Mass General Brigham

Cytopathology of Soft Tissue Tumors, part 1

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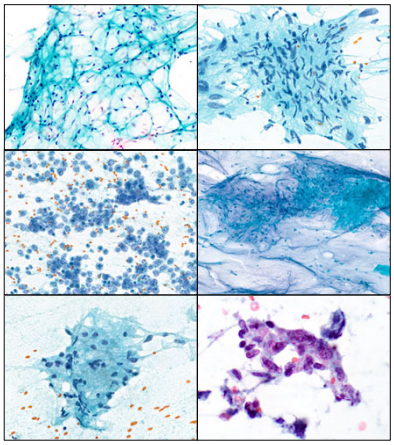
No Disclosures

Morphologic Approach to Soft Tissue Tumors

1. Adipocytic
2. Spindle cell
3. Round cell
4. Myxoid
5. Epithelioid
6. Pleomorphic



Immunohistochemistry for Tissue Differentiation

Line of Differentiation	Immunohistochemical Markers
Epithelial	Keratin, EMA
Smooth Muscle	Smooth muscle actin (SMA), desmin, caldesmon, calponin
Skeletal Muscle	Desmin, muscle-specific actin, myogenin (myf4), MyoD1
Endothelial	CD34, CD31, ERG
Fibroblastic/Myofibroblastic	CD34, SMA, Desmin
Myoepithelial	Keratin, EMA, S-100, GFAP, p63 (40%)
Neural crest	S-100, GFAP, SOX10
Perineurial	EMA, CD34, Claudin-1
Osteoblastic	SATB2
Melanocytic	S-100, SOX10, Mart-1, HMB-45, MiTF
Histiocytic	CD68, CD163, PU.1

Immunohistochemical Surrogates for Molecular Alterations

Alteration Type	IHC Marker	Tumor Type	Staining Pattern
Gene inactivation	SMARCB1/INI1	- Epithelioid sarcoma, extrarenal rhabdoid tumour	Loss of nuclear expression
		- Poorly differentiated chordoma	
		- Epithelioid MPNST	
		- Epithelioid schwannoma	
		- Myoepithelial tumour (subset)	
	RB1	- Spindle cell lipoma/pleomorphic lipoma	Nuclear loss of expression
		- Myofibroblastoma	
		- Cellular angiofibroma	
		- Atypical spindle cell/pleomorphic lipomatous tumour	
	SDHB	- SDH-Deficient GIST	Loss of cytoplasmic staining
		- Paraganglioma	
	PRKAR1A	- Malignant melanotic nerve sheath tumour	Cytoplasm
Amplification leading to overexpression	MDM2	- Atypical lipomatous tumour/well-differentiation liposarcoma	Nuclear
		- Dedifferentiated liposarcoma	
		- Intimal sarcoma	
	CDK4	- Atypical lipomatous tumour/well-differentiation liposarcoma	Nuclear
		- Dedifferentiated liposarcoma	
		- Intimal sarcoma	
	MYC	- Radiation and lymphedema-associated angiosarcoma	Nuclear
Activating Mutations leading to overexpression	PDGFRA	- GIST	Membranous, Cytoplasm
		- Inflammatory fibroid polyp	
	B-catenin	- Desmoid fibromatosis	Nuclear

Immunohistochemical Surrogates for Molecular Alterations

Gene Fusion leading to overexpression	Pan-TRK	- NTRK-rearranged spindle cell neoplasm	Cytoplasm, Nuclear
		- Infantile fibrosarcoma	
		- Inflammatory myofibroblastic tumour (subset)	
	ALK	- Inflammatory myofibroblastic tumour (subset)	Cytoplasm
		- Epithelioid fibrous histiocytoma	
	ROS1	- Inflammatory myofibroblastic tumour	Cytoplasm
	STAT6	- Solitary fibrous tumour	Nuclear
	DDIT3	- Myxoid liposarcoma	Nuclear
	WT1 c-terminus	- Desmoplastic small round cell tumor	Nuclear
	FOSB	- Epithelioid haemangioma	Nuclear
		- Pseudomyogenic haemangioendothelioma	
	TFE3	- Alveolar soft part sarcoma	Nuclear
		- TFE3-associated epithelioid hemangioendothelioma	
		- PEComa (subset)	
	CAMTA1	- Epithelioid haemangioendothelioma	Nuclear
	YAP1 c-terminus	- TFE3-associated epithelioid hemangioendothelioma	Nuclear
	PLAG1	- Lipoblastoma	Nuclear
		- Myoepithelial neoplasms (mixed tumours) with PLAG1 rearrangements	
	HMGA2	- Lipoma (subset)	Nuclear
		- Atypical lipomatous tumor/well-differentiated liposarcoma	
		- Dedifferentiated liposarcoma	
		- Aggressive angiomyxoma	
	BCOR	- Sarcoma with BCOR genetic aberration	Nuclear
		- Primitive myxoid mesenchymal tumor of infancy	
		- Clear cell sarcoma of kidney	
	CCNB3	- Sarcoma with BCOR genetic aberration (subset)	Nuclear

Immunohistochemical Surrogates for Molecular Alterations

Translocation specific markers	SS18-SSX	- Synovial sarcoma	Nuclear
	SSX c-terminus	- Synovial sarcoma	Nuclear
	PAX3/7-FOXO1	- Alveolar rhabdomyosarcoma	
Mutation specific markers	BRAF V600E	- Glomus tumor (rare subset)	Cytoplasm
Epigenetic	Histone 3 K27 trimethylation (H3K27me3)	- MPNST	Nuclear loss of expression
Overexpression	NKX2.2	- Ewing sarcoma	Nuclear
	NKX3.1	- Mesenchymal chondrosarcoma - EWSR1/FUS-NFATC2 sarcoma	Nuclear
	WT1 and ETV4	- CIC-rearranged sarcoma	Nuclear
	MUC4	- Low-grade fibromyxoid sarcoma/ sclerosing epithelioid fibrosarcoma	Cytoplasmic
	DOG1	Gastrointestinal stromal tumour	Cytoplasmic

Fusions in Soft Tissue Tumors

Angiomatoid fibrous histocytoma	EWSR1::CREB1 or EWSR1::ATF1
Alveolar rhabdomyosarcoma	PAX3::FOXO1 or a PAX7::FOXO1
Alveolar soft part sarcoma	ASPSCR1::TFE3
BCOR gene associated sarcoma	BCOR::CCNB3, BCOR-ITD
CIC-gene rearranged sarcomas	CIC::DUX4
Clear cell sarcoma	EWSR1::ATF1 or EWSR1::CREB1
Dermatofibrosarcoma protuberans	COL1A1::PDGFB
Desmoplastic small round cell tumour	EWSR1::WT1
Epithelioid hemangioma	fusions in the cFOS and FOSB genes
Epithelioid hemangioentothelioma	WWTR1::CAMTA1 or YAP1::TFE3
Ewing sarcoma	Fusions of the EWSR1 gene and a member of the ETS family of transcription factors (mostely FLI1, rare ERG gene)
Extraskeletal myxoid chondrosarcoma	NR4A3::EWSR1 or NR4A3::TAF15
Infantile fibrosarcoma	ETV6-NTRK3
Inflammatory myofibroblastic tumour	ALK1 gene rearagement with various partners (TPM3, TPM4, CLTC, CARS, ATIC, SEC31L1, PPFIBP1, DCTN1, EML4, PRKAR1A, LMNA, TFG, FN1, HNRNPA1)
Low grade fibromyxoid sarcoma	FUS::CREB3L2 or FUS::CREB3L1
Mesenchymal chondrosarcoma	HEY1::NCOA2
Myxoid liposarcoma	FUS::DDIT3 or rarely EWSR::-DDIT3
Nodular fasciitis	USP6::MYH9
PEComa	TFE3 gene fusions
Solitary fibrous tumor	NAB2::STAT6
Synovial sarcoma	SS18::SSX1/2/4
Tenosynovial giant cell tumour	CSF1 gene fusions

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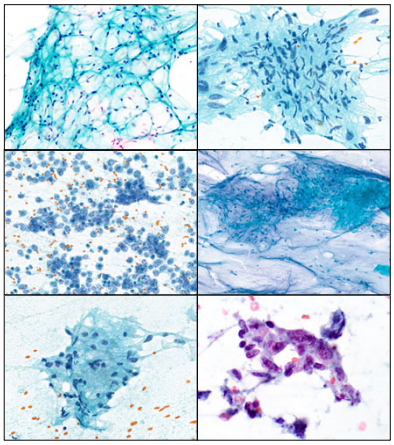
6. Pleomorphic



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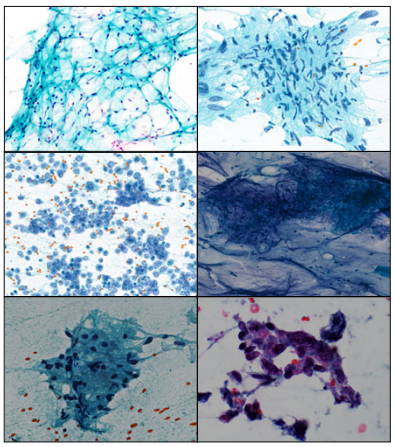
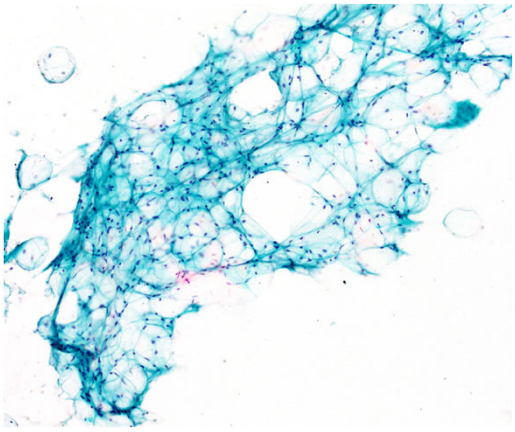


Adipocytic tumors

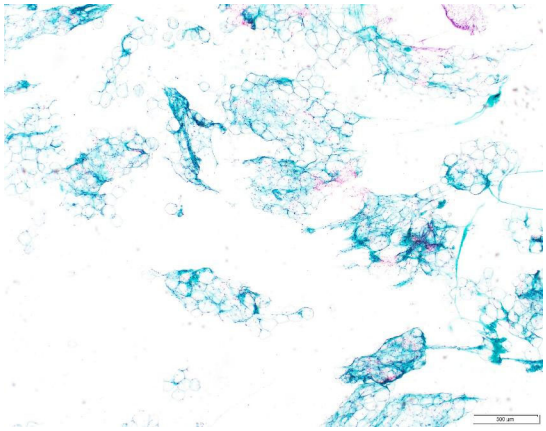
Adipocytic Soft Tissue Tumors

- Lipoma and variants
  - Lipoma
  - Spindle cell lipoma
  - Hibernoma
- Lipoblastoma
- Atypical lipomatous tumor/Well-differentiated liposarcoma
- Dedifferentiated liposarcoma
- Pleomorphic liposarcoma



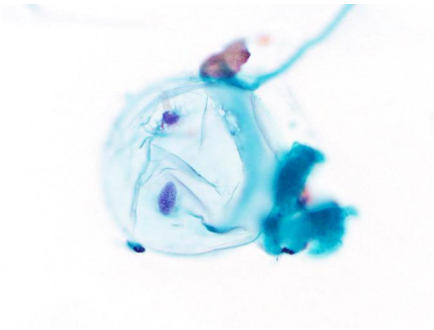
Lipoma

- Benign tumor composed of mature adipocytes
- Most common soft tissue tumor of adults
- Fragments of fatty tissue



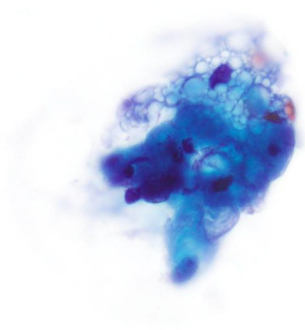
Lipoma

- Benign tumor composed of mature adipocytes
- Most common soft tissue tumor of adults
- Fragments of fatty tissue
- Single fat vacuole
- Small dark peripheral nucleus
- Intramuscular – fragments of striated muscle



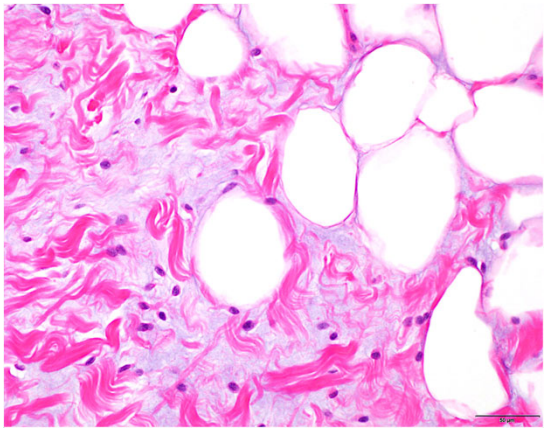
Lipoma

- DDx:
  - Subcutaneous tissue
  - Fat necrosis
  - Atypical lipomatous tumor
- IHC: not usually necessary
  - S100
  - MDM2-negative
- MP: not usually necessary
  - Chr12 (*HMGA2), chr6 (HMGA1*)



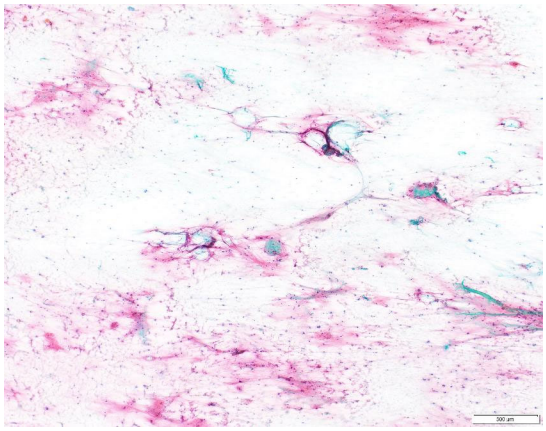
Spindle cell lipoma

- Benign adipocytic tumor composed of
  - variable adipocytes
  - bland spindle cells
  - ropy collagen



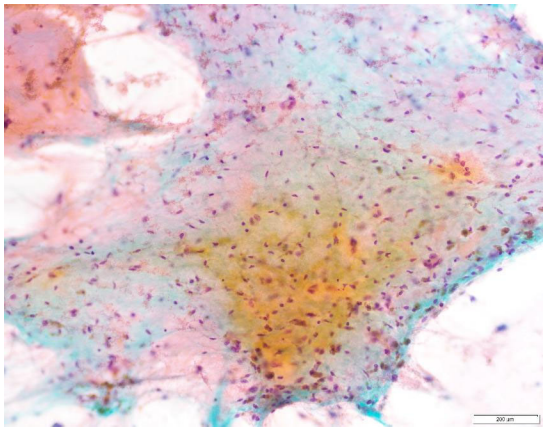
Spindle cell lipoma

- Subcutaneous tumors
- Posterior neck/back/shoulders



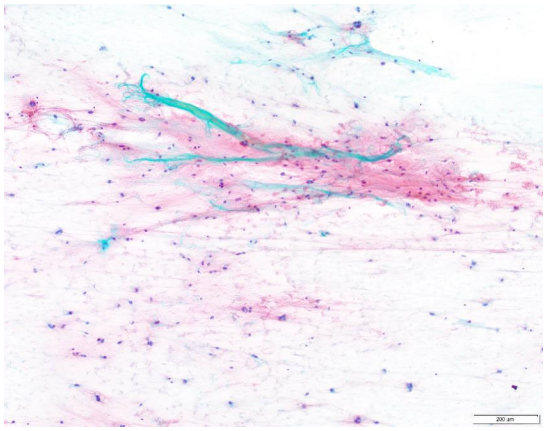
Spindle cell lipoma

- Subcutaneous tumors
- Posterior neck/back/shoulders
- Variable combinations of:
  - Mature adipose tissue
  - Bland spindle cells



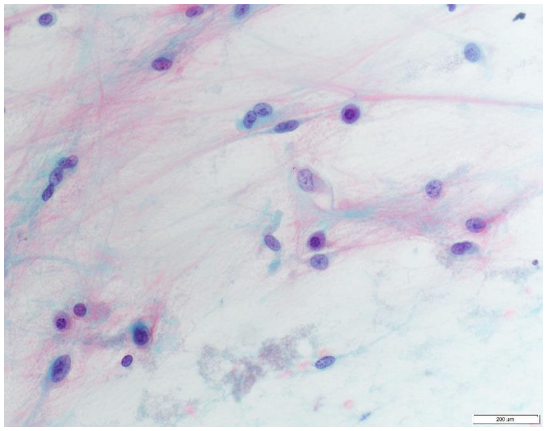
Spindle cell lipoma

- Subcutaneous tumors
- Posterior neck/back/shoulders
- Variable combinations of:
  - Mature adipose tissue
  - Bland spindle cells
  - Myxoid stroma
  - Collagen-hyaline fibers



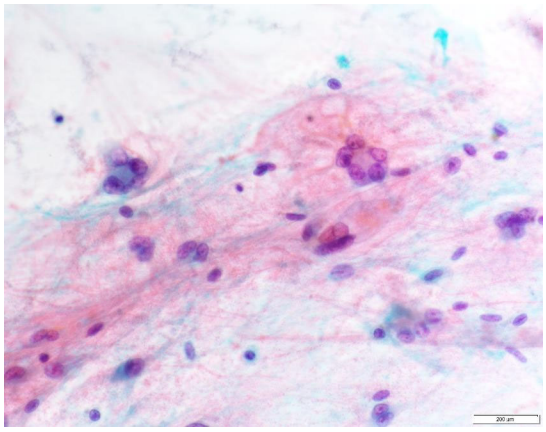
Spindle cell lipoma

- Subcutaneous tumors
- Posterior neck/back/shoulders
- Variable combinations of:
  - Mature adipose tissue
  - Bland spindle cells
  - Myxoid stroma
  - Collagen-hyaline fibers
  - Mast cells



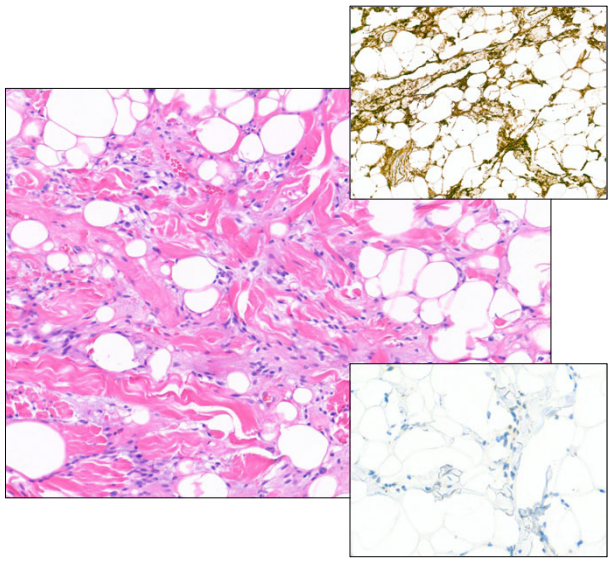
Spindle cell lipoma

- Subcutaneous tumors
- Posterior neck/back/shoulders
- Variable combinations of:
  - Mature adipose tissue
  - Bland spindle cells
  - Myxoid stroma
  - Collagen-hyaline fibers
  - Mast cells
  - Floret cells (pleomorphic lipoma)



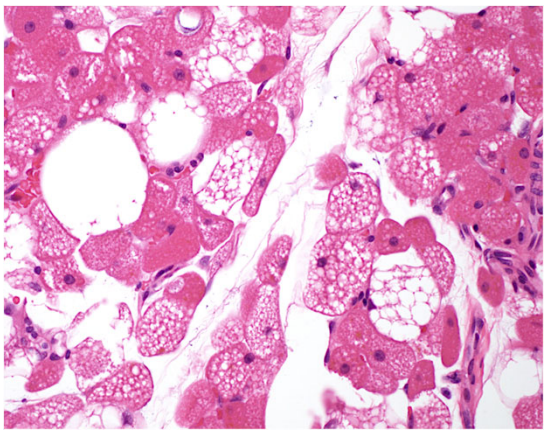
Spindle cell lipoma

- DDx:
  - myxoid neoplasm
  - atypical lipomatous tumor
- IHC:
  - S100
  - CD34
  - MDM2-retained
  - RB1-loss
- MP:
  - 13q deletion
  - RB1 loss



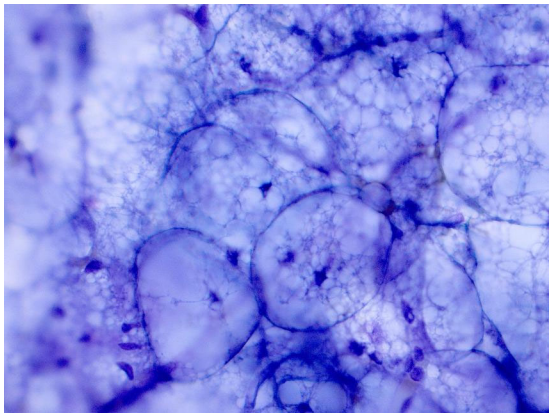
Hibernoma

- Benign adipocytic tumor showing brown fat differentiation.



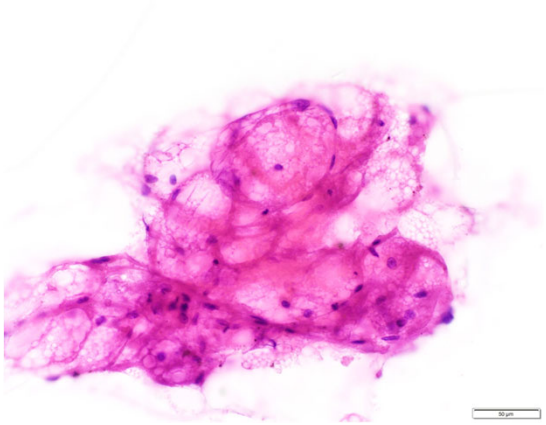
Hibernoma

- Subcutaneous neck, back, chest
- Intramuscular thigh, back



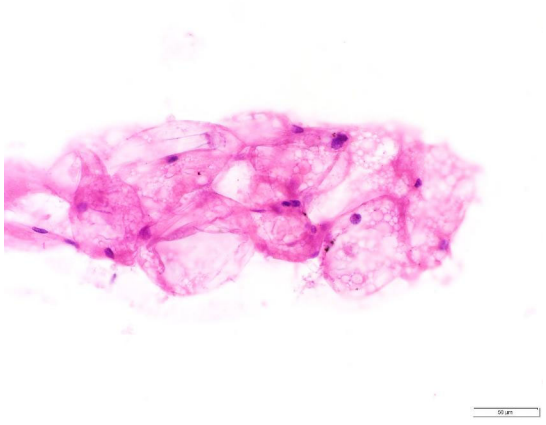
Hibernoma

- Subcutaneous neck, back, chest
- Intramuscular thigh, back
- Fragments of adipocytes with granular to multivacuolated ("hibernoma") cells
- Variable mature adipocytes
- Numerous capillaries



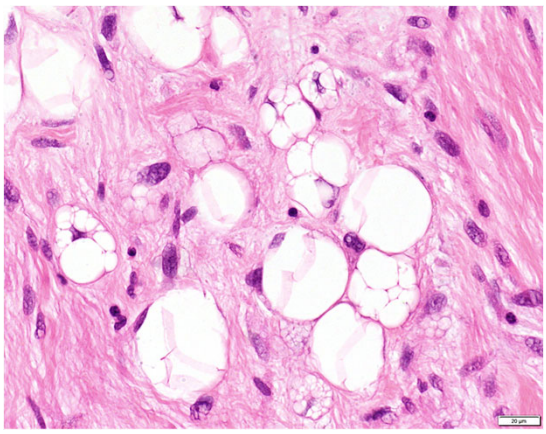
Hibernoma

- DDx:
  - Normal brown fat
  - Fat necrosis
  - Sebaceous glands
  - Granular cell tumor
  - Lipoblastoma
  - Adult-type rhabdomyoma
- IHC: not necessary (CD10)
- MP: not necessary (breakpoint/deletions chr11q)



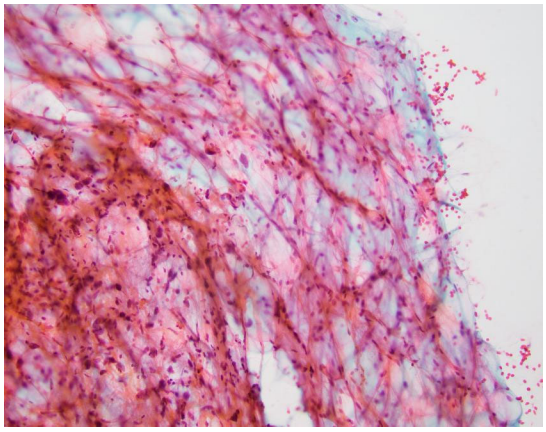
Atypical Lipomatous Tumor/Well-differentiated liposarcoma (ALT/WDLPS)

- Locally aggressive adipocytic neoplasm showing at least focal nuclear atypia in both adipocytes and stromal cells



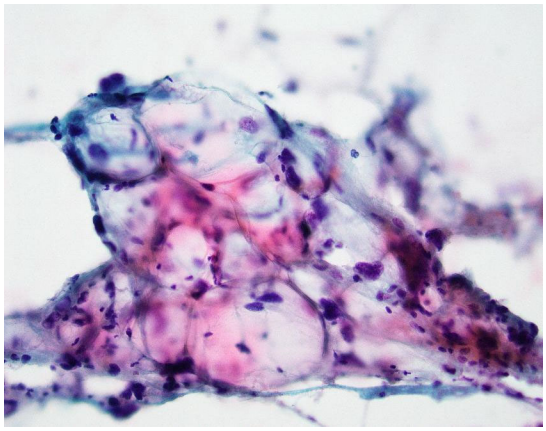
ALT/WDLPS

- Locally aggressive adipocytic neoplasm showing at least focal nuclear atypia in both adipocytes and stromal cells
- Variable mature-appearing adipocytes



ALT/WDLPS

- Locally aggressive adipocytic neoplasm showing at least focal nuclear atypia in both adipocytes and stromal cells
- Variable mature-appearing adipocytes
- Hyperchromatic, mono- or multinucleated stromal cells
- Lipoblasts (multiple cytoplasmic vacuoles, scalloped nuclei) are rare



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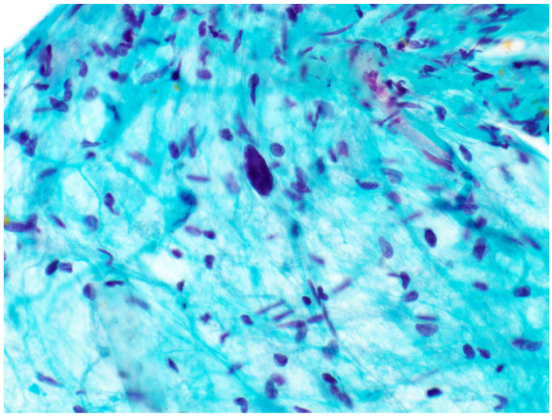
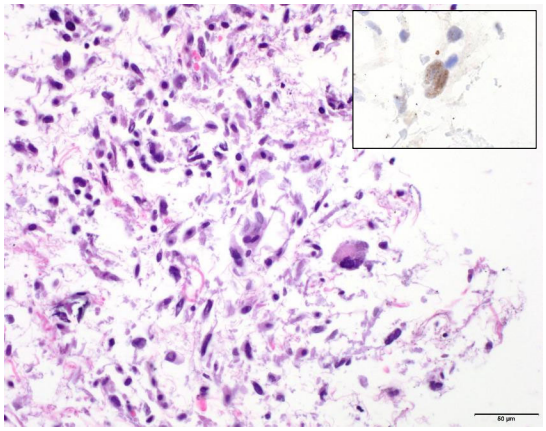


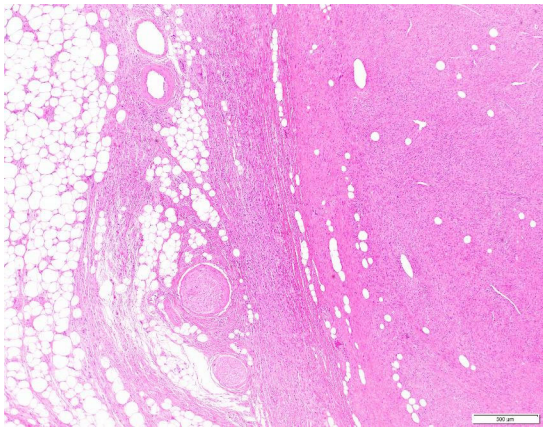
Atypical Lipomatous Tumor/Well-differentiated liposarcoma

- IHC:
  - MDM2
  - CDK4
  - HMGA2
  - p16
- MP:
  - *MDM2* amplification FISH



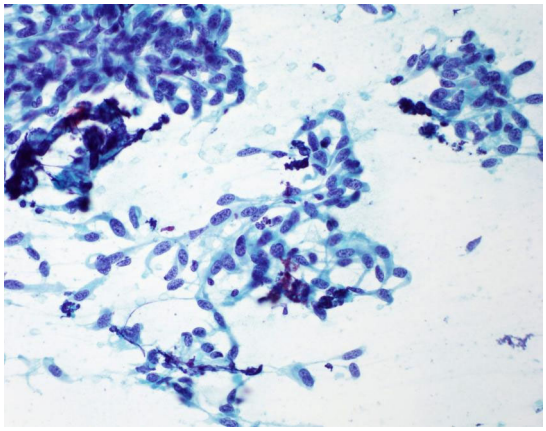
Dedifferentiated liposarcoma

- ALT/WDLPS showing progression (usually non-lipogenic) sarcoma of variable histological grade.



Dedifferentiated liposarcoma

- ALT/WDLPS showing progression (usually non-lipogenic) sarcoma of variable histological grade.
- Variable morphologies – often high-grade spindled and pleomorphic cells
- Intermixed inflammatory cells (neutrophils) in subset



Dedifferentiated liposarcoma

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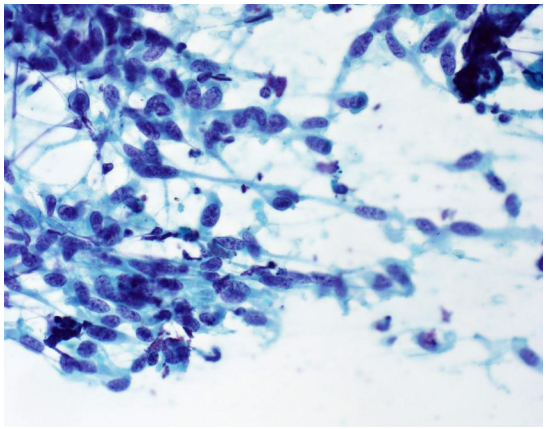
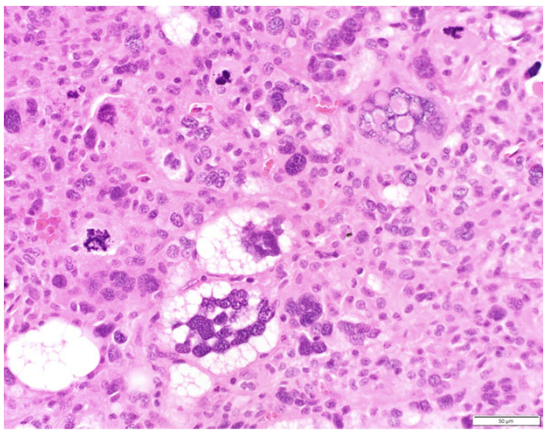


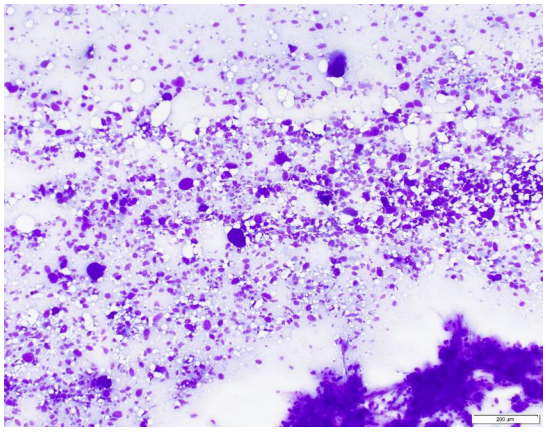
Pleomorphic liposarcoma

- Rare high-grade sarcoma in adults



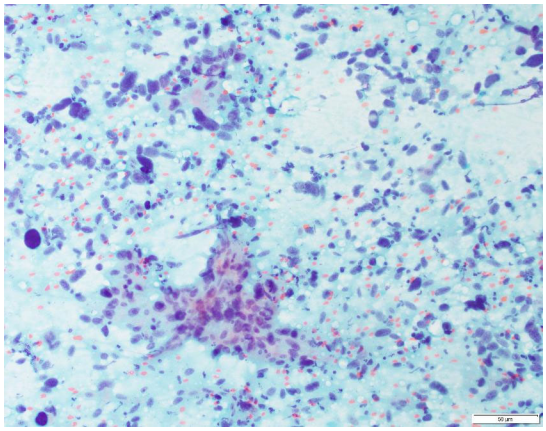
Pleomorphic liposarcoma

- Rare high-grade sarcoma in adults
- High-grade sarcoma with pleomorphic lipoblasts



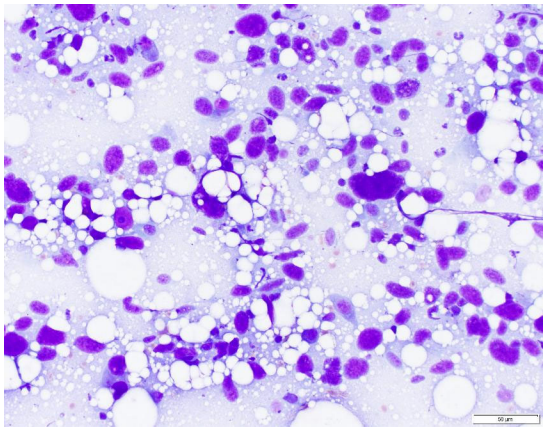
Pleomorphic liposarcoma

- Rare high-grade sarcoma in adults
- High-grade sarcoma with pleomorphic lipoblasts
- Pleomorphic spindle to epithelioid cells
- Mitoses and necrosis



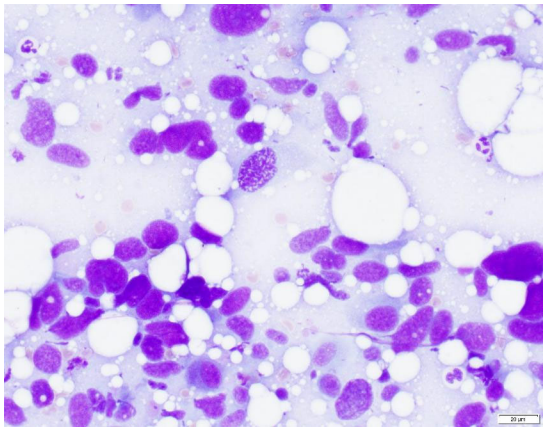
Pleomorphic liposarcoma

- Pleomorphic lipoblasts is diagnostic
- Definition of lipoblast:
  - Hyperchromatic, indented, sharply scalloped nucleus
  - Lipid-filled cytoplasmic droplets
  - An appropriate cytologic background!
- Lipoblast-like cells may be seen in fat necrosis, brown fat/hibernoma, MFS (pseudolipoblasts), artifact
- Pleomorphic liposarcoma-like morphology may be seen in DDLPS with homologous lipoblastic differentiation



Pleomorphic liposarcoma

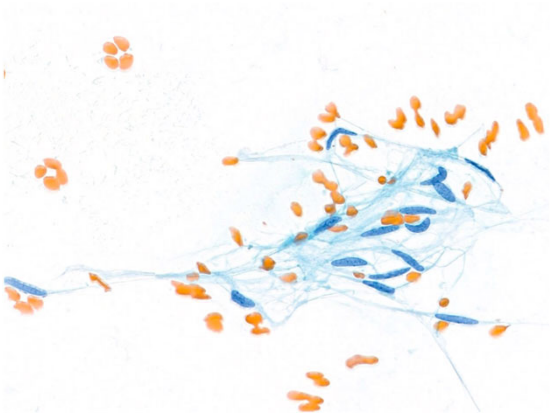
- DDx:
  - UPS
  - myxofibrosarcoma
- IHC:
  - MDM2-negative
- MP:
  - Lack MDM2 amplification
  - Complex chromosomal aberrations structural rearrangements



Spindle cell tumors

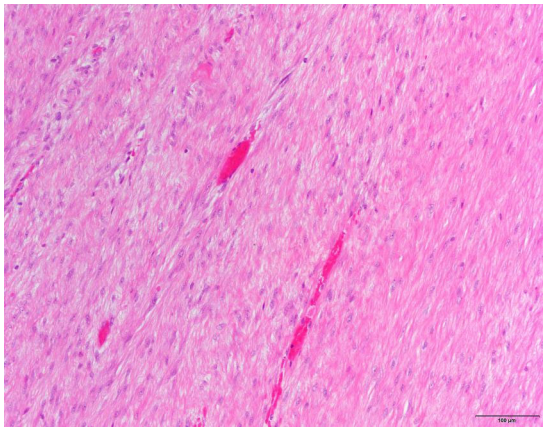
Spindle Cell Tumors

- Desmoid fibromatosis
- Nodular fasciitis
- Schwannoma
- Solitary fibrous tumor
- Leiomyoma/Leiomyosarcoma
- Low-grade fibromyxoid sarcoma
- Synovial sarcoma



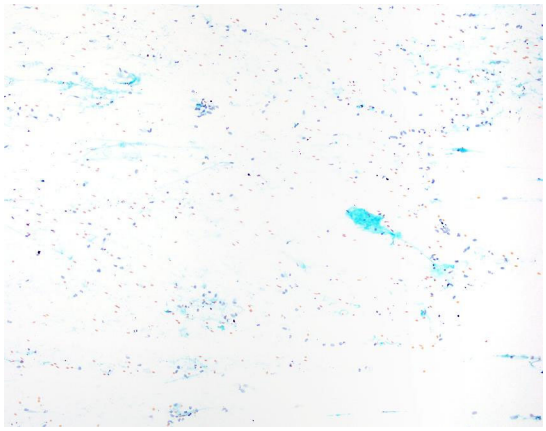
Desmoid fibromatosis

- Locally aggressive neoplasm composed of fibroblasts/ myofibroblasts in fascicles with infiltrative growth



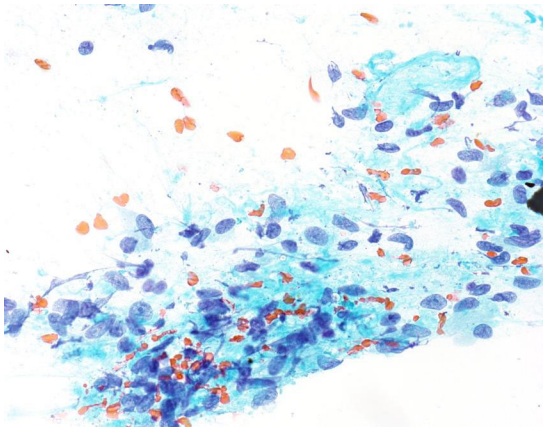
Desmoid fibromatosis

- Locally aggressive neoplasm composed of fibroblasts/ myofibroblasts in fascicles with infiltrative growth
- Smears are often hypocellular



Desmoid fibromatosis

- Locally aggressive neoplasm composed of fibroblasts/ myofibroblasts in fascicles with infiltrative growth
- Smears are often hypocellular
- Uniform population of bland-appearing spindle cells
- Dispersed cells in the background, including stripped nuclei



Desmoid fibromatosis

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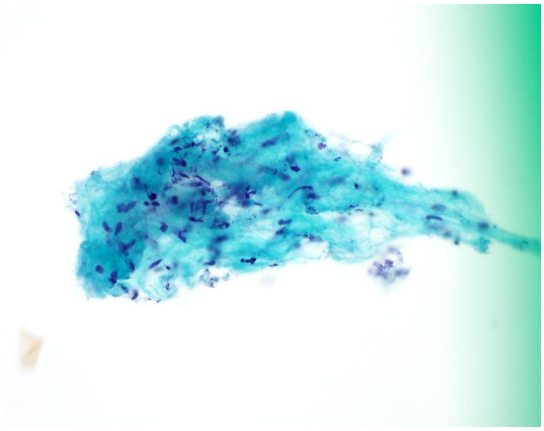
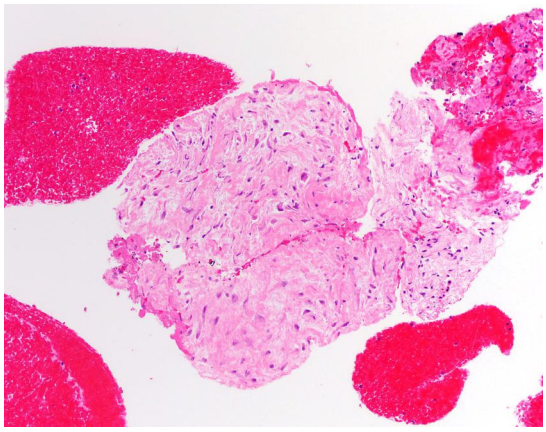
- Smears are often hypocellular
- Uniform population of bland-appearing spindle cells
- Dispersed cells in the background, including stripped nuclei
- Collagenous fragments associated with crush artifact



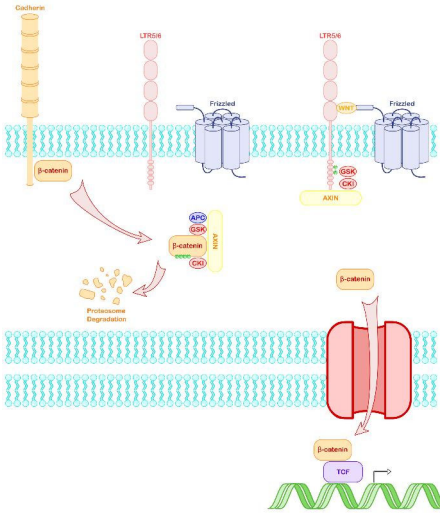
Desmoid fibromatosis

- DDx:
  - Scar
  - Desmoplasia
  - Benign and low-grade monomorphic spindle cell tumors
- IHC:
  - β-catenin nuclear staining
  - LEF1



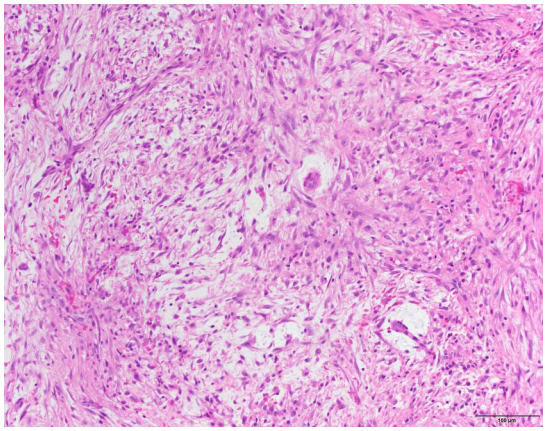
Desmoid fibromatosis

- MP:
  - *CTNNB1* (codon 41, 45)
  - *APC* mutations



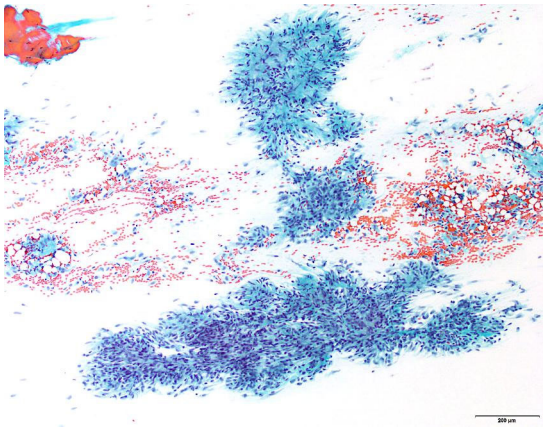
Nodular fasciitis

- Self-limiting myofibroblastic neoplasm of subcutaneous tissue.



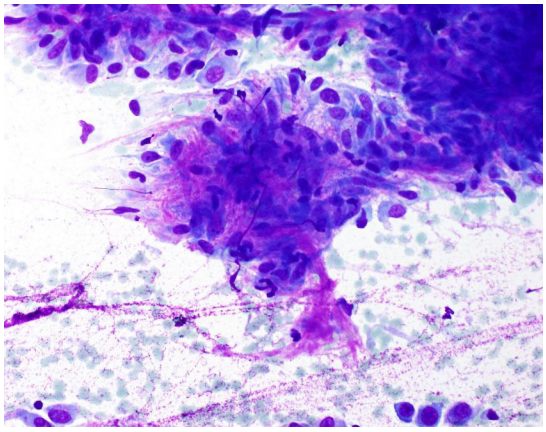
Nodular fasciitis

- Common soft tissue neoplasm within subcutaneous tissue and fascia
- Often cellular aspirates



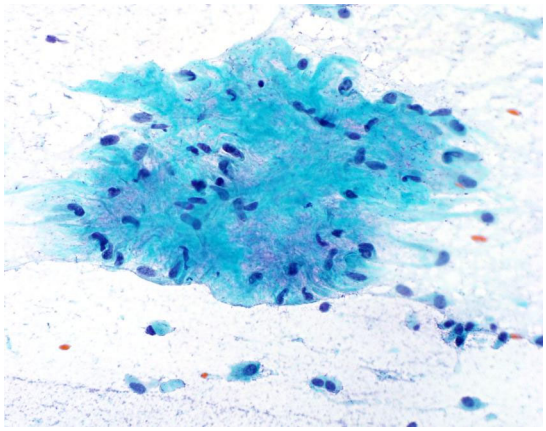
Nodular fasciitis

- Common soft tissue neoplasm within subcutaneous tissue and fascia
- Often cellular aspirates
- Clusters of cells within fibromyxoid stroma and single cells



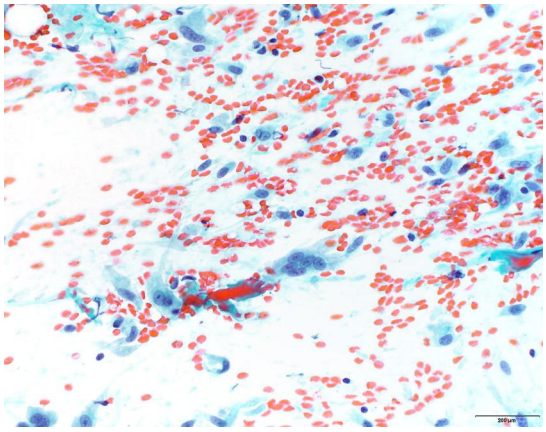
Nodular fasciitis

- Common soft tissue neoplasm within subcutaneous tissue and fascia
- Often cellular aspirates
- Clusters of cells within fibromyxoid stroma and single cells
- Spindled to plump ovoid cells, ganglion-like cells



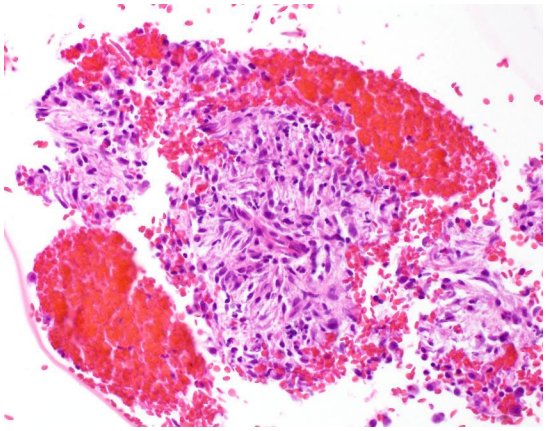
Nodular fasciitis

- Common soft tissue neoplasm within subcutaneous tissue and fascia
- Often cellular aspirates
- Clusters of cells within fibromyxoid stroma and single cells
- Spindled to plump ovoid cells, ganglion-like cells
- Scattered inflammatory cells (lymphocytes, histiocytes)
- Multinucleated giant cells



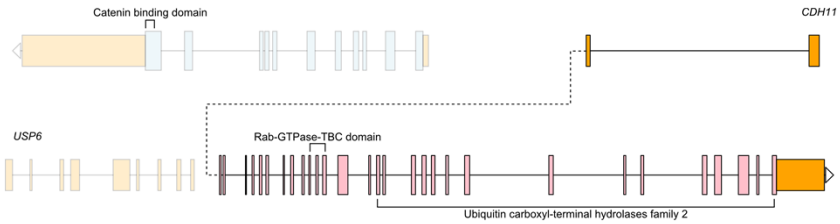
Nodular fasciitis

- DDx:
  - Spindle cell tumors
  - Tumors with myxoid stroma
  - Other spindle cell sarcoma
- IHC:
  - SMA



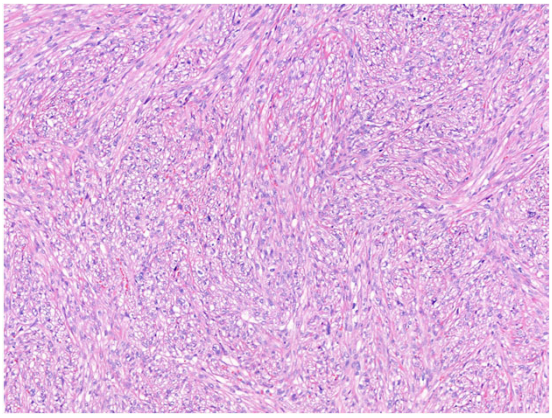
Nodular fasciitis

- MP:
  - *USP6* translocation



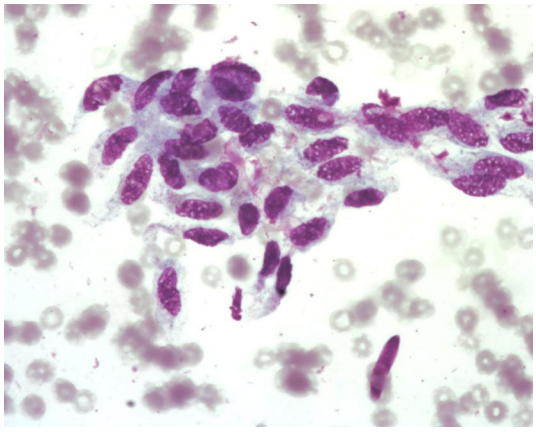
Leiomyoma and Low-grade Leiomyosarcoma

- Neoplasm with smooth muscle differentiation
- Leiomyoma:
  - Most often EUS-FNA of GI tract
  - Soft tissue leiomyoma is uncommon
- Leiomyosarcoma:
  - Skin
  - GI tract
  - Deep soft tissue
  - Large vessels



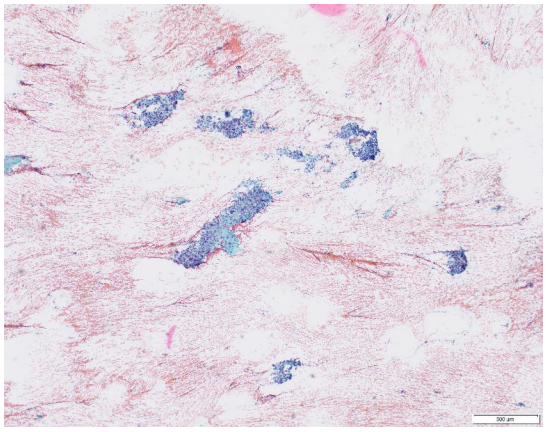
Leiomyoma and Low-grade Leiomyosarcoma

- Most often EUS-FNA of GI tract
- Soft tissue leiomyoma is uncommon
- Variable cellularity, typically hypocellular on smears
- Large cohesive spindle cell fragments with smooth edges and variable cellularity
- Bland slender spindle cells with vesicular chromatin, blunt ended nuclei
- Clean background without stroma or single cells
- Lack of cytologic atypia, mitotic figures, or necrosis



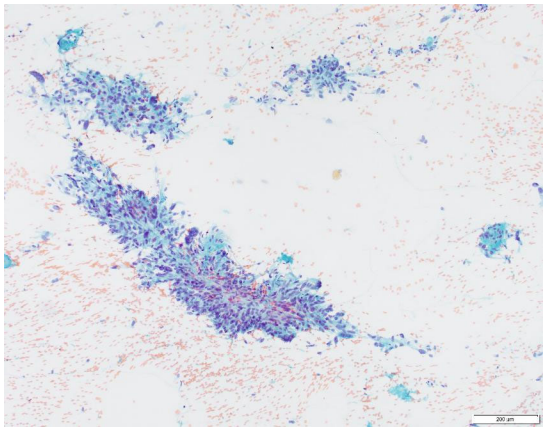
Leiomyosarcoma

- Hypercellular smears to hypocellular smears in tumors with fibrosis



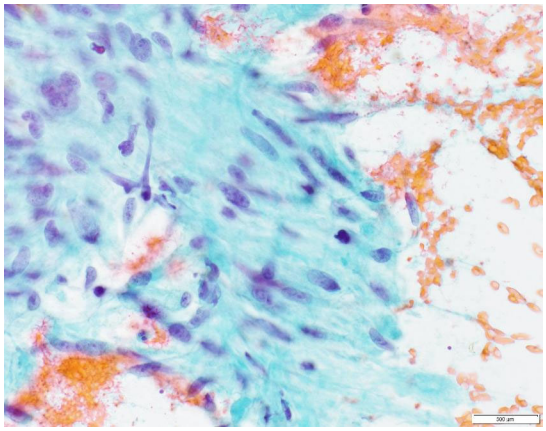
Leiomyosarcoma

- Hypercellular smears to hypocellular smears in tumors with fibrosis
- Fascicles and sheets of spindle to pleomorphic cells



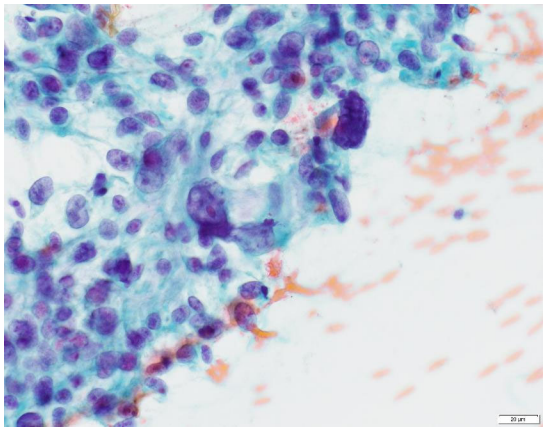
Leiomyosarcoma

- Hypercellular smears to hypocellular smears in tumors with fibrosis
- Fascicles and sheets of spindle to pleomorphic cells
- Cigar-shaped blunt-ended, occasionally indented or segmented nuclei



Leiomyosarcoma

- Hypercellular smears to hypocellular smears in tumors with fibrosis
- Fascicles and sheets of spindle to pleomorphic cells
- Cigar-shaped blunt-ended, occasionally indented or segmented nuclei
- Pleomorphic, multinucleated cells
- Stripped atypical nuclei
- Epithelioid tumor cells in epithelioid LMS
- Occasional intranuclear inclusions
- Necrosis, mitoses, and rare osteoclast-like giant cells

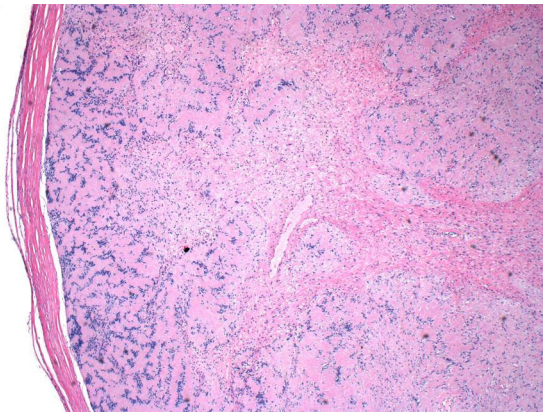


Leiomyosarcoma

- DDx:
  - Low-grade
    - Schwannoma
    - GIST
    - Other bland spindle cell tumors
  - High-grade
    - Other high-grade sarcomas
    - Spindle cell melanoma
    - Sarcomatoid carcinoma
- IHC:
  - SMA
  - Desmin
  - Caldesmon
- MP:
  - *TP53*
  - *RB1*
  - *ATRX* alterations

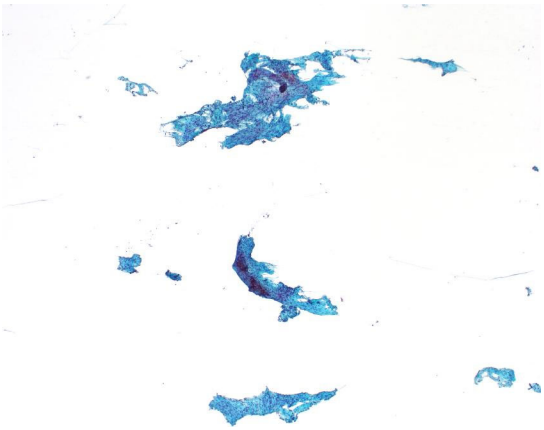
Schwannoma

- Benign nerve sheath tumor composed of differentiated neoplastic Schwann cells



Schwannoma

- Fascicular and/or syncytial fragments of spindle cells at low power
- Syncytial groups in netlike or twisted rope pattern
- Single spindle cells in the background rarely present



Schwannoma

- Fascicular and/or syncytial fragments of spindle cells at low power
- Syncytial groups in netlike or twisted rope pattern
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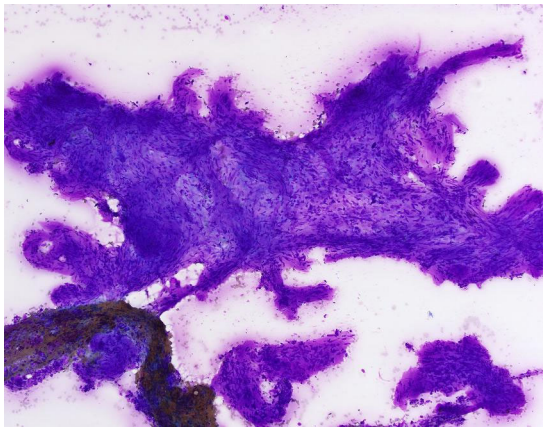

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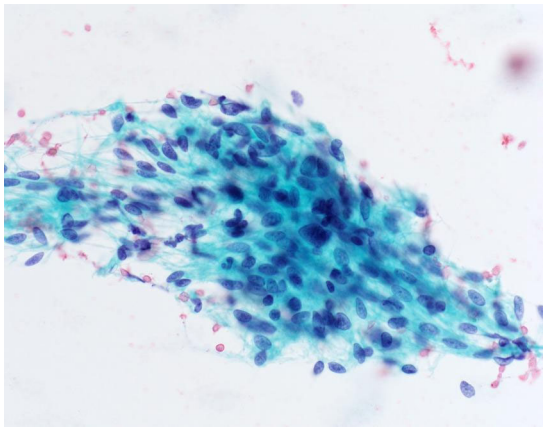

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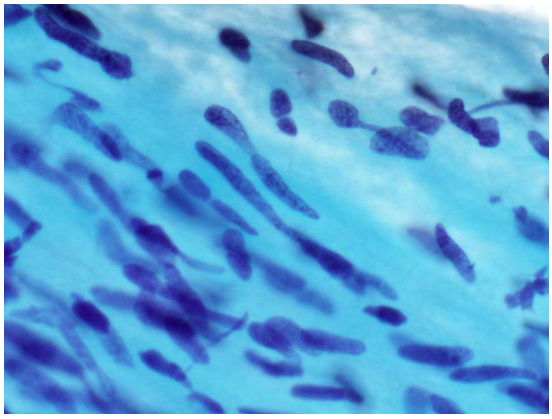
- Tumors cells have elongated, “fish-hook” nuclei, often with tapered tips, anisonucleosis



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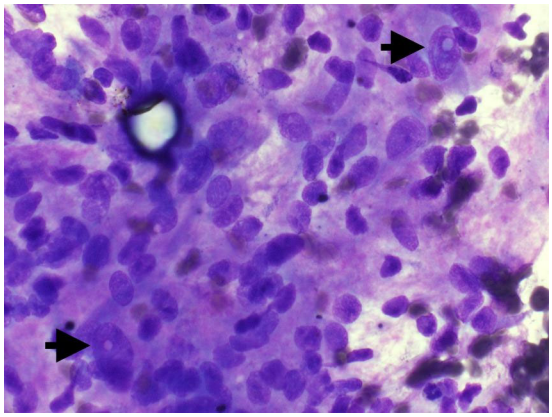
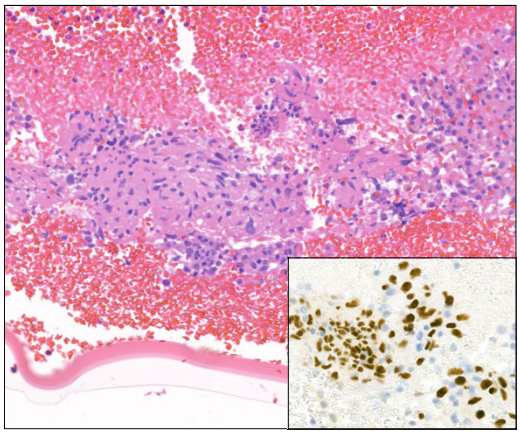
- Intranuclear inclusions



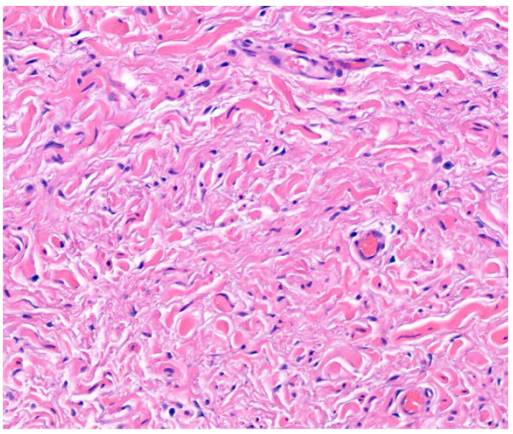
Schwannoma

- DDx:
  - Monomorphic low-grade spindle cell tumors
    - GIST
    - Leiomyoma/Leiomyosarcoma
  - Spindle cell melanoma
- IHC:
  - S100, SOX10
  - Loss of merlin
- MP: rarely necessary
  - NF2-inactivating mutations, rare fusions
  - Familial schwannomatosis SMARCB1 or LZTR1 mutations
  - CNS schwannoma with SOX10 mutations



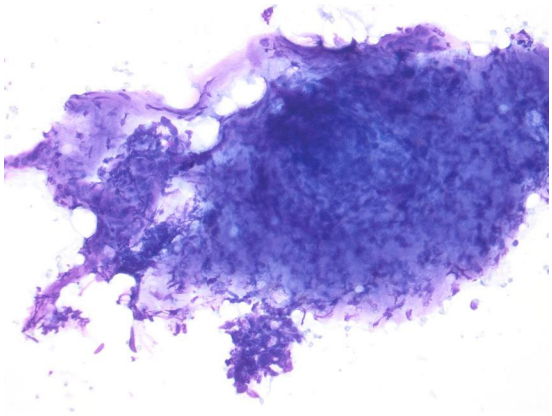
Neurofibroma

- Benign nerve sheath tumor consisting of mixture of Schwann cells, perineurial cells, fibrobalst, mast cells, axons, in collagenous to myxoid matrix



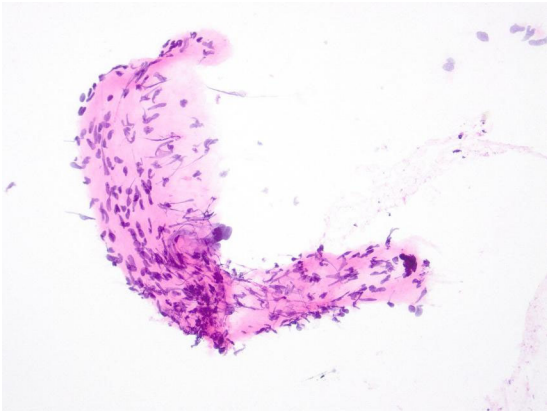
Neurofibroma

- Typically hypocellular smears
- Myxoid, fibromyxoid, collagenous matrix



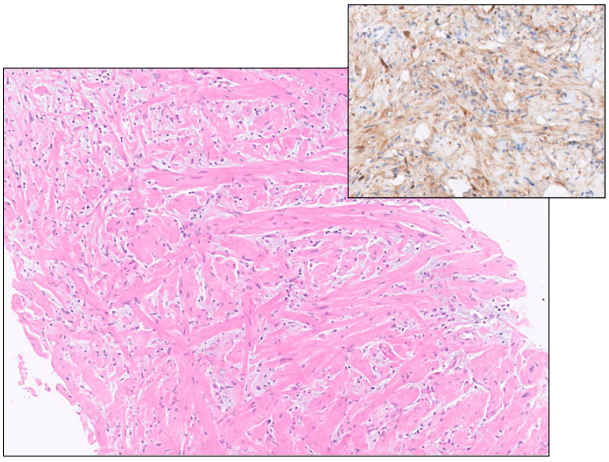
Neurofibroma

- Typically hypocellular smears
- Small fragments of cohesive spindle cells with curved, comma-shaped, bent or wavy nuclei
- May have occasional stripped nuclei
- Myxoid, fibromyxoid, collagenous matrix



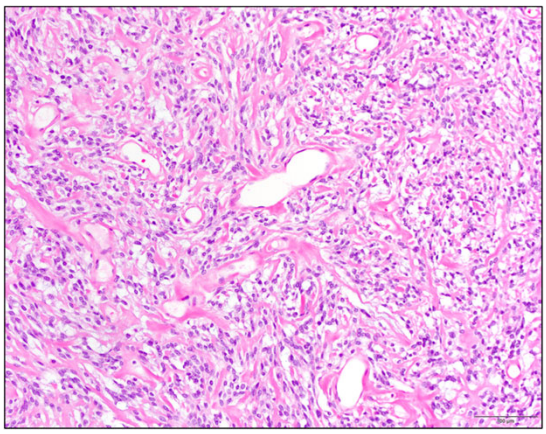
Neurofibroma

- DDx:
  - Monomorphic low-grade spindle cell tumors
  - Spindle cell melanoma
- IHC: rare sufficient material
  - SOX10, S100
  - EMA, CD34, Neurofilament
- MP: rarely necessary
  - NF1 mutations/inactivation



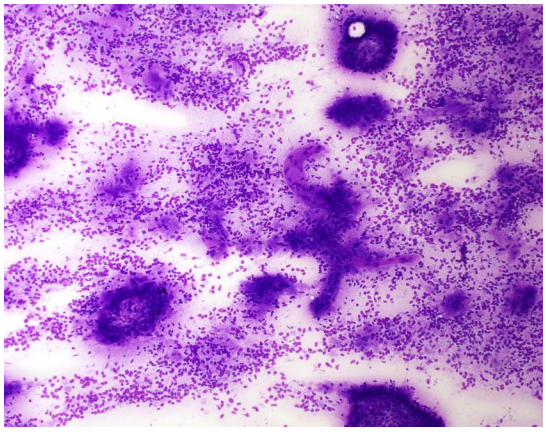
Solitary fibrous tumor

- Fibroblastic neoplasm characterized by prominent branching thin-walled vasculature and NAB2::STAT6 fusion



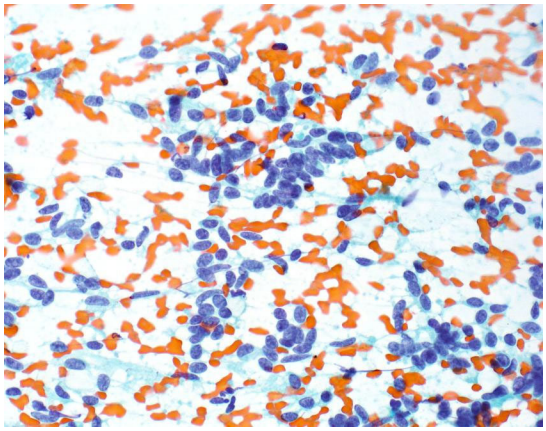
Solitary fibrous tumor

- Variable cellularity composed of clusters and single cells



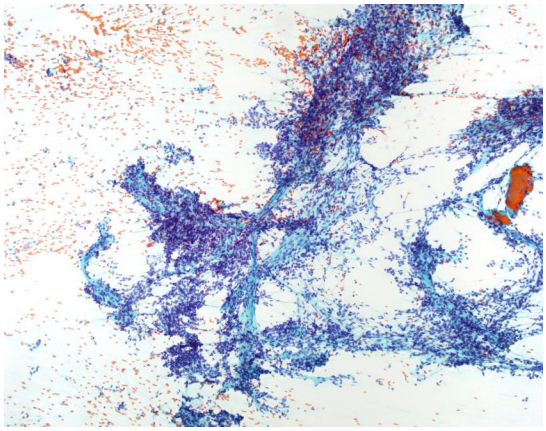
Solitary fibrous tumor

- Variable cellularity composed of clusters and single cells
- Uniform spindle cells with finely granular chromatin, inconspicuous to absent nucleoli, stripped (“naked”) nuclei
- Cytoplasmic processes are thin and wispy



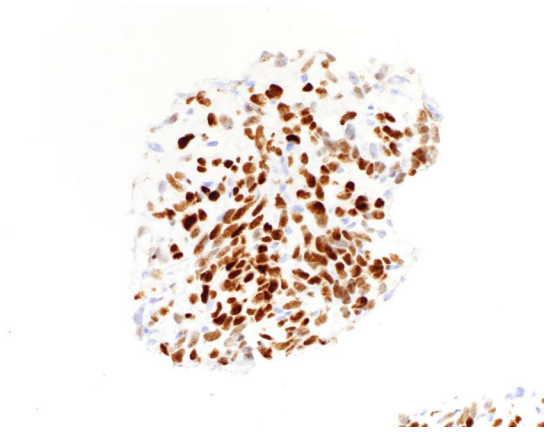
Solitary fibrous tumor

- Variable cellularity composed of clusters and single cells
- Uniform spindle cells with finely granular chromatin, inconspicuous to absent nucleoli, stripped (“naked”) nuclei
- Cytoplasmic processes are thin and wispy
- Hypocellular fragments of fibrous tissue to small fragments of ropy or wispy collagen
- Often have bloody background
- May have fat, multinucleated giant cells, myxoid stroma or rarely mast cells
- Increased mitoses, atypia, hypercellularity, and necrosis can be associated with a high-grade transformation or dedifferentiation
- *Risk stratification cannot be adequately performed on cell block or small biopsy



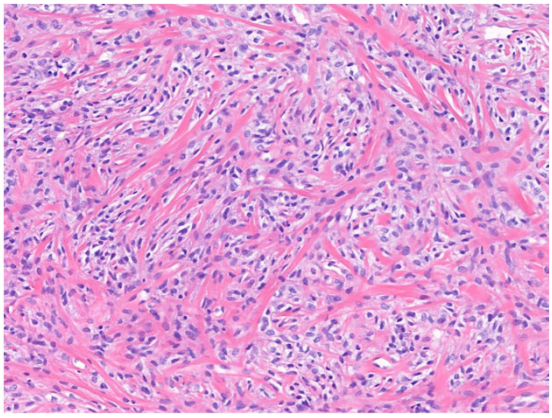
Solitary fibrous tumor

- DDx:
  - Synovial sarcoma
  - GIST
  - Other cellular monomorphic spindle cell tumors
- IHC:
  - STAT6, CD34
- MP:
  - *NAB2*::*STAT6*



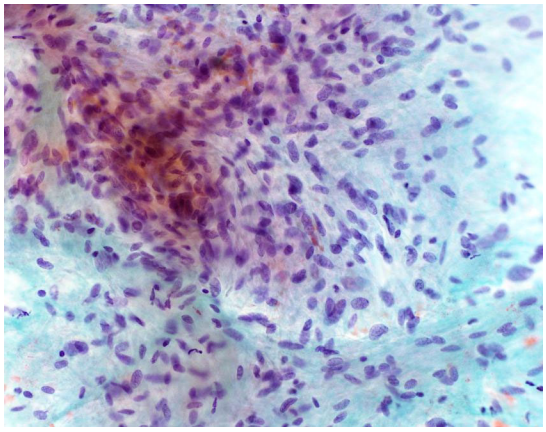
Low-grade fibromyxoid sarcoma

- Malignant fibroblastic neoplasm characterized by alternating collagenous and myxoid areas, bland spindle cells, vascular arcades, and FUS::CREB3L2/3L1 fusions



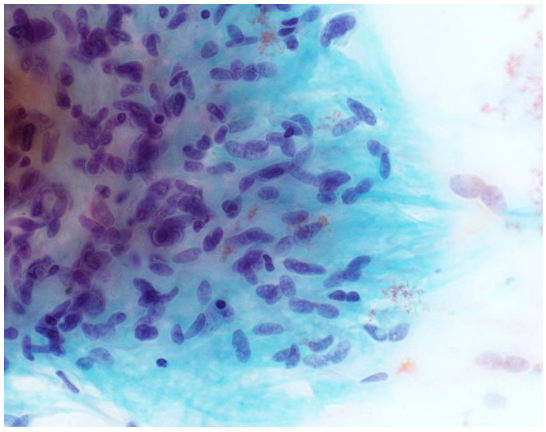
Low-grade fibromyxoid sarcoma

- Irregular fibrous/collagenous fragments, loosely cohesive fascicles, and single cells in myxoid background



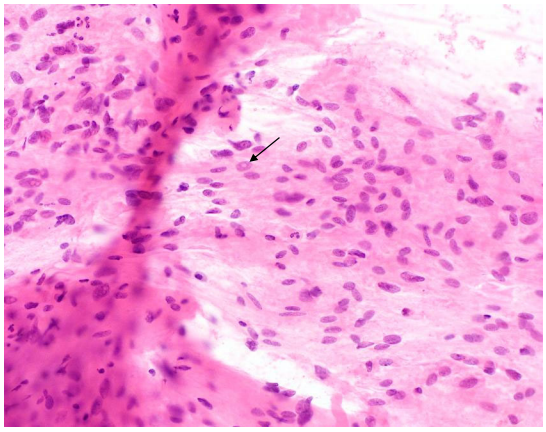
Low-grade fibromyxoid sarcoma

- Irregular fibrous/collagenous fragments, loosely cohesive fascicles, and single cells in myxoid background
- Uniform bland-to-mildly atypical, elongated spindle cells
- Finely granular to vesicular chromatin, without nucleoli, hyperchromasia or significant anisonucleosis



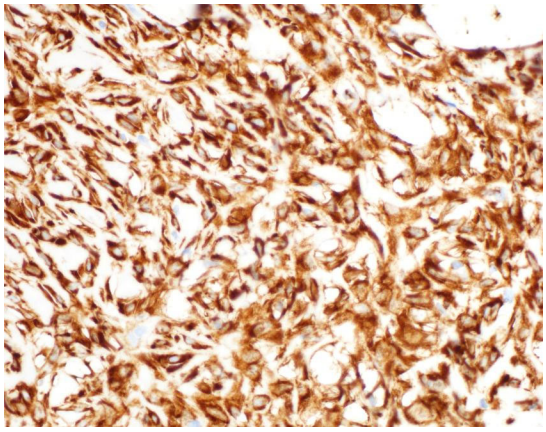
Low-grade fibromyxoid sarcoma

- Irregular fibrous/collagenous fragments, loosely cohesive fascicles, and single cells in myxoid background
- Uniform bland-to-mildly atypical, elongated spindle cells
- Finely granular to vesicular chromatin, without nucleoli, hyperchromasia or significant anisonucleosis
- Naked nuclei and intranuclear cytoplasmic pseudoinclusions may be seen
- Fibrous to myxoid matrix
- Rare arteriole-sized curvilinear vessels; may contain an admixture of fat



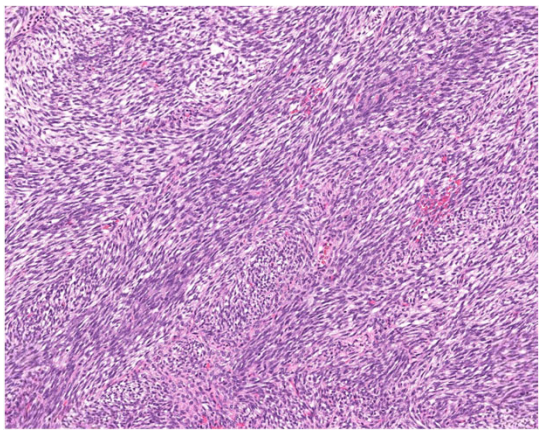
Low-grade fibromyxoid sarcoma

- DDx:
  - Desmoid fibromatosis
  - Perineurioma
  - Other monomorphic spindle cell or myxoid neoplasms
- IHC:
  - MUC4
- MP:
  - *FUS*::*CREB3L2/CREB3L1*, *EWSR1*::*CREB3L1*



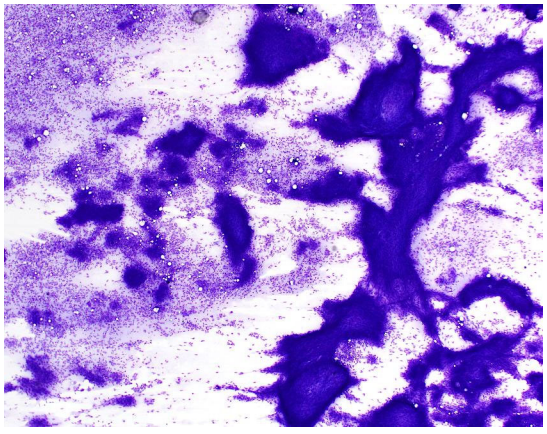
Synovial sarcoma

- Malignant monomorphic blue spindle cell tumor showing variable epithelial differentiation and characterized by SS18::SSX1/2/4 fusions



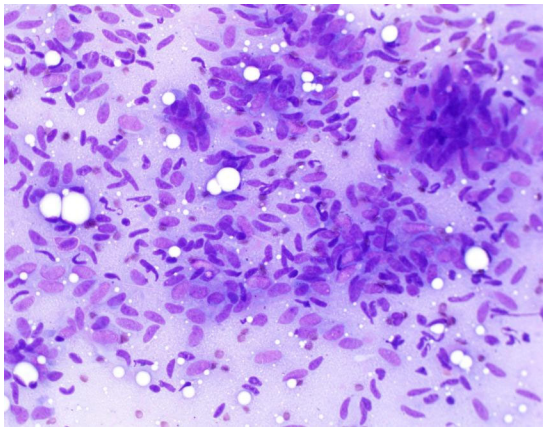
Synovial sarcoma

- Hypercellular smears composed of branching tissue fragments and single cells.



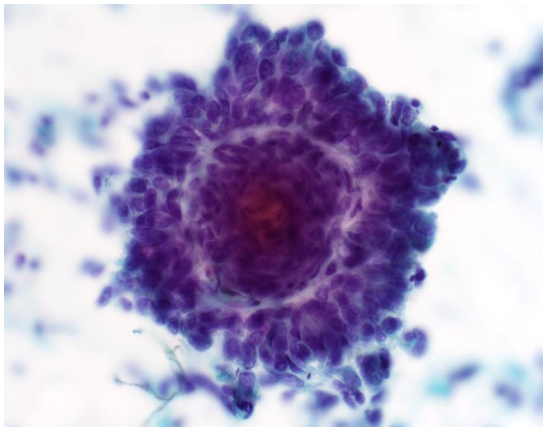
Synovial sarcoma

- Hypercellular smears composed of branching tissue fragments and single cells.
- Monophasic synovial sarcoma shows uniform oval to fusiform cells with hyperchromasia, small to absent nucleoli, and stripped (“naked”) nuclei.
- Scant thin uni- or bipolar cytoplasm.



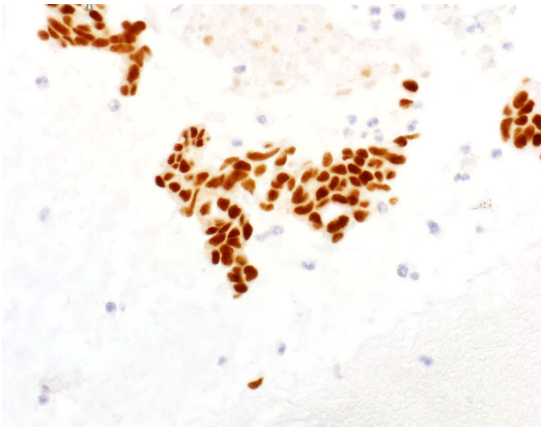
Synovial sarcoma

- Hypercellular smears composed of branching tissue fragments and single cells.
- Monophasic synovial sarcoma shows uniform oval to fusiform cells with hyperchromasia, small to absent nucleoli, and stripped (“naked”) nuclei.
- Scant thin uni- or bipolar cytoplasm.
- Biphasic synovial sarcoma shows mixed uniform oval to fusiform spindle cells and epithelial tumor cells in clusters and gland/alveolar/acinar formation.
- Epithelial component may be better demonstrated on Papanicolaou stain.
- Poorly differentiated synovial sarcoma shows small round cell morphology (similar to Ewing sarcoma), and rarely rhabdoid-like cells.
- Mast cells may also be present.



Synovial sarcoma

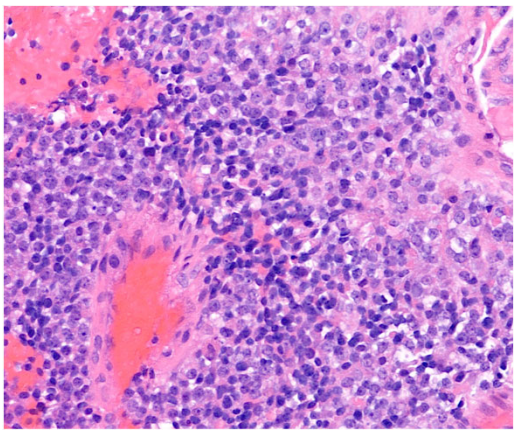
- DDx:
  - Solitary fibrous tumor
  - Malignant peripheral nerve sheath tumors
  - Other cellular monomorphic spindle cell tumors
- IHC:
  - CK, EMA, CD99,
  - TLE1,
  - SS18::SSX IHC, SSX c-terminus
- MP:
  - *SS18*::*SSX1/2/4*



Round cell sarcoma

Round cell sarcoma

- Ewing sarcoma
- CIC-rearranged sarcoma
- Sarcoma with BCOR genetic alteration
- Round cell sarcoma with NFATc2-rearrangement
- Desmoplastic small round cell tumor
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Neuroblastoma
- Poorly differentiated synovial sarcoma
- High-grade (round cell) myxoid liposarcoma
- Small cell carcinoma
- Merkel cell carcinoma
- Lymphoma

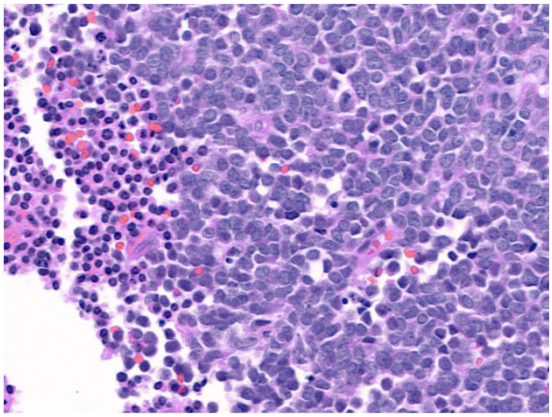


IHC and Molecular Pathology of Round Cell Tumors

Tumour Type	Immunocytochemistry (positive)	Molecular Genetics
Ewing sarcoma	CD99, NKX2.2	EWSR1-FLI1 (90%) EWSR1-ERG (10%)
Round cell sarcoma with EWSR1-non-ETS fusions	CD99 variable (~50%)	EWSR1-NFATC2, FUS-NFATC2, EWSR1-PATZ1
CIC-rearranged sarcoma	CD99 variable (~85%), ETV4, WT1	CIC-DUX2 (95%), CIC-FOX04, CIC-LEUTZ, CIC-NUTM1, CIC-NUTM2A
Sarcoma with BCOR alterations	CD99 variable (~50%), BCOR, CCNB3, SATB2, CyclinD1, TLE1	BCOR-CCNB3 (90%), BCOR-MAML3, BCOR ITDs

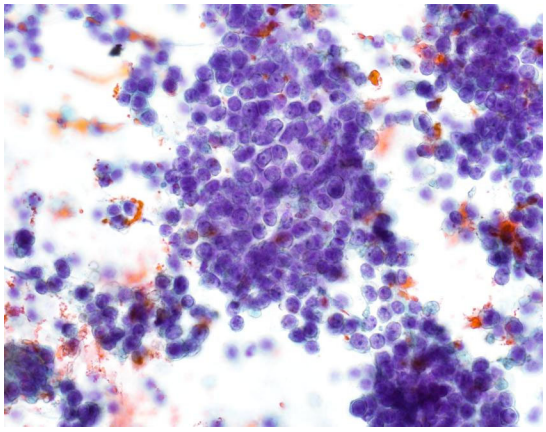
Ewing Sarcoma

- Small round cell sarcoma with gene fusions involving FET family of genes (EWSR1, FUS) and members of the ETS family of transcription factors (ERG, FLI1, ETV4, ETV1, others)



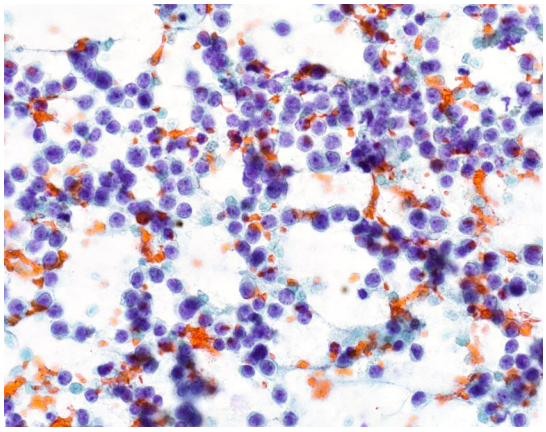
Ewing Sarcoma

- Cellular aspirates composed of single cells and small clusters
- Typical admixture of “light” and dark” cells



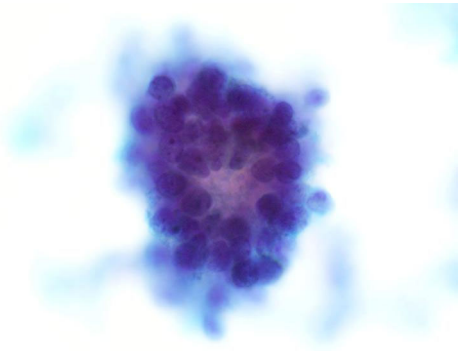
Ewing Sarcoma

- Cellular aspirates composed of single cells and small clusters
- Typical admixture of “light” and dark” cells
- Round-to-ovoid nuclei, fine chromatin, indistinct or small nucleoli, may have nuclear molding
- Cytoplasm may be scant to abundant pale cytoplasm
- Background naked nuclei and cytoplasmic contents smearing imparting “tigroid” appearance on air-dried smear.



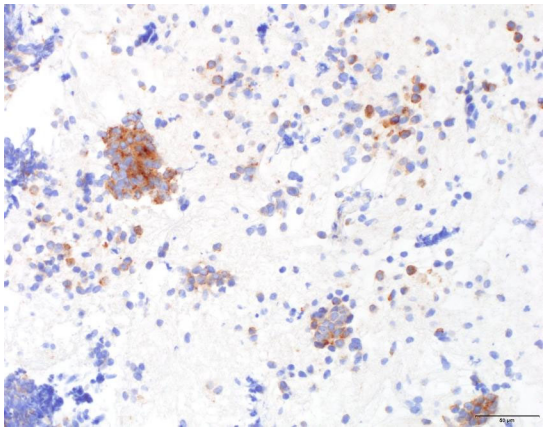
Ewing Sarcoma

- Cellular aspirates composed of single cells and small clusters
- Typical admixture of “light” and dark” cells
- Round-to-ovoid nuclei, fine chromatin, indistinct or small nucleoli, may have nuclear molding
- Cytoplasm may be scant to abundant pale cytoplasm
- Background naked nuclei and cytoplasmic contents smearing imparting “tigroid” appearance on air-dried smear.
- Rosette formation is rare



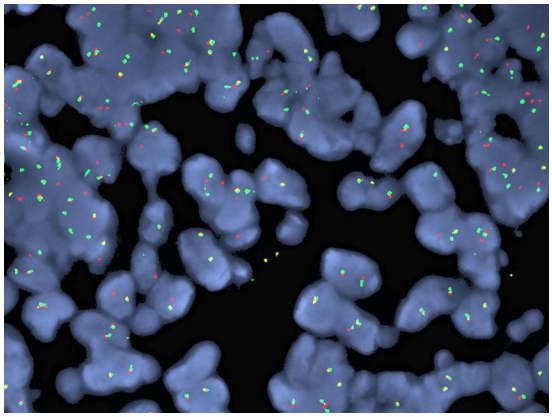
Ewing Sarcoma

- IHC:
  - CD99, NKX2.2
  - +/- FLI1/ERG
  - Rarely CK, desmin



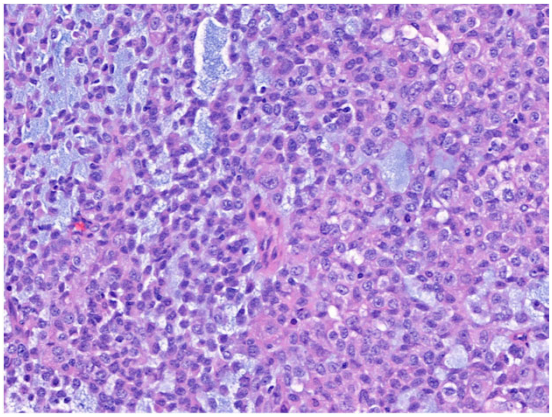
Ewing Sarcoma

- MP:
  - *EWSR1::FLI1, EWSR1::ERG*



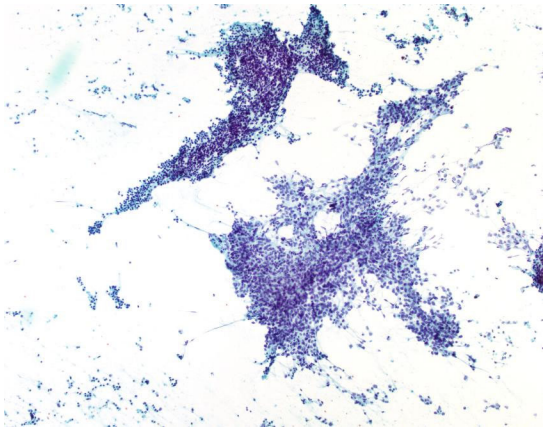
CIC-rearranged Sarcoma

- High-grade round cell undifferentiated sarcoma defined by CIC-related gene fusions.



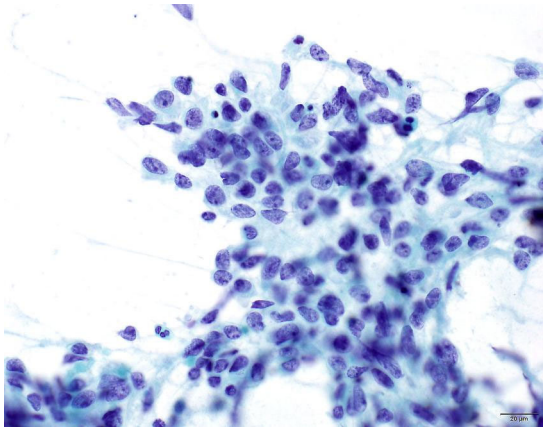
CIC-rearranged Sarcoma

- Hypercellular smears arranged as single cells, sheets, clusters
- Syncytial arrangement with poorly defined cell borders



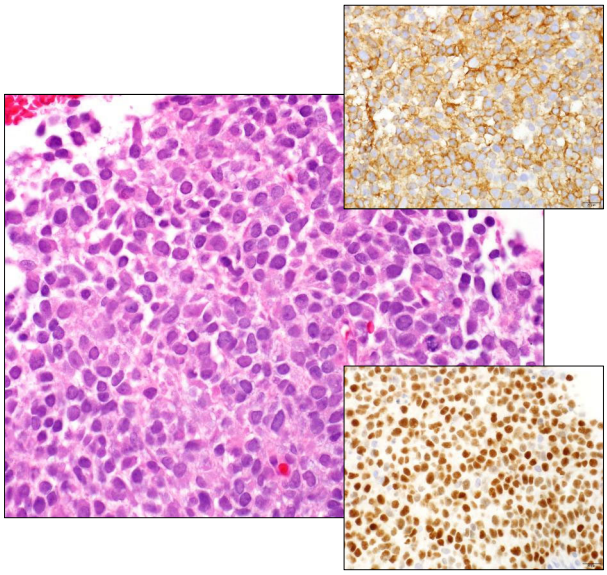
CIC-rearranged Sarcoma

- Hypercellular smears arranged as single cells, sheets, clusters
- Syncytial arrangement with poorly defined cell borders
- Round cells with scant to moderate, often vacuolated cytoplasm
- Central or eccentric nuclei, occasional nuclear molding
- Nuclei round to ovoid with fine, evenly dispersed, hyperchromatic chromatin, irregular membranes and often prominent nucleoli
- Mild anisocytosis, pleomorphism and atypia
- Variable mitotic figures, necrosis, myxoid matrix and tigroid background



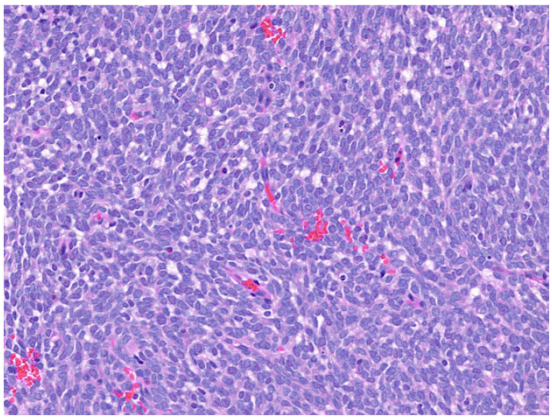
CIC-rearranged Sarcoma

- IHC:
  - variable CD99
  - WT1, ETV4
- MP:
  - *CIC*-fusions (*CIC*::*DUX4*)



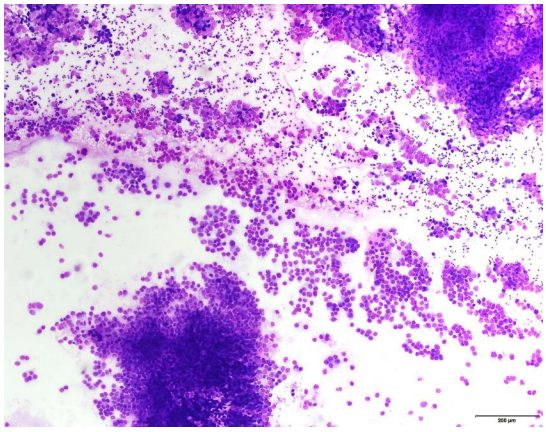
Sarcoma with BCOR genetic alteration

- Primitive round cell sarcoma with BCOR-genetic alterations resulting in BCOR overexpression.



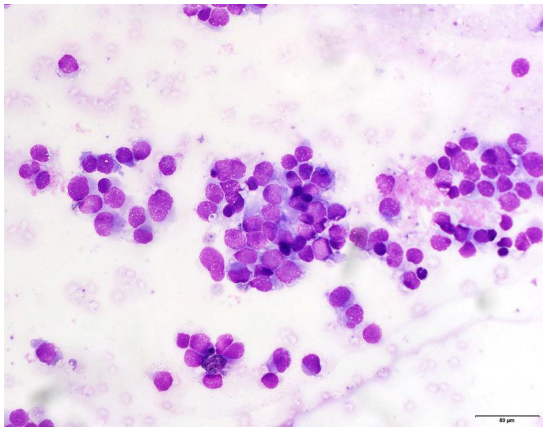
Sarcoma with *BCOR* genetic alteration

- Hypercellular smears arranged as single cells and pseudopapillary clusters with vascular cores
- Light and dark pattern similar to Ewing sarcoma



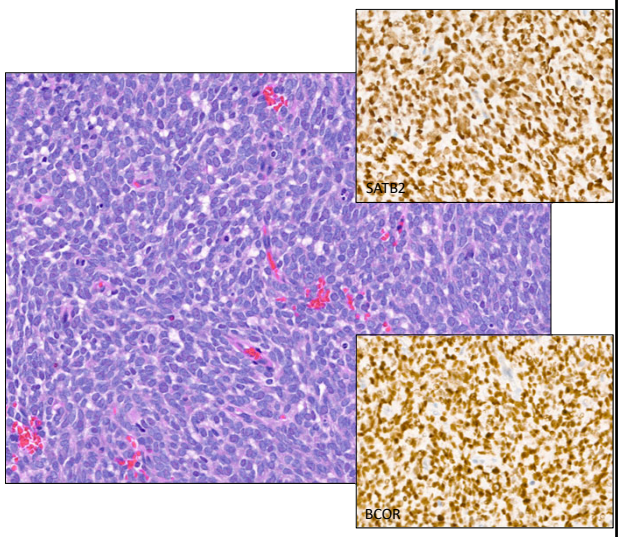
Sarcoma with *BCOR* genetic alteration

-Hypercellular smears arranged as single cells and pseudopapillary clusters with vascular cores
-Light and dark pattern similar to Ewing sarcoma
-Round cells with variable numbers of spindle cells; rare single rhabdoid-like cells
-Scant to abundant cytoplasm, pale nuclei with fine chromatin and inconspicuous nucleoli
-Variable pleomorphism
-Variable stromal and delicate vascular fragments, myxoid matrix and necrosis
-IHC: variable CD99, BCOR, SATB2, +/- CCNB3, TLE1, cyclin D1
-MP: *BCOR* fusion (*BCOR*::*CCNB3*), *BCOR*-ITD



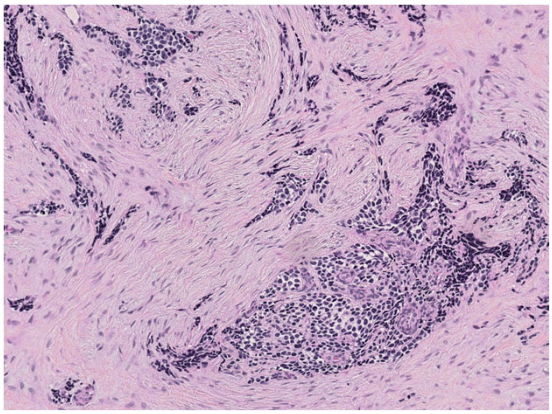
Sarcoma with *BCOR* genetic alteration

- IHC:
  - variable CD99
  - BCOR, SATB2
  - +/- CCNB3, TLE1, cyclin D1
- MP:
  - *BCOR* fusion (*BCOR*::*CCNB3*)
  - *BCOR*-ITD



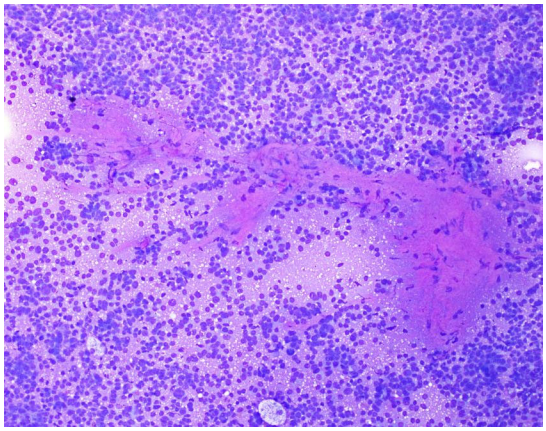
Desmoplastic small round cell tumor

- Malignant neoplasm composed of small round tumor cells associated with stromal desmoplasia, polyphenotypic differentiation, and EWSR1::WT1 fusion.



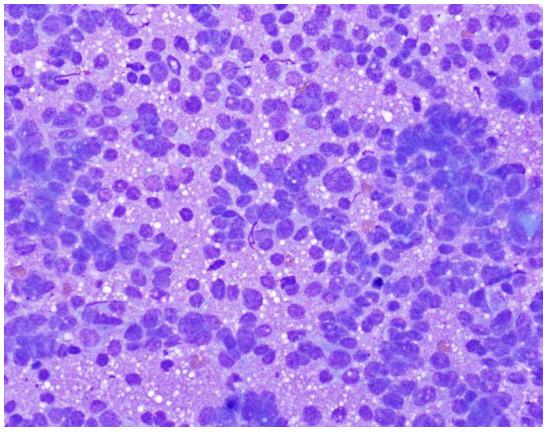
Desmoplastic small round cell tumor

- Most common abdominal cavity (retroperitoneum, pelvis, omentum, and mesentery)
- Metachromatic stromal material in the background on smears and cell block material



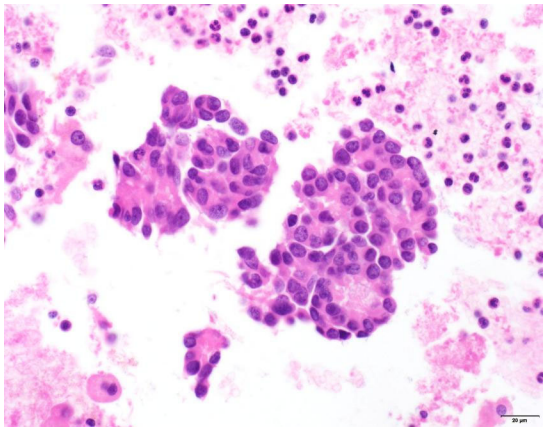
Desmoplastic small round cell tumor

- Most common abdominal cavity (retroperitoneum, pelvis, omentum, and mesentery)
- Metachromatic stromal material in the background on smears and cell block material
- Cellular specimens with loosely cohesive, hyperchromatic round cells with scant-to-moderate amounts of cytoplasm and variable molding



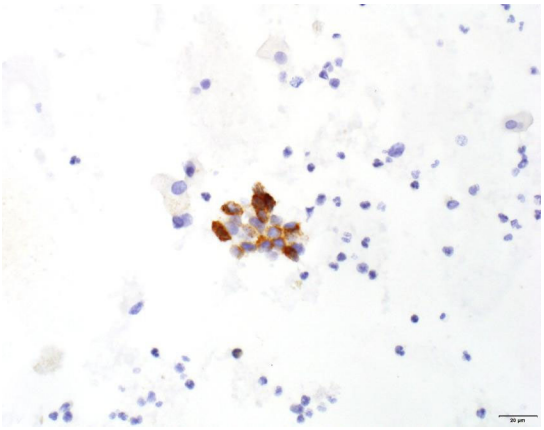
Desmoplastic small round cell tumor

- Most common abdominal cavity (retroperitoneum, pelvis, omentum, and mesentery)
- Metachromatic stromal material in the background on smears and cell block material
- Cellular specimens with loosely cohesive, hyperchromatic round cells with scant-to-moderate amounts of cytoplasm and variable molding
- Occasional pseudorosettes, paranuclear cytoplasmic densities, heart/kidney-shaped nuclei, and cytoplasmic vacuolization



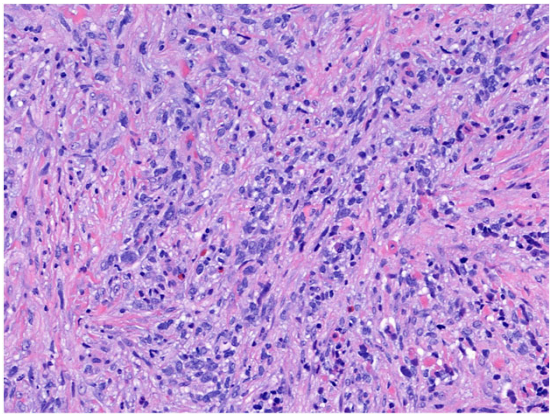
Desmoplastic small round cell tumor

- IHC:
  - Keratin, desmin (perinuclear dot-like)
  - +/- neuroendocrine markers
  - WT1 c-terminus
- MP:
  - *EWSR1::WT1*



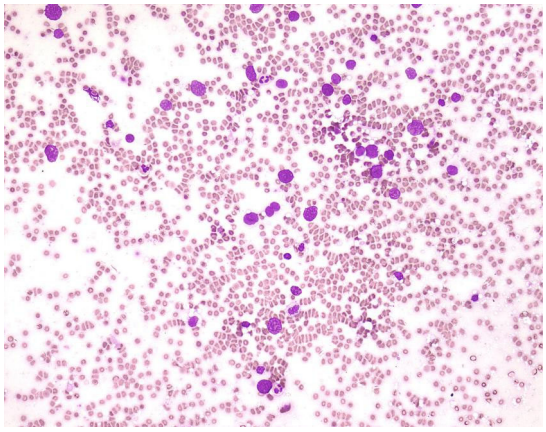
Rhabdomyosarcoma

- Embryonal rhabdomyosarcoma: malignant soft tissue tumor with morphologic and immunophenotypic features of embryonal skeletal muscle (fusion-negative)
- Alveolar rhabdomyosarcoma: malignant neoplasm composed of monomorphic primitive round cells showing skeletal muscle differentiation, with PAX3/7::FOXO1 fusion.



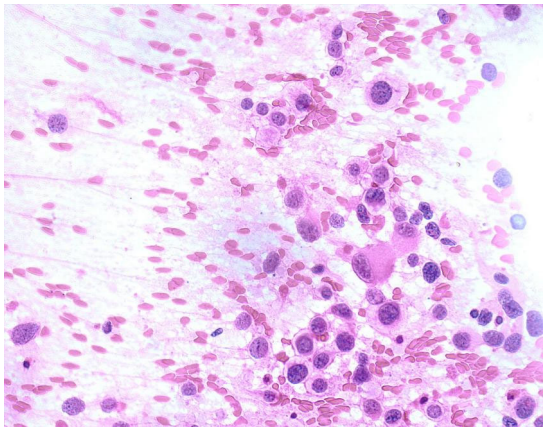
Embryonal Rhabdomyosarcoma

- Morphological and immunophenotypic features of embryonic skeletal muscle
- Cellular smears composed of single cells loosely cohesive clusters
- Primitive small round, stellate and short spindle cells with scant cytoplasm



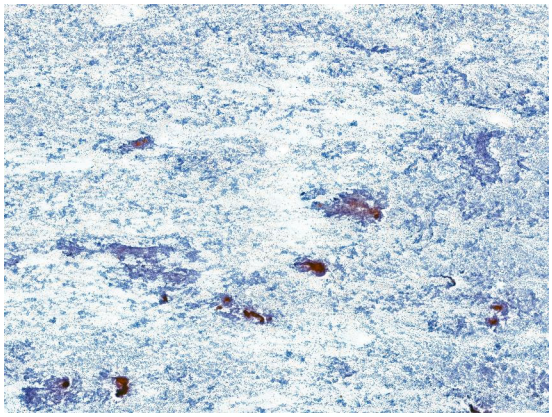
Embryonal Rhabdomyosarcoma

- Morphological and immunophenotypic features of embryonic skeletal muscle
- Cellular smears composed of single cells loosely cohesive clusters
- Primitive small round, stellate and short spindle cells with scant cytoplasm
- Variable rhabdomyoblastic differentiation; tadpole/ribbon-like cells with eosinophilic cytoplasm, rarely cross-striations
- Binucleate and multinucleate cells variably present
- Variably prominent loose myxoid matrix



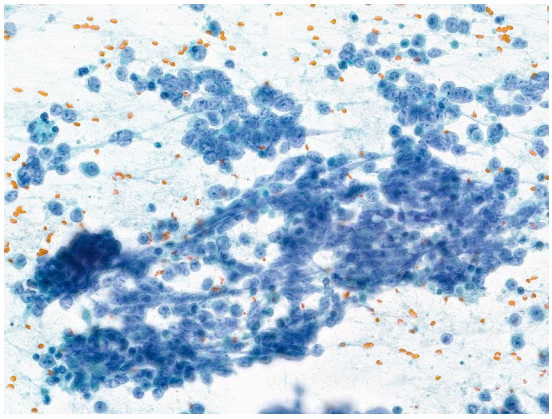
Alveolar Rhabdomyosarcoma

- Hypercellular smears, single cells and loosely cohesive aggregates



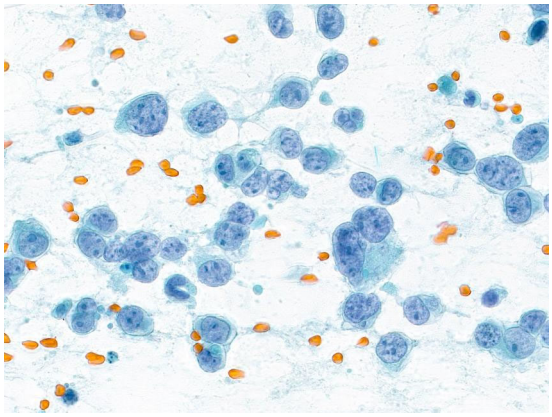
Alveolar Rhabdomyosarcoma

- Hypercellular smears, single cells and loosely cohesive aggregates
- Monomorphic round cells, scant to moderate cytoplasm
- Variable rhabdomyoblastic differentiation, tadpole/ribbon-like cells with eosinophilic cytoplasm, rarely cross-striations



Alveolar Rhabdomyosarcoma

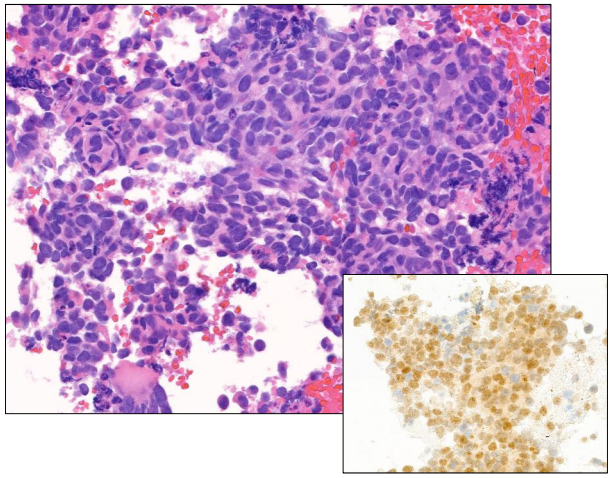
- Hypercellular smears, single cells and loosely cohesive aggregates
- Monomorphic round cells, scant to moderate cytoplasm
- Variable rhabdomyoblastic differentiation, tadpole/ribbon-like cells with eosinophilic cytoplasm, rarely cross-striations
- Binucleate and multinucleated forms, including wreath-like (circular arrangement of nuclei)



Alveolar Rhabdomyosarcoma

- Embryonal RMS IHC:
  - Desmin, MyoD1, variable myogenin (MYF4)
  - H3K27me3 loss
  - HMGA2
- Alveolar RMS IHC:
  - Desmin, MyoD1, myogenin (MYF4)
  - PAX3

- Embryonal RMS MP:
  - *RAS* pathway mutations, *PTEN*, *PIK3CA*, *CTNNB1* mutations
- Alveolar RMS MP:
  - *FOXO1* (*FKHR*) fusions (*PAX3*/*PAX7*::*FOXO1*)




Mass General Brigham