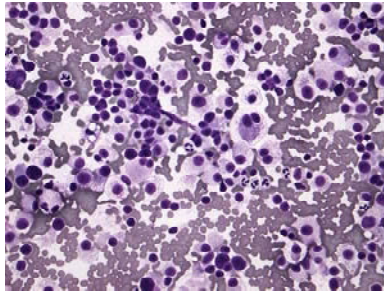
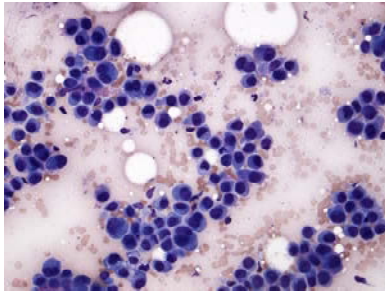
Undifferentiated Pleomorphic Sarcoma

- Formerly known as ~~malignant fibrous histiocytoma (MFH)~~
- Diagnosis of exclusion
 - Need to exclude all other entities and lines of differentiation by thorough examination and IHC
 - May not be possible on biopsy
- FNA diagnosis is usually descriptive: “High-grade pleomorphic sarcoma” with DDX



Undifferentiated Pleomorphic Sarcoma





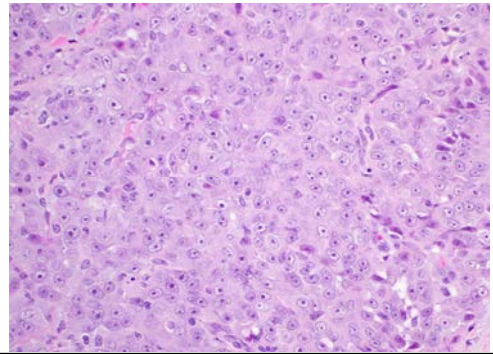
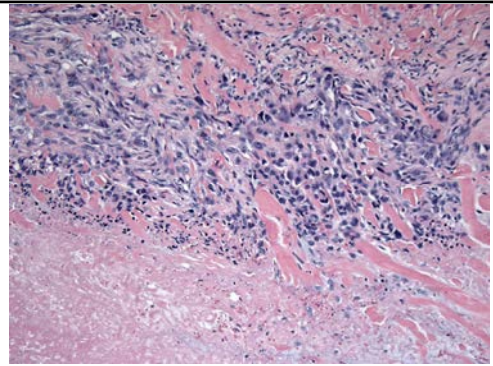
EPITHELIOID TUMORS

Epithelioid Soft Tissue Tumors

- Diverse group of tumors, most are malignant
 - Includes epithelioid variants of known tumors
- Resemble carcinoma or melanoma: round or polygonal tumor cells with moderate-to-ample amount of cytoplasm
- Require ancillary studies and inclusive panels
- Many soft tissue tumors show keratin/EMA expression
 - Some by definition (e.g. epithelioid sarcoma)
 - Aberrant expression can be seen in many entities (e.g. vascular tumors)

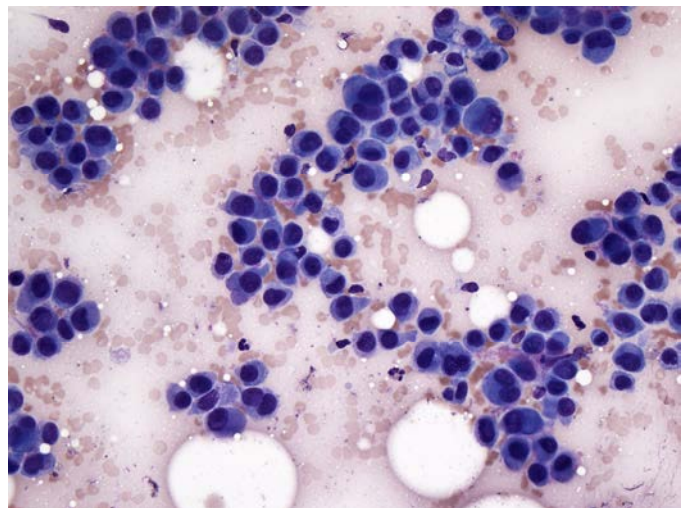
Epithelioid Sarcoma

- Distal-type epithelioid sarcoma
 - 10-40 years, distal extremities (upper > lower)
 - Epithelioid and spindle cells, pseudogranulomatous appearance
- Proximal-type epithelioid sarcoma
 - Older patients, pelvis, trunk, perineum, axilla
 - Sheet-like growth of epithelioid cells
- Frequent recurrence and metastasis, including to LN
- Inactivation of *SMARCB1* (ch 22q11)



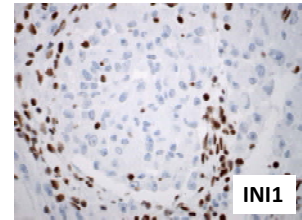
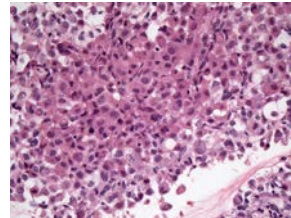
Epithelioid Sarcoma

- Smears (either subtype): singly dispersed round, polygonal, spindle cells
 - Tumor cells with eccentric nuclei with vesicular chromatin, small nucleoli; some binucleated
 - Dense cytoplasm, occasional small vacuoles
- Rhabdoid cells may be seen in proximal-type
- Necrosis may be present in distal-type



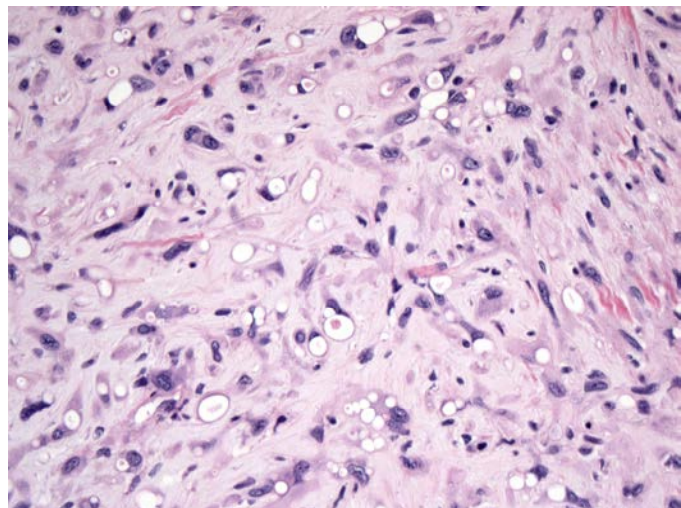
Epithelioid Sarcoma

- IHC: + EMA, cytokeratin, CD34 (50%)
- Subset are positive for ERG (40%) depending on antibody
 - Pitfall for epithelioid vascular tumors
- Loss of SMARCB1 (INI1) by IHC is a useful diagnostic surrogate
 - Not specific to epithelioid sarcoma (ddx includes malignant rhabdoid tumor, myoepithelial carcinoma of soft tissue)



Epithelioid Hemangioendothelioma

- Slight F>M, adults
- Anatomically ubiquitous, but extremities most common
 - 50% show origin from a large vessel
- Tumors can be multicentric (locoregional metastases)
- Many indolent, but 20-30% metastasize
- *WWTR1::CAMTA1* fusion
- *YAP1::TFE3* in 5-10% - voluminous eosinophilic cytoplasm, vasoformative
 - TFE3 IHC +

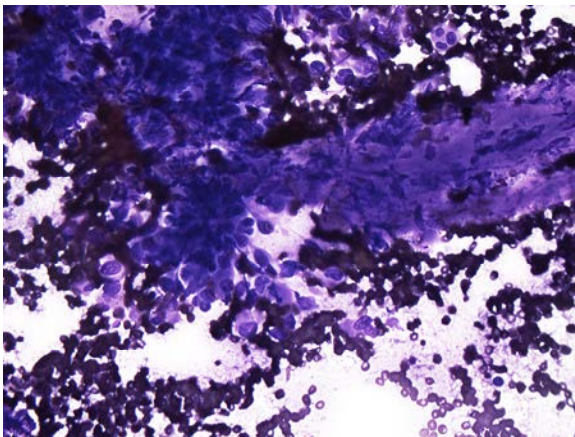


Epithelioid Hemangioendothelioma

- Singly dispersed round and polygonal epithelioid cells
- Eccentric nuclei, frequent binucleation
 - May see nuclear grooves, pseudoinclusions
 - 1-2 small nucleoli
- Dense cytoplasm, less defined borders
 - Single intracytoplasmic vacuole (more obvious on histologic sections)
- May see aggregates with myxoid or fibrous stroma

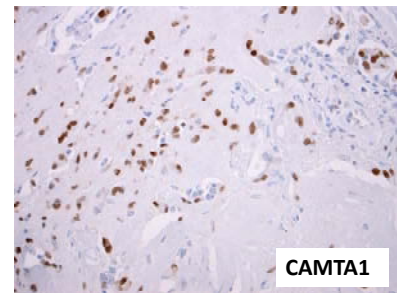
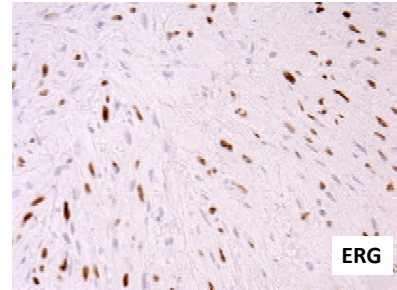


Epithelioid Hemangioendothelioma



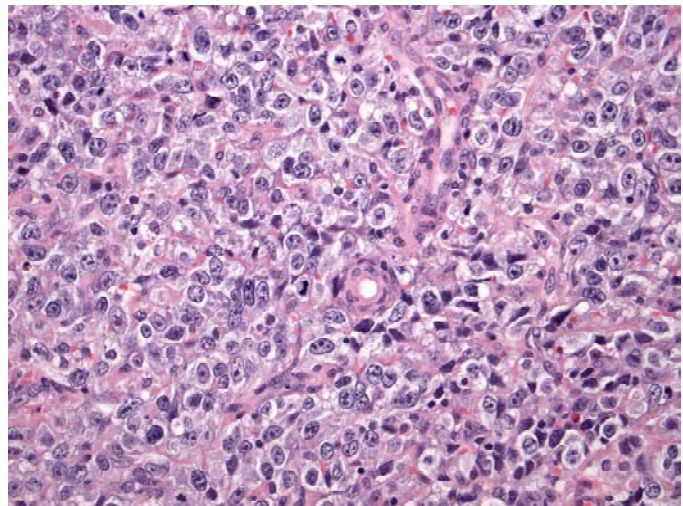
Epithelioid Hemangioendothelioma

- IHC: Positive for vascular endothelial markers CD31, CD34, ERG
- CAMTA1+ in all cases with *WWTR1::CAMTA1*
- 30% of EHE are positive for keratins
- Important to distinguish EHE from epithelioid angiosarcoma, which has far worse prognosis



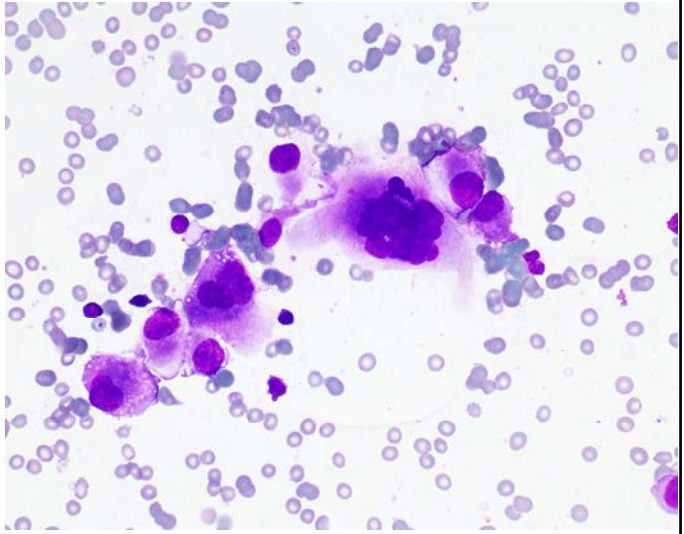
Epithelioid Angiosarcoma

- Aggressive: 50% mortality within 1 year of dx
- IHC: + CD31, CD34, ERG (most sensitive)
 - ~1/3 show keratin expression
 - Negative for CAMTA1
- Heterogeneous molecular features
 - MYC amplification in radiation-associated tumors (MYC IHC +)

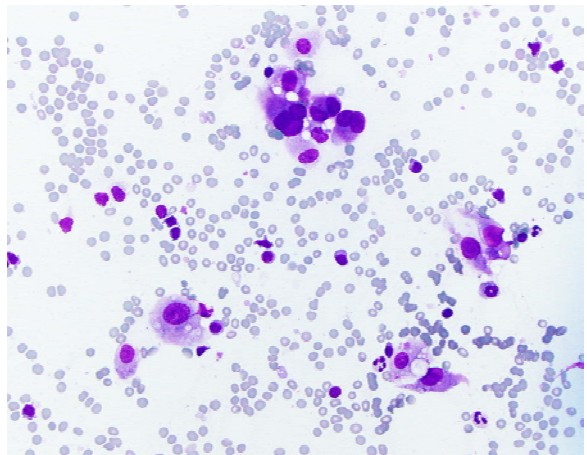
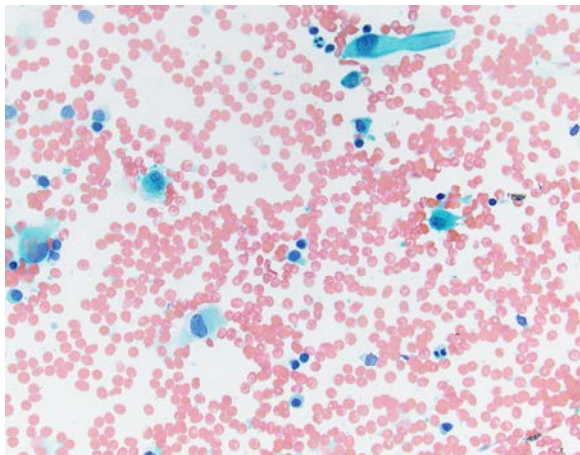


Epithelioid Angiosarcoma

- Dispersed atypical cells in a bloody background (may be hypocellular)
- Variably shaped – spindle and pleomorphic cells common
- Large nucleus with prominent nucleolus
 - Often binucleated or multinucleated
- Cytoplasm dense, frequent vacuoles or hemosiderin
- Pronounced pleomorphism and atypia
 - Greater than seen in EHE

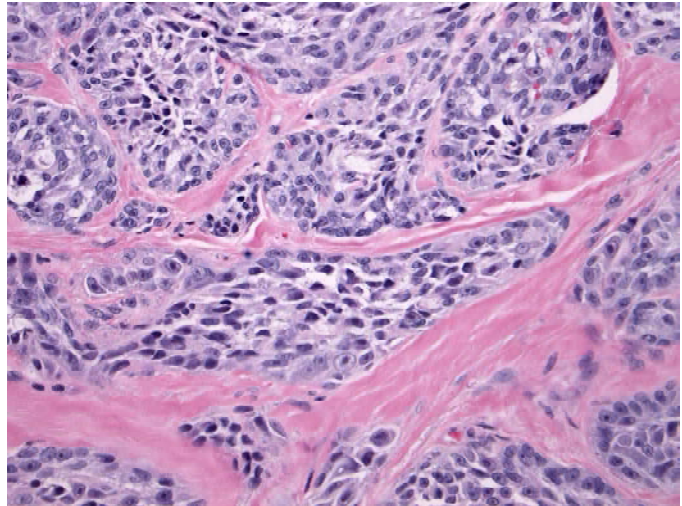


Epithelioid Angiosarcoma



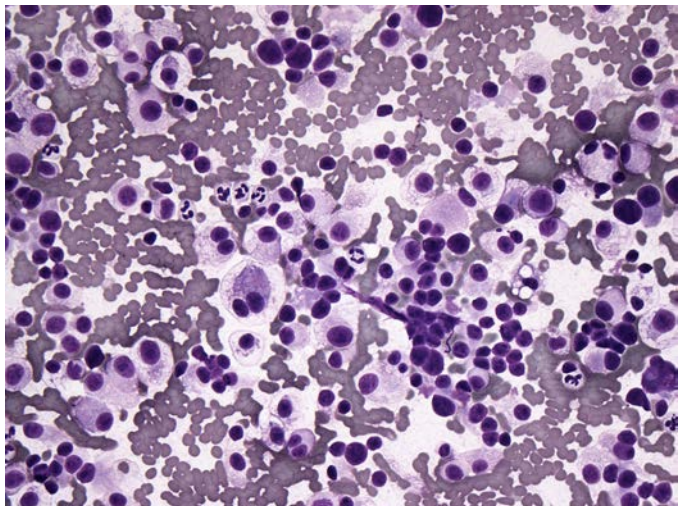
Clear Cell Sarcoma of Soft Parts

- Young adults (3rd-4th decades), M=F
- Frequent in the extremities
- *EWSR1::ATF1* fusion
- IHC: + S-100, SOX10, HMB-45, Melan A
- Must distinguish from malignant melanoma
 - *EWSR1* FISH may be necessary



Clear Cell Sarcoma of Soft Parts

- Cellular, singly dispersed, frequent binucleated cells
- Eccentric round nuclei and prominent nucleoli
 - Intranuclear pseudoinclusions common
- Abundant cytoplasm is palely eosinophilic or clear, well-defined borders
 - May be finely vacuolated
- Wreath-like giant cells helpful if present

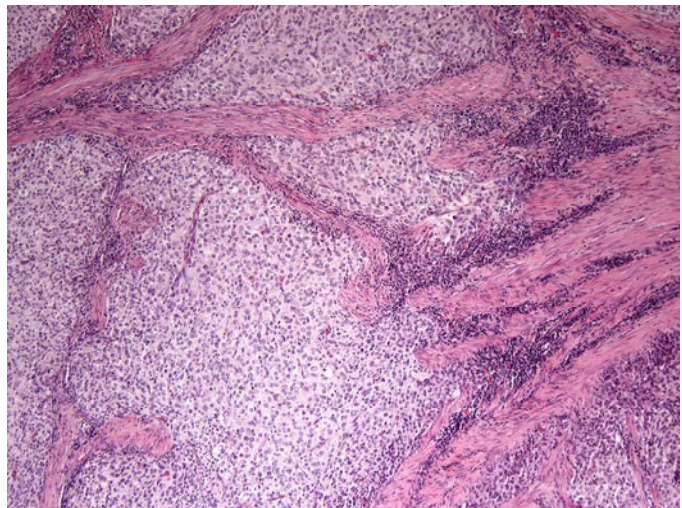


DDX of Epithelioid Soft Tissue Tumors

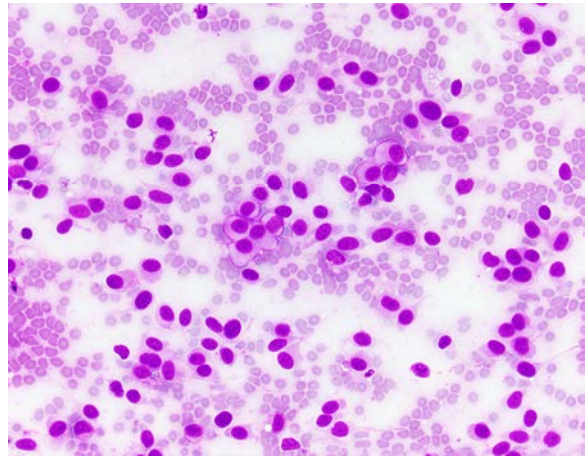
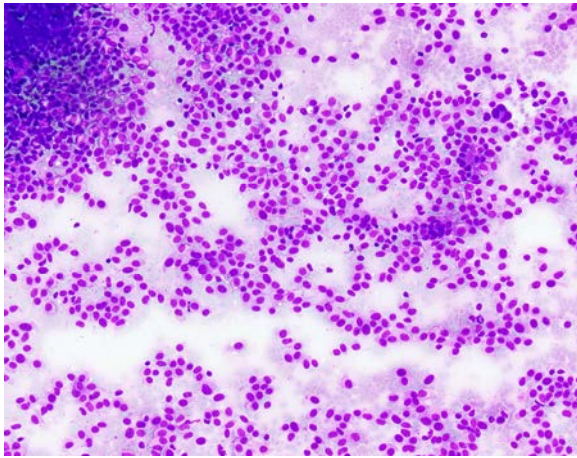
Tumor Type	IHC Features	Molecular/Genetic Features
Epithelioid sarcoma	Keratin, EMA, CD34, INI1 loss	<i>SMARCB1</i> alterations
Epithelioid hemangioendothelioma	ERG, CD31, CD34, CAMTA1 ± keratin	<i>WWTR1::CAMTA1</i>
Epithelioid angiosarcoma	ERG, CD31, CD34 ± keratin	Heterogeneous
Clear cell sarcoma of soft tissue	S-100, HMB-45, Mart1	<i>EWSR1::ATF1</i>

SDH-Deficient Gastrointestinal Stromal Tumor

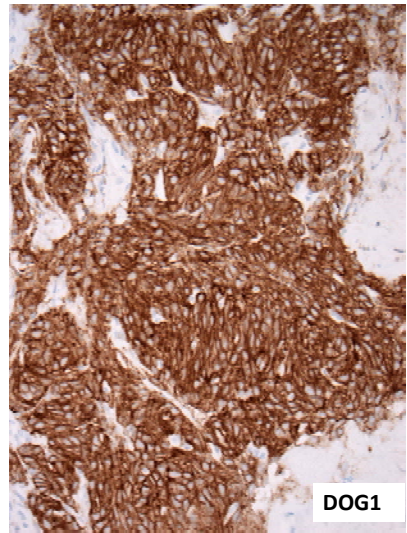
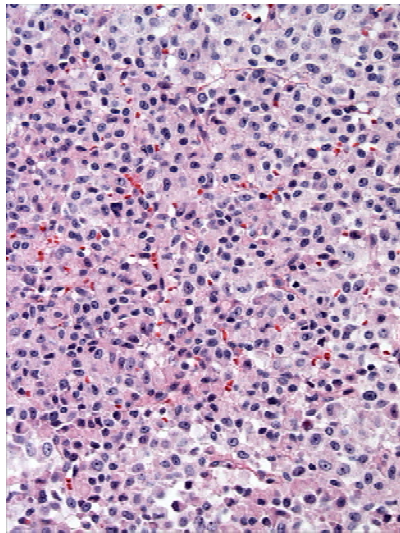
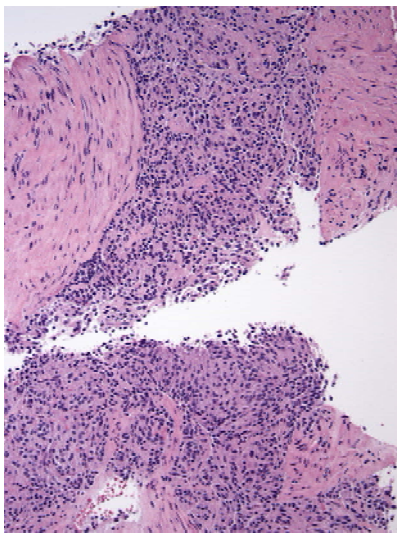
- ~5-10% of *KIT* wild-type gastric GISTs
 - Still positive for KIT and DOG1 IHC
- Arise in stomach, multinodular growth through muscularis propria
- Young patients (including children), F>M
 - Carney triad (GIST, pulmonary chondroma, paraganglioma)
 - Carney-Stratakis syndrome (GIST & paraganglioma) - AD



SDH-Deficient Gastrointestinal Stromal Tumor

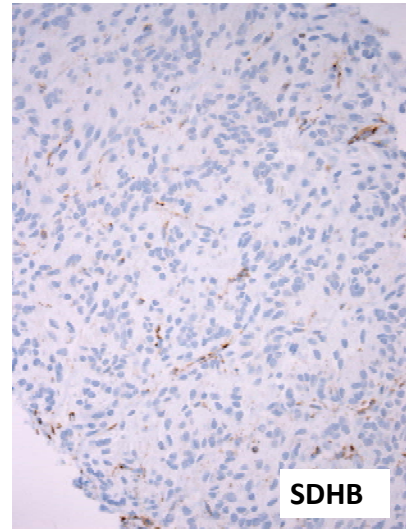


SDH-Deficient Gastrointestinal Stromal Tumor



SDH-Deficient Gastrointestinal Stromal Tumor

- SDHB loss of expression is diagnostic; occurs secondary to any mechanism of SDH deficiency
 - Mutation of any of the 4 SDH subunit genes (*SDHA*, *SDHB*, *SDHC*, or *SDHD*)
 - Epigenetic mechanisms
- *SDHA* IHC loss highly correlated with *SDHA* mutation
- Important clinical implications of diagnosis
 - Patients are referred for genetic counseling
 - Limited response to imatinib
 - Protracted clinical course and difficult to predict behavior
 - Frequent metastases to lymph nodes, liver, and peritoneum



Summary

- A pattern-based approach is practical for ST FNA, allowing refinement of differential diagnoses and judicious application of ancillary testing
- Many soft tissue entities have characteristic morphologic features and specific immunophenotypes and molecular hallmarks
- There are many reliable diagnostic markers that facilitate accurate diagnosis
 - Important to triage material for ancillary testing (cell block recommended)
- IHC and molecular test selection and interpretation should be in the context of clinical and morphologic features