5th Edition WHO Classification of Soft Tissue Tumours

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Educational Objectives

- List the various categories in the classification of soft tissue tumours
- List new entities in each category
- List main distinguishing features (essential and desired criteria) of new entities

Soft Tissue Tumours

5th Edition WHO Bone and Soft Tissue

- Adipocytic Tumours
- Fibroblastic / Myofibroblastic Tumours
- So-called Fibrohistiocytic Tumours
- Vascular Tumours
- Pericytic (perivascular) Tumours
- Smooth Muscle Tumours
- Skeletal Muscle Tumours
- Gastrointestinal Stromal Tumour
- Chondro-osseous Tumours
- Peripheral Nerve Sheath Tumours
- Tumours of Uncertain Differentiation
- Undifferentiated small round cell sarcomas of bone and soft tissue

Atypical spindle cell / pleomorphic lipomatous tumor
Pleomorphic myxoid liposarcoma

EWSR1-SMAD3 positive fibroblastic tumour (emerging)
Superficial CD34 positive fibroblastic tumour

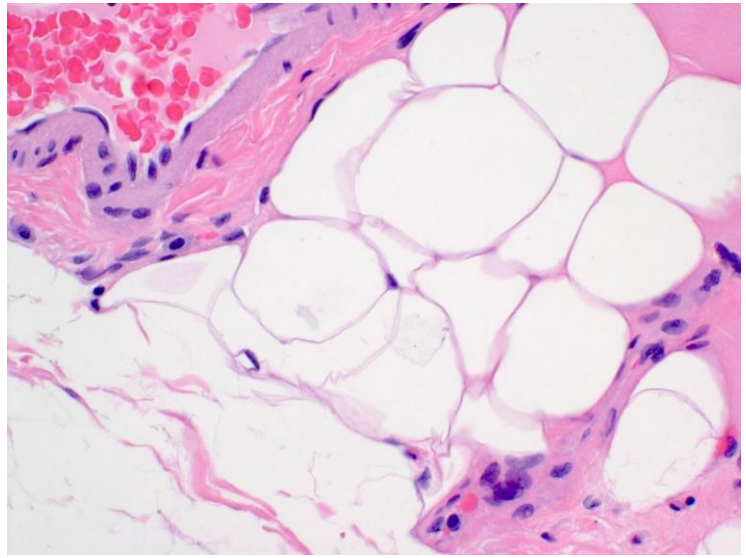
EBV associated smooth muscle tumor
Inflammatory leiomyosarcoma

Malignant melanotic nerve sheath tumour

NTRK-rearranged spindle cell neoplasm (emerging)

Round cell sarcoma with EWSR1-non-ETS fusion
CIC-rearranged sarcoma
Sarcoma with BCOR genetic alterations

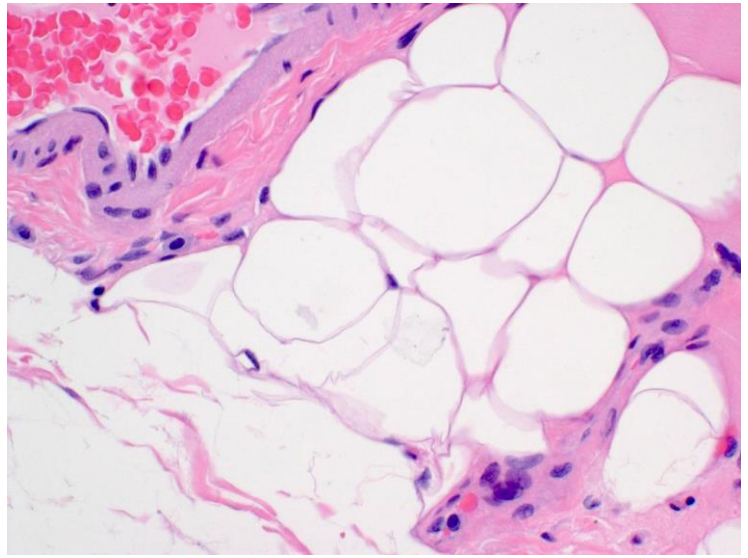
Adipocytic Tumours



Benign

- Lipoma
- Lipomatosis
- Lipomatosis of nerve
- Lipoblastoma and lipoblastomatosis
- Angiolipoma
- Myolipoma of soft tissue
- Chondroid lipoma
- Spindle cell lipoma and pleomorphic lipoma
- Atypical spindle cell / pleomorphic lipomatous tumour
- Hibernoma

Adipocytic Tumours



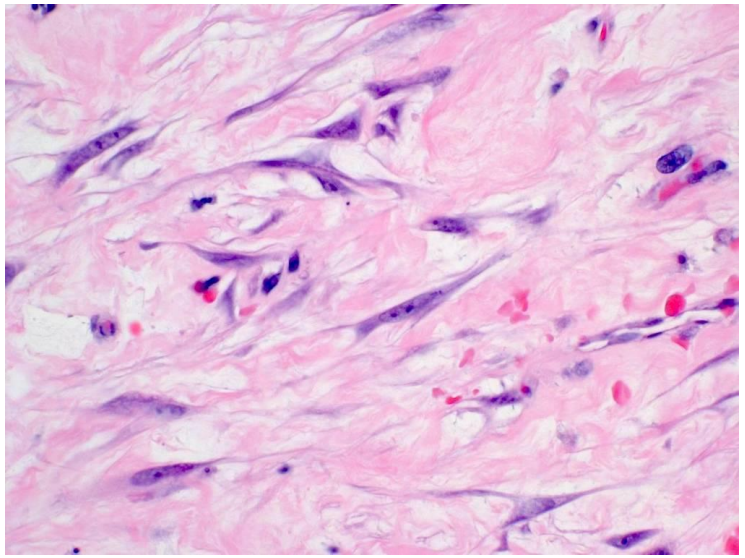
Intermediate

- Atypical lipomatous tumour / well-differentiated liposarcoma

Malignant

- Dedifferentiated liposarcoma
- Myxoid liposarcoma
- Pleomorphic liposarcoma
- Myxoid pleomorphic liposarcoma

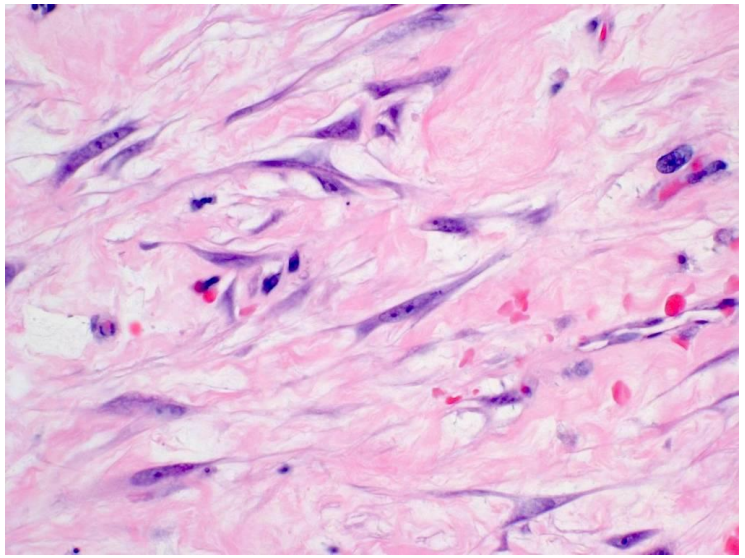
Fibroblastic / Myofibroblastic



Benign

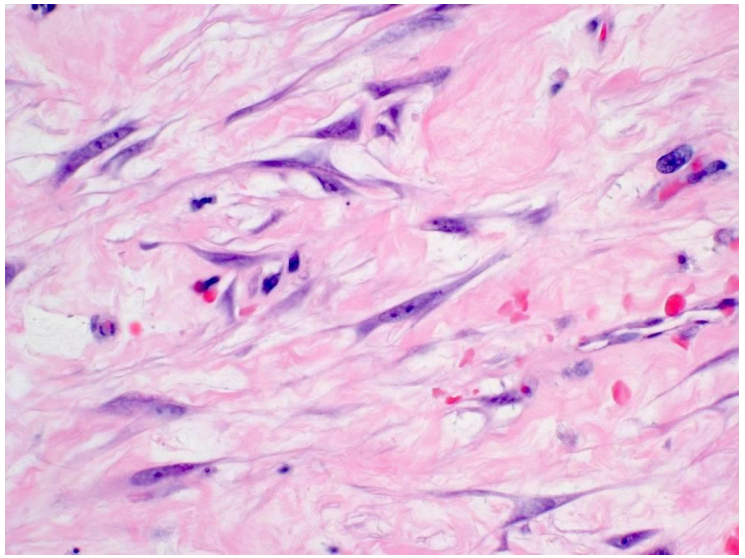
- Nodular fasciitis
- Proliferative fasciitis and proliferative myositis
- Myositis ossificans and fibro-osseous pseudotumour of digits
- Ischaemic fasciitis
- Elastofibroma
- Fibrous hamartoma of infancy
- Fibromatosis colli
- Juvenile hyaline fibromatosis
- Inclusion body fibromatosis

Fibroblastic / Myofibroblastic



- Fibroma of tendon sheath
- Desmoplastic fibroblastoma
- Myofibroblastoma
- Calcifying aponeurotic fibroma
- EWSR1-SMAD3-positive fibroblastic tumour (emerging)
- Angiomyofibroblastoma
- Cellular angiofibroma
- Angiofibroma of soft tissue
- Nuchal-type fibroma
- Acral fibromyxoma
- Gardner fibroma

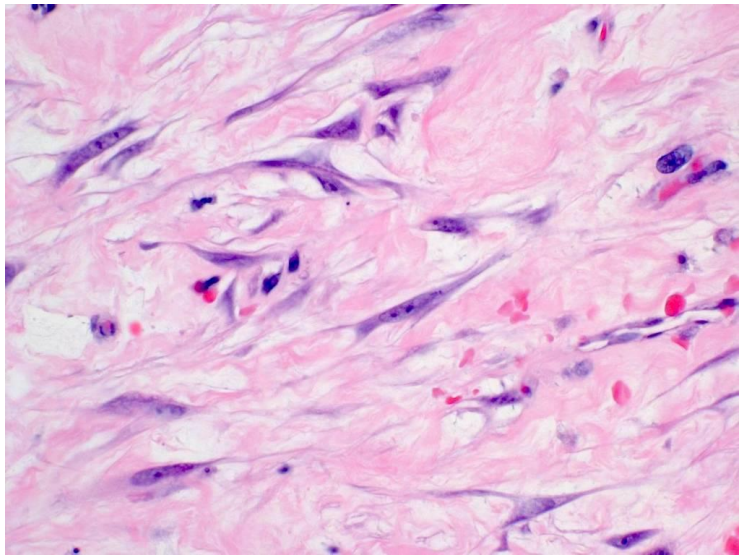
Fibroblastic / Myofibroblastic



Intermediate (locally aggressive)

- Solitary fibrous tumour, benign
- Palmar and plantar fibromatosis
- Desmoid fibromatosis
- Lipofibromatosis
- Giant cell fibroblastoma

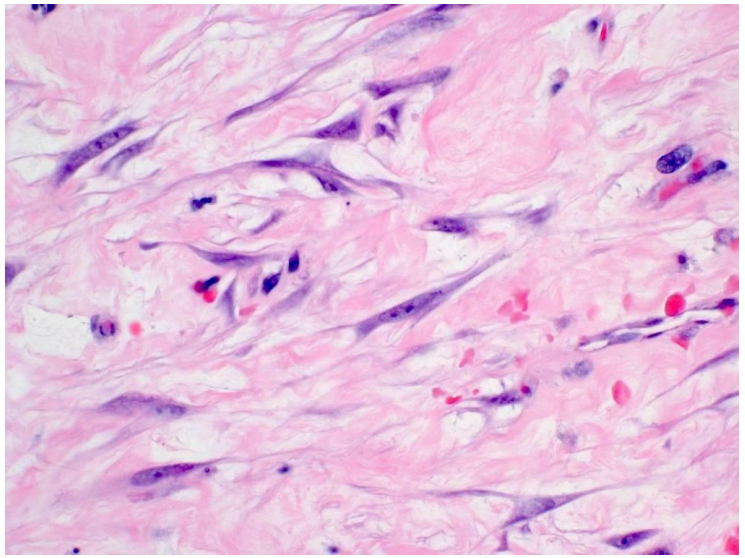
Fibroblastic / Myofibroblastic



Intermediate (rarely metastasizing)

- Dermatofibrosarcoma protuberans, NOS, pigmented, fibrosarcomatous, myoid, plaque-like
- Solitary fibrous tumour, NOS, fat forming, and giant cell rich
- Inflammatory myofibroblastic tumour and epithelioid inflammatory myofibroblastic sarcoma
- Myofibroblastic sarcoma
- Superficial CD34-positive fibroblastic tumour
- Myxoinflammatory fibroblastic sarcoma
- Infantile fibrosarcoma

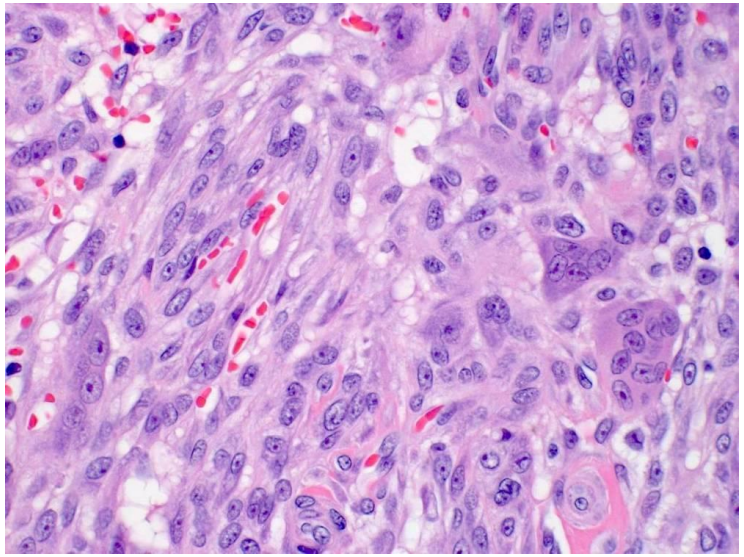
Fibroblastic / Myofibroblastic



Malignant

- Solitary fibrous tumor, malignant
- Fibrosarcoma, NOS
- Myxofibrosarcoma and Epithelioid myofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-called fibrohistiocytic tumours



Benign

- Tenosynovial giant cell tumour, NOS, diffuse
- Benign deep fibrous histiocytoma

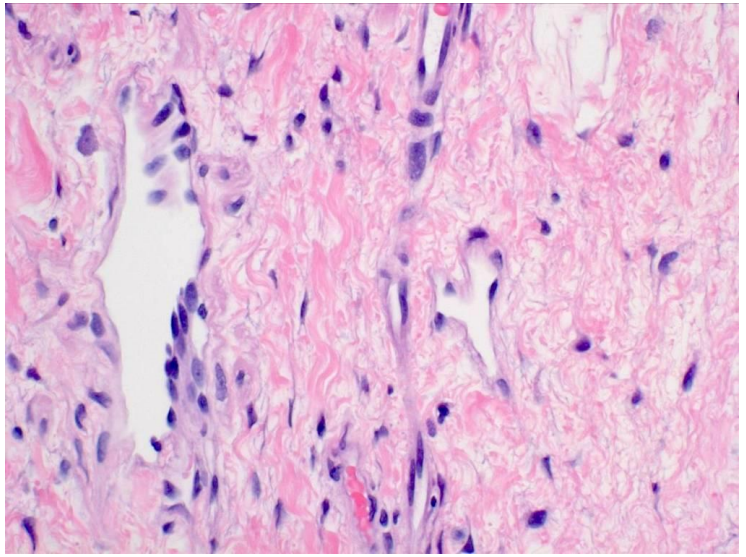
Intermediate (rarely metastasizing)

- Plexiform fibrohistiocytic tumour
- Giant cell tumour of soft tissue

Malignant

Malignant tenosynovial giant cell tumor

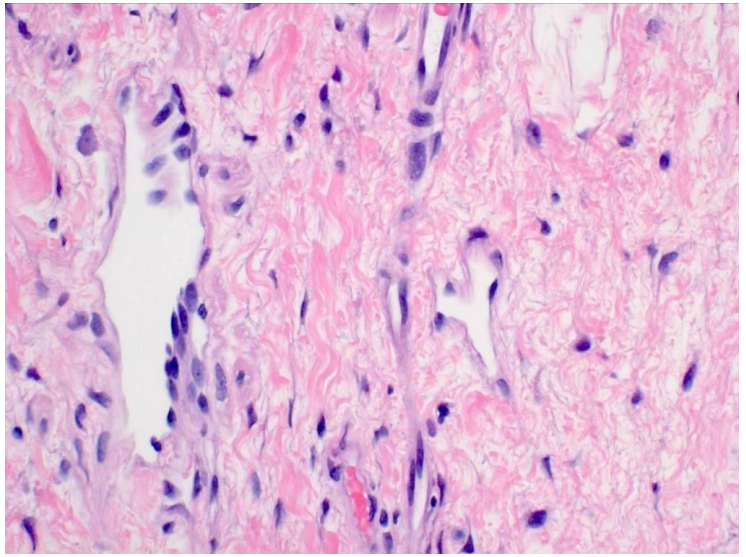
Vascular Tumours



Benign

- Haemangioma, NOS
- Synovial haemangioma
- Intramuscular angioma
- Arteriovenous malformation/haemangioma
- Venous haemangioma
- Anastomosing haemangioma
- Epithelioid haemangioma
- Lymphangioma and lymphangiomatosis
- Cystic lymphangioma
- Acquired tufted haemangioma

Vascular Tumours



Intermediate (locally aggressive)

- Kaposiform haemangioendothelioma

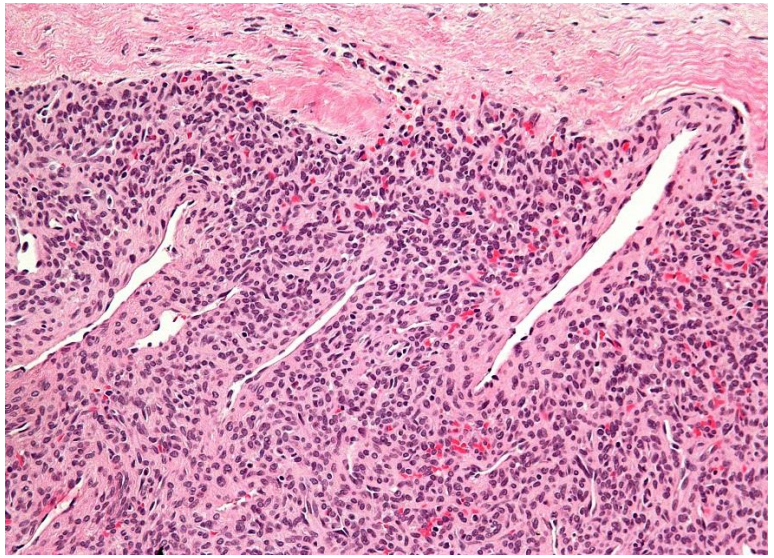
Intermedate (rarely metastasizing)

- Retiform haemangioendothelioma
- Papillary intralymphatic angioendothelioma
- Composite haemangioendothelioma
- Kaposi sarcoma
- Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma

Malignant

- Epithelioid haemangioendothelioma, NOS
- Epithelioid haemangioendothelioma with WWTR1-CAMTA1 fusion
- Epithelioid haemangioendothelioma with YAP1-TFE3 fusion
- Angiosarcoma

Pericytic (perivascular) tumours



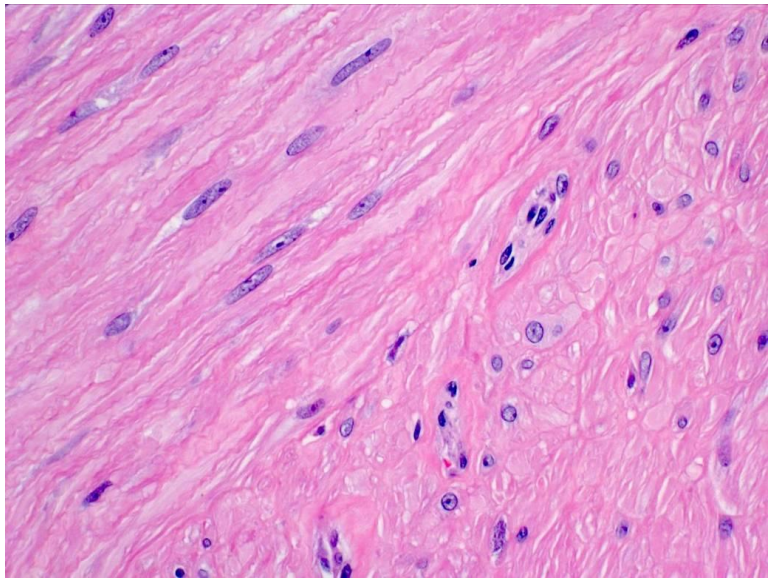
Benign and intermediate

- Glomus tumour, NOS
  - Glomangioma
  - Glomaniomyoma
  - Glomangiomatosis
  - Glomus tumor of uncertain malignant potential
- Myopericytoma
  - Myofibroma
  - Myofibromatosis
  - Infantile myofibromatosis
- Angioleiomyoma

Malignant

- Glomus tumor, malignant

Smooth muscle tumours



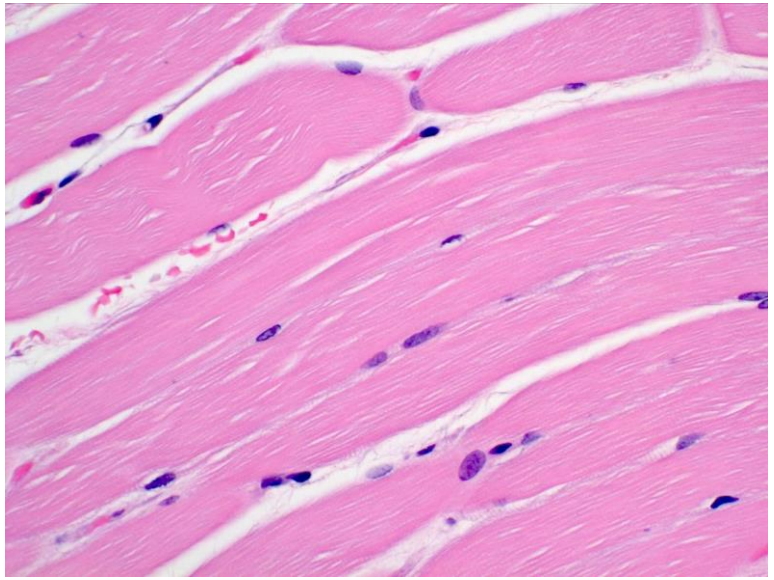
Benign and intermediate

- Leiomyoma
- EBV-associated smooth muscle tumour

Malignant

- Inflammatory leiomyosarcoma
- Leiomyosarcoma

Skeletal muscle tumours



Benign

- Rhabdomyoma, NOS, fetal, adult, genital

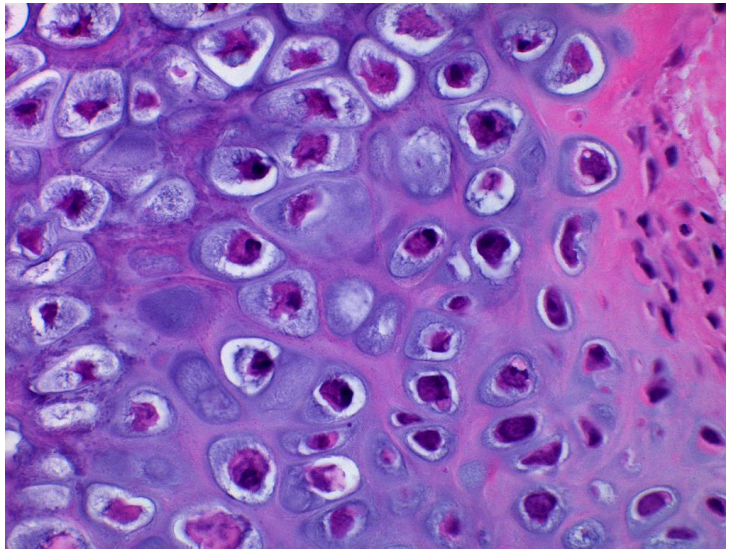
Malignant

- Embryonal rhabdomyosarcoma, NOS, pleomorphic
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma, NOS
- Spindle cell rhabdomyosarcoma
  - Congenital spindle cell rhabdomysarcoma with VGLL2/NCOA2/CITED2 rearrangements
  - MYOD1-mutant spindle cell / sclerosing rhabdomyosarcoma
  - Intraosseous spindle cell rhabdomyosarcoma (with TFCP2/NCOA2 rearrangements
- Ectomesenchymoma

Gastrointestinal stromal tumours

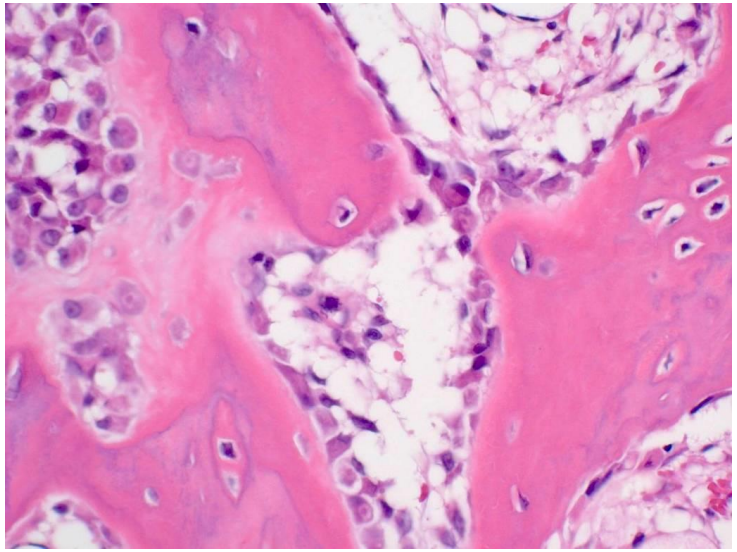
- Gastrointestinal stromal tumor

Chondro-osseous tumours



Benign

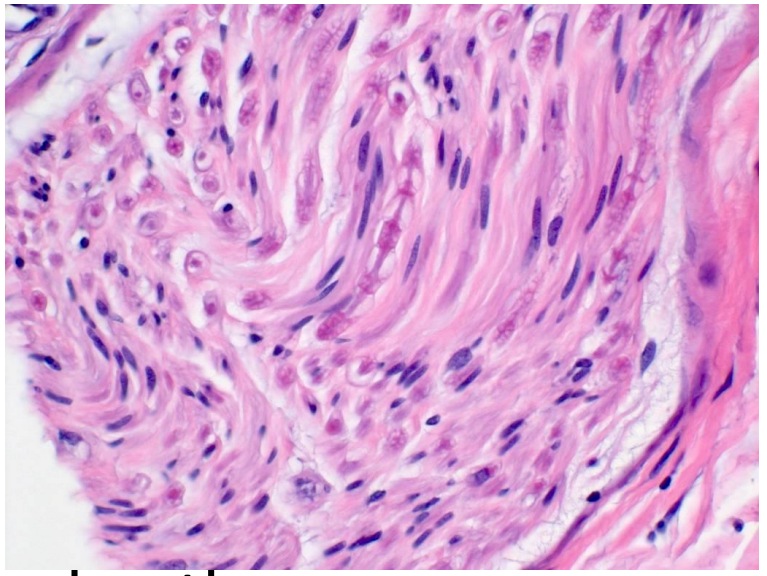
- Soft tissue chondroma, NOS
- Chondroblastoma-like soft tissue chondroma



Malignant

- Extraskeletal osteosarcoma

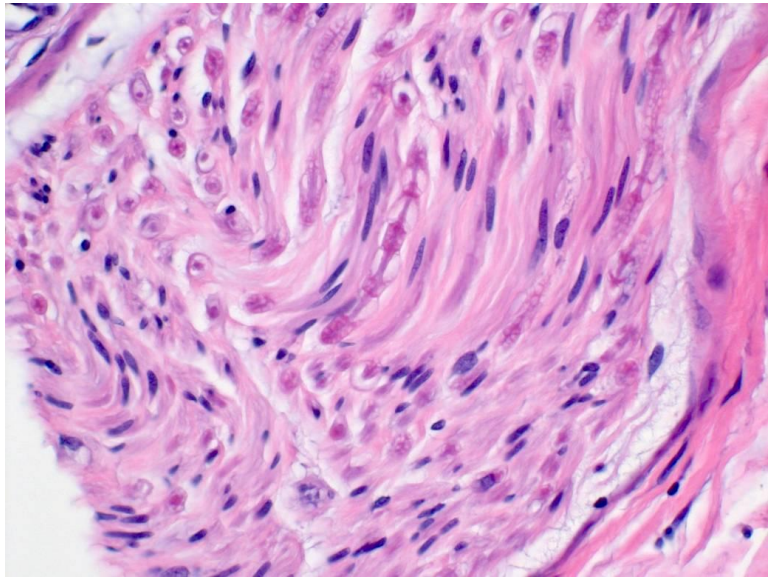
Peripheral nerve sheath tumours



Benign

- Schwannoma, NOS
  - Ancient, cellular, plexiform, epithelioid, microcystic/reticular
- Neurofibroma, NOS
  - Ancient, cellular, atypical, plexiform
- Perineurioma, NOS
  - Reticular perineurioma
  - Sclerosing perineurioma
- Granular cell tumour, NOS
- Dermal nerve sheath myxoma
- Solitary circumscribed neuroma
- Ectopic meningioma and meningothelial hamartoma
- Benign triton tumour / neuromuscular choristoma
- Hybrid nerve sheath tumour

Peripheral nerve sheath tumours



Malignant

- Malignant peripheral nerve sheath tumour, NOS
- Epithelioid malignant peripheral nerve sheath tumor
- Malignant melanotic nerve sheath tumour
- Granular cell tumor, malignant
- Perineurioma, malignant

Tumours of uncertain differentiation

Benign

- Myxoma, NOS
- Myxoma, cellular
- Intramuscular myxoma
- Juxta-articular myxoma
- Deep (aggressive) angiomyxoma
- Pleomorphic hyalinizing angiectatic tumour of soft parts
- Phosphaturic mesenchymal tumour, NOS
- PEComa, benign
- Angiomyolipoma

Tumours of uncertain differentiation

Intermediate (rarely metastasizing)

- Atypical fibroxanthoma
- Angiomatoid fibrous histiocytoma
- Ossifying fibromyxoid tumour, NOS
- Mixed tumour, NOS
- Myoepithelioma, NOS

Intermediate (locally aggressive)

- Haemosiderotic fibrolipomatous tumour
- Angiomyolipoma, epithelioid

Tumours of uncertain differentiation

Malignant

- Phosphaturic mesenchymal tumour
- NTRK-rearranged spindle cell neoplasm (emerging)
- Synovial sarcoma, NOS, monophasic spindle cell, biphasic, poorly differentiated
- Epithelioid sarcoma, classic, proximal (large cell)
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Desmoplastic small round cell tumour
- Extrarenal rhabdoid tumour
- PEComa, malignant
- Intimal sarcoma
- Ossifying fibromyxoid tumor, malignant
- Myoepithelial carcinoma
- Undifferentiated sarcoma
  - Spindle cell sarcoma, undifferentiated
  - Pleomoprhic sarcoma, undifferentiated
  - Round cell sarcoma, undifferentiated

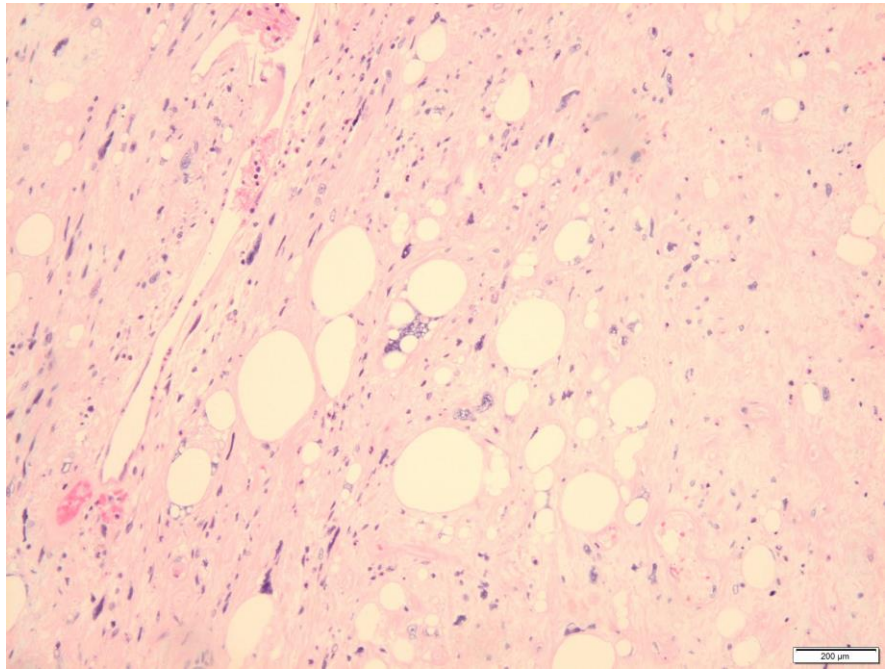
Undifferentiated small round cell sarcomas of bone and soft tissue

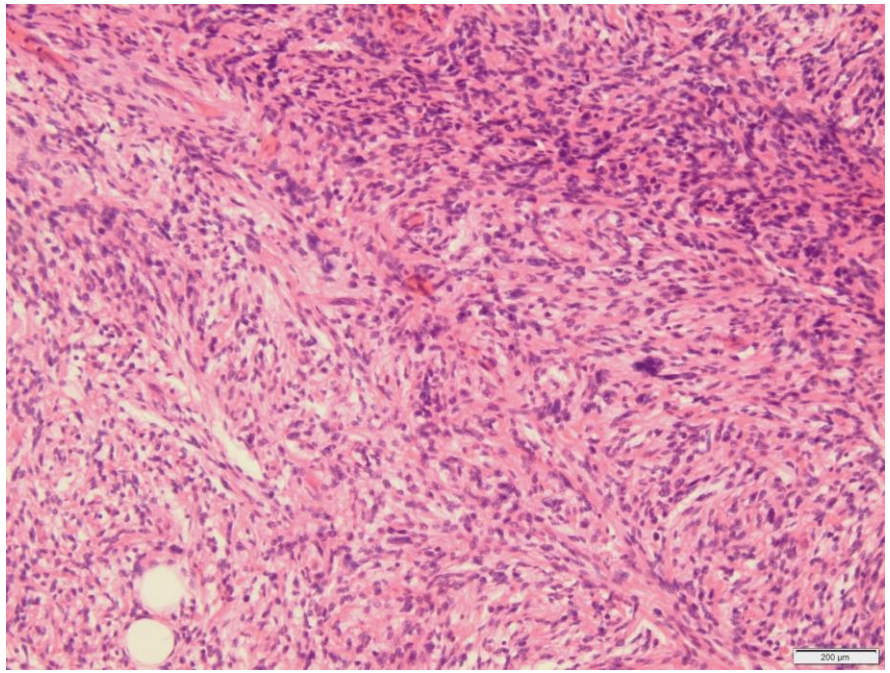
- Ewing sarcoma
- Round cell sarcoma with EWSR1-non-ETS fusions
- CIC-rearranged sarcoma
- Sarcoma with BCOR genetic alterations

New Entities

Atypical spindle cell / pleomorphic lipomatous tumour

- **Benign** adipocytic neoplasm most commonly involves **hands or feet**
- Multinodular growth with **ill-defined tumour margins**
- **Variable proportions of atypical spindle cells, adipocytes, lipoblasts, pleomorphic cells, multinucleated giant cells, and a myxoid or collagenous extracellular matrix**.
- Variable CD34, desmin, S100 expression by IHC
- **No MDM2 nuclear expression** by IHC / No for MDM2 amplification by FISH
- **Loss of RB1 nuclear expression** by IHC / Deletion of RB1 by FISH
- Low tendency for **local recurrence (10-15%)** if incompletely excised
- **No risk for dedifferentiation / No documented metastasis**





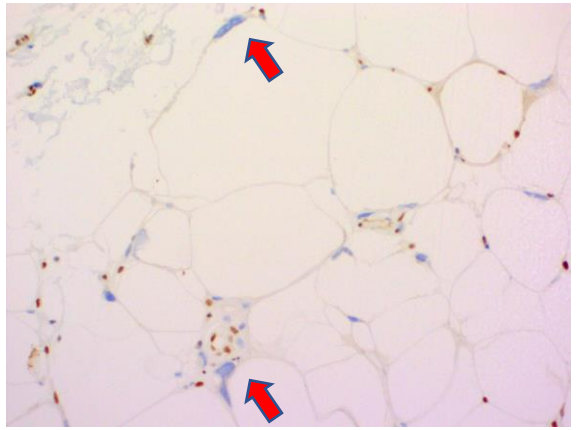
Histology:

Marked variation in adipocytic size with univacuolated to pleomorphic multivacuolated lipoblasts, and **bizarre pleomorphic (multinucleated) cells**, **collagenous** and/or **myxoid** extracellular matrix.

Variable proportions of atypical spindle cells and adipocytes ranging from spindle cell poor to spindle cell rich patterns

- **Spindle cell poor subtype**: Low-cellularity with bland spindle cells, mild atypia and abundant myxoid matrix which tend to occur in the **hands and feet**

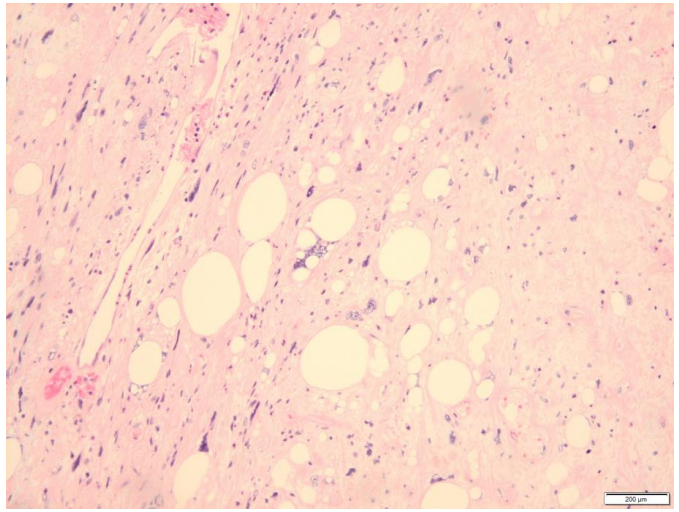
- **Spindle cell rich subtype**: High-cellularity with numerous spindle cells showing diffuse, mild to moderate cytonuclear atypia, easily identified lipoblasts, less extracellular matrix, and fibrosarcoma-like patterns.



Loss of RB nuclear expression in tumour cells

Atypical spindle cell / pleomorphic lipomatous tumour

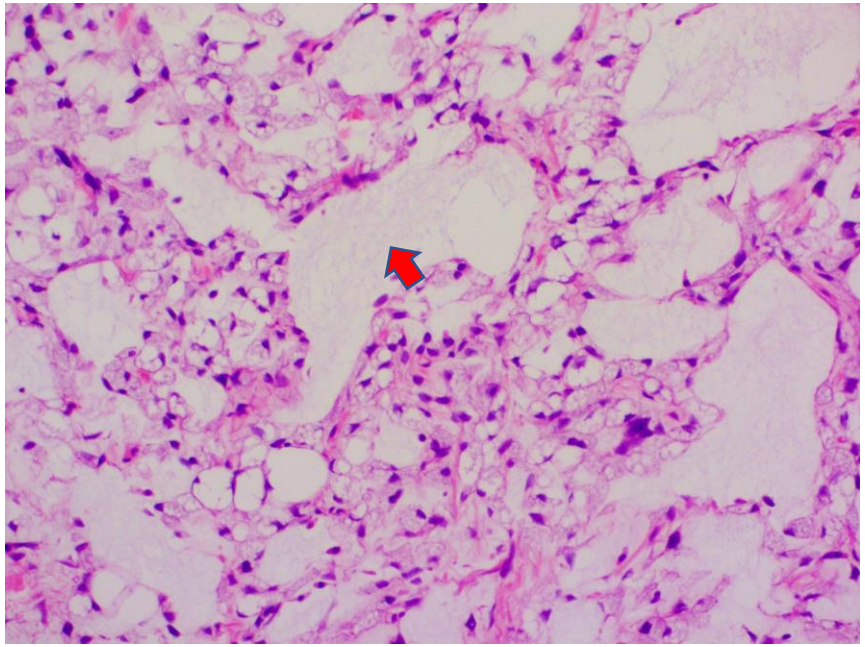
- ***Essential Criteria:*** variable proportions of atypical spindle cells, adipocytes, univacuolated or bivacuolated to multivacuolated lipoblasts, pleomorphic (multinucleated) cells, and a myxoid to collagenous extracellular matrix.

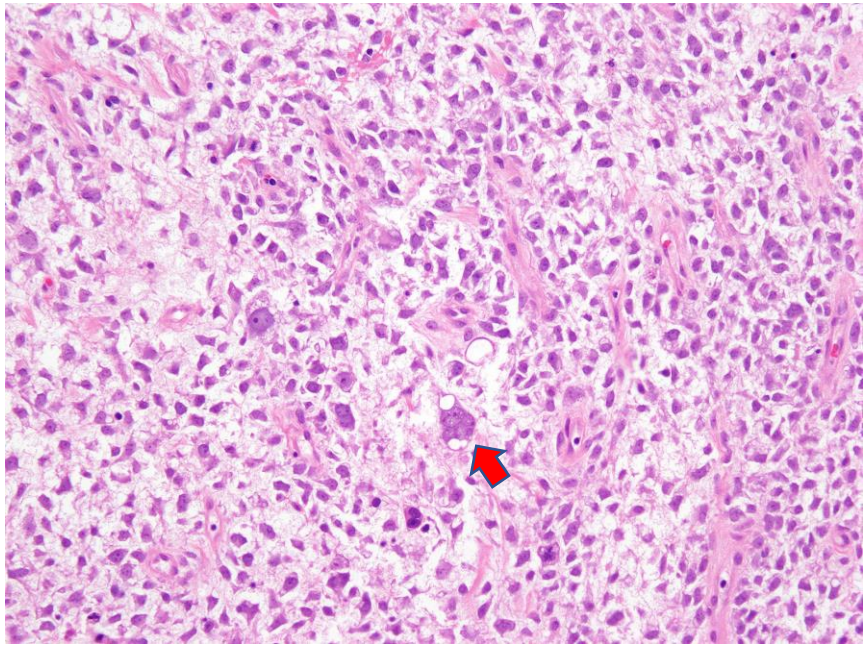


- ***Desirable Criteria (in selected cases):*** in a substantial subset of cases, RB1 expression is lost, correlating with *RB1* deletion; lack of *MDM2* or *CDK4* amplification.

Myxoid pleomorphic liposarcoma

- Rare **aggressive malignant adipocytic neoplasm with high recurrence rate, propensity for metastasis to lung, bone, soft tissue, and poor overall survival**
- **Children and adolescents (most common < age 30 years)**
- **Infiltrative growth with variable proportions of myxoid liposarcoma–like areas transitioning to high-grade pleomorphic liposarcoma–like areas**
- **Lacks the *FUS*/*EWSR1-DDIT3* gene fusions** seen in conventional myxoid liposarcoma
- **Lacks *MDM2* amplification seen in** atypical lipomatous tumour and dedifferentiated liposarcoma.
- May be associated with **Li–Fraumeni syndrome**, numerical chromosomal aberrations, and **inactivation of the *RB1* tumour suppressor gene**.





Histology:
Delicate curvilinear to plexiform capillary network

Lymphangioma-like myxoid pools

Numerous lipoblasts

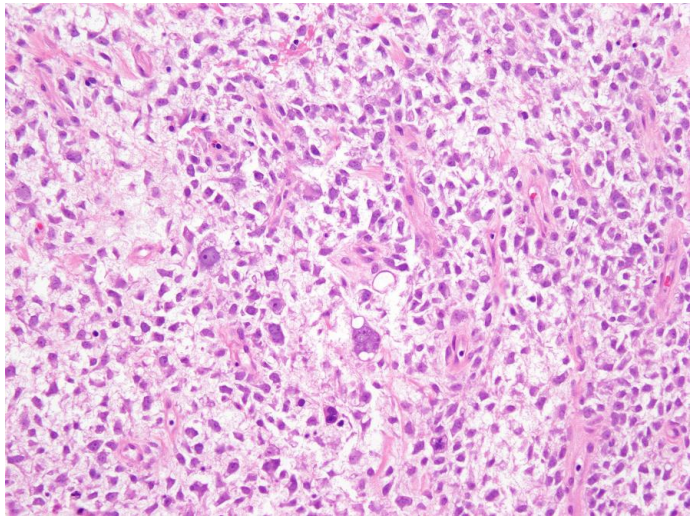
Pleomorphic liposarcoma–like areas with pleomorphic spindled or ovoid cells with hyperchromatic nuclei scattered within the myxoid component

Progressive transition into more-cellular areas with severe **cytological atypia, mitotic activity, and pleomorphic lipoblasts**

Myxoid pleomorphic liposarcoma

- ***Essential Criteria:*** Distinctive admixture of relatively bland zones resembling conventional myxoid liposarcoma and much more cellular and atypical areas, resembling pleomorphic liposarcoma.

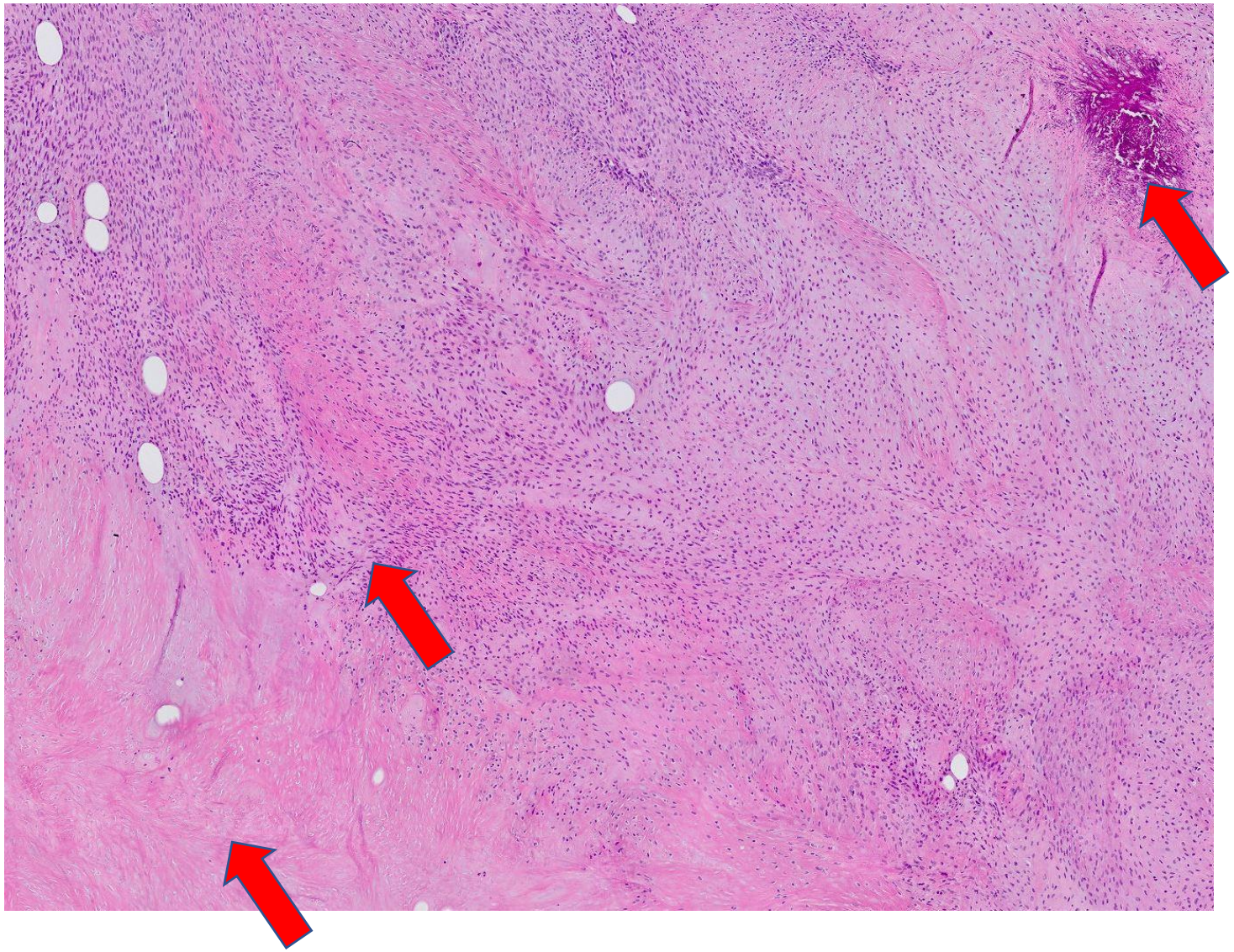
- ***Desirable Criteria (in selected cases):*** Absence of *FUS/EWSR1-DDIT3* gene fusions and *MDM2* amplifications.



EWSR1-SMAD3-positive fibroblastic tumour (emerging/provisional)

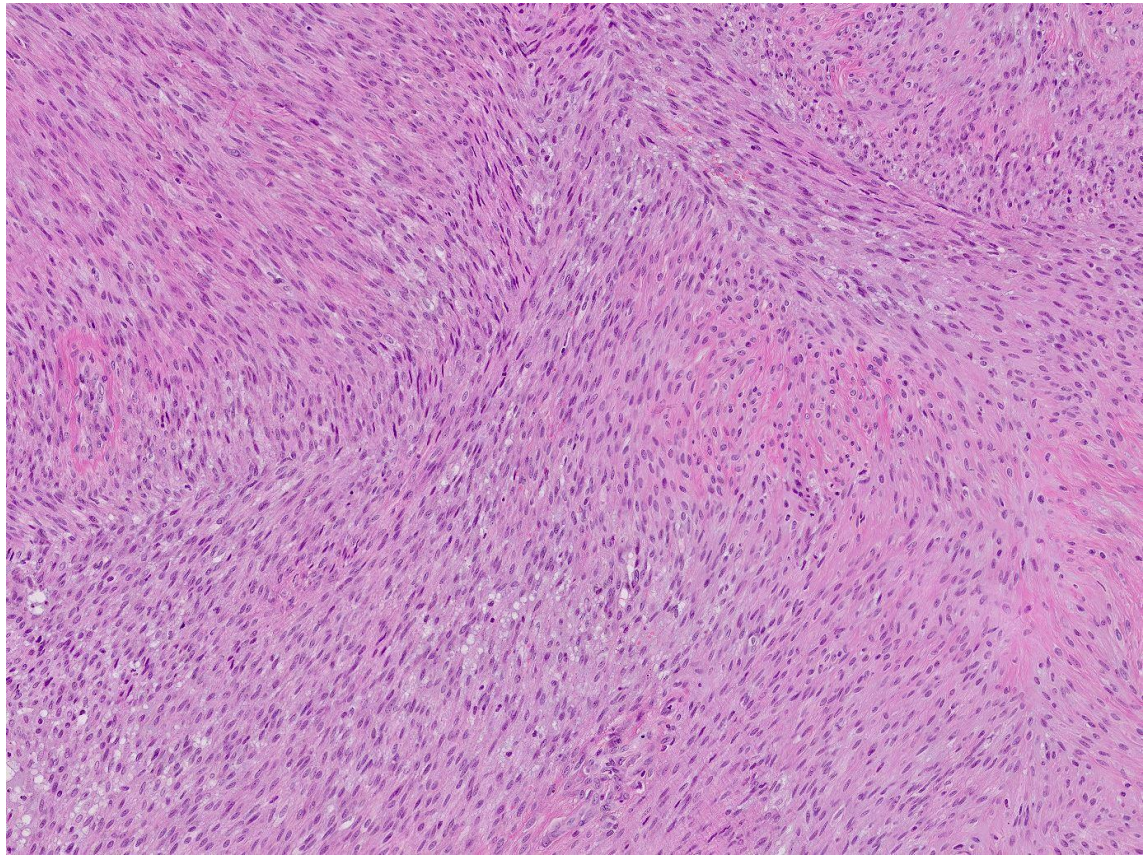
Definition:

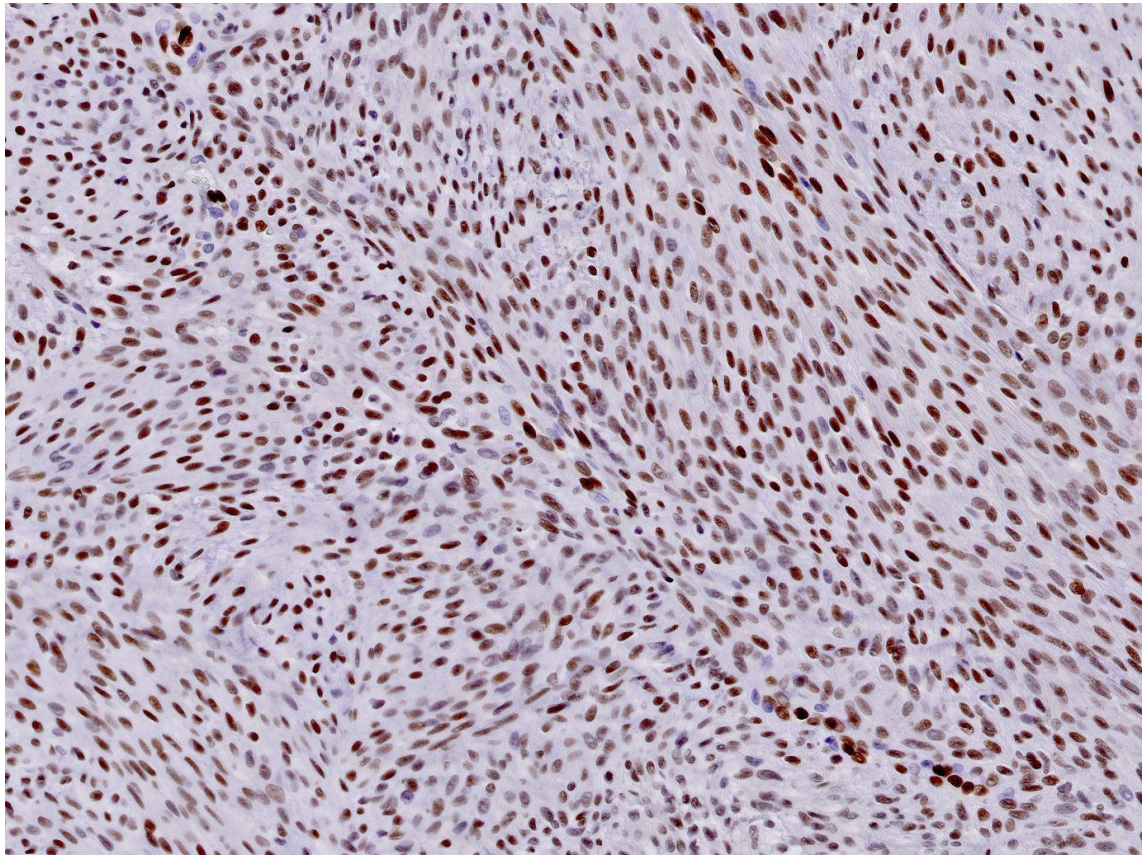
- **Small (1-2 cm)** benign neoplasm of **dermis or subcutis**
- Strong predilection for the hands and feet (**acral sites**)
- **Zonation** with central hyalization and peripheral cellularity
- **Bland monomorphic spindle cells** and areas of **dystrophic calcification**
- Uniform **strong ERG nuclear expression**
- SMA and CD34 negative
- **EWSR1-SMAD3 fusion**
- Local recurrence if incompletely excised



Gross: The tumours are small, measuring **1–2 cm in greatest dimension,** and have a nodular appearance.

Histology: The tumours are typically **well demarcated but show infiltration into subcutaneous fat**. Low-power view showing the characteristic **zonation with an acellular hyalinized centre** and **peripheral areas composed of a cellular spindle cell component**. Focally stippled **dystrophic calcification** may be found.





Peripheral area showing **intersecting fascicles of monomorphic spindle cells** with pale eosinophilic cytoplasm and uniform ovoid nuclei.

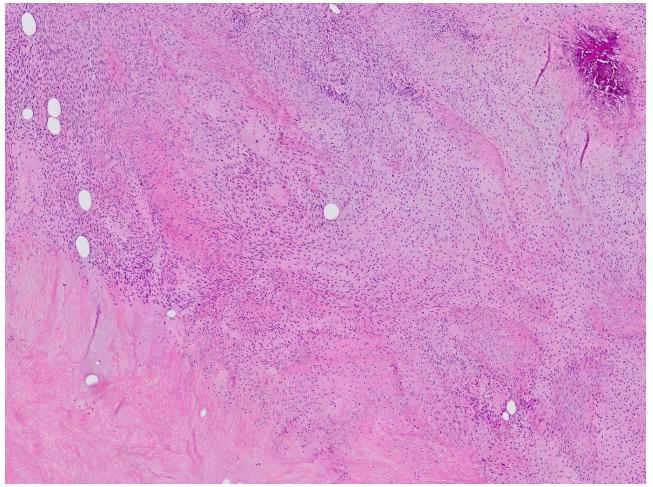
Tumor cells **lack nuclear pleomorphism, hyperchromasia, prominent nucleoli, or mitotic activity**.

Uniform nuclear expression of ERG.
SMA and CD34 are negative.

EWSR1-SMAD3-positive fibroblastic tumour (emerging)

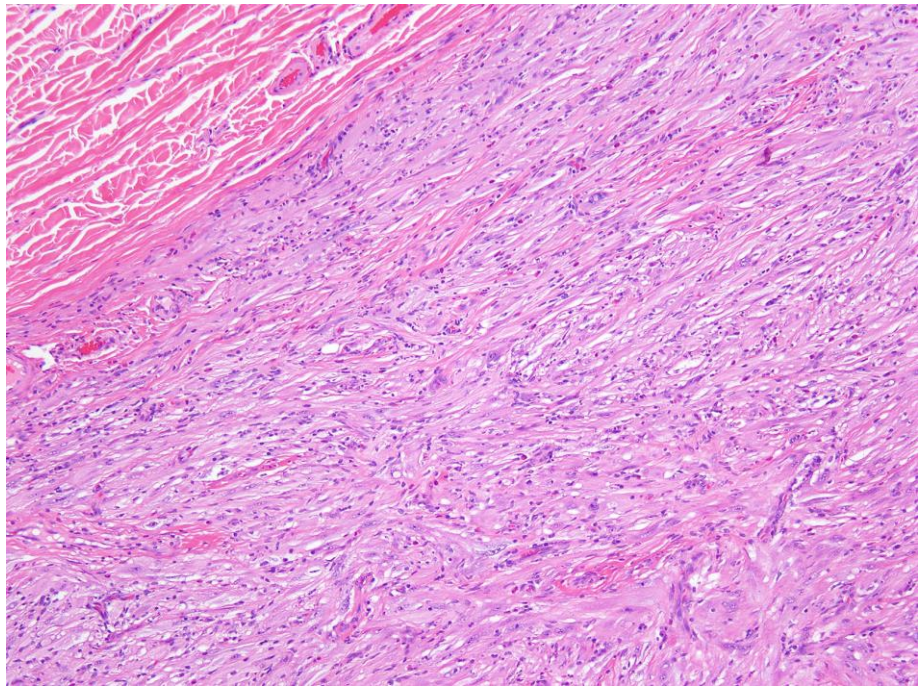
- ***Essential Criteria:*** small dermal and subcutaneous acral nodule; histological zonation with acellular hyalinized centre and peripheral fascicular spindle cell growth; immunoreactivity for ERG.

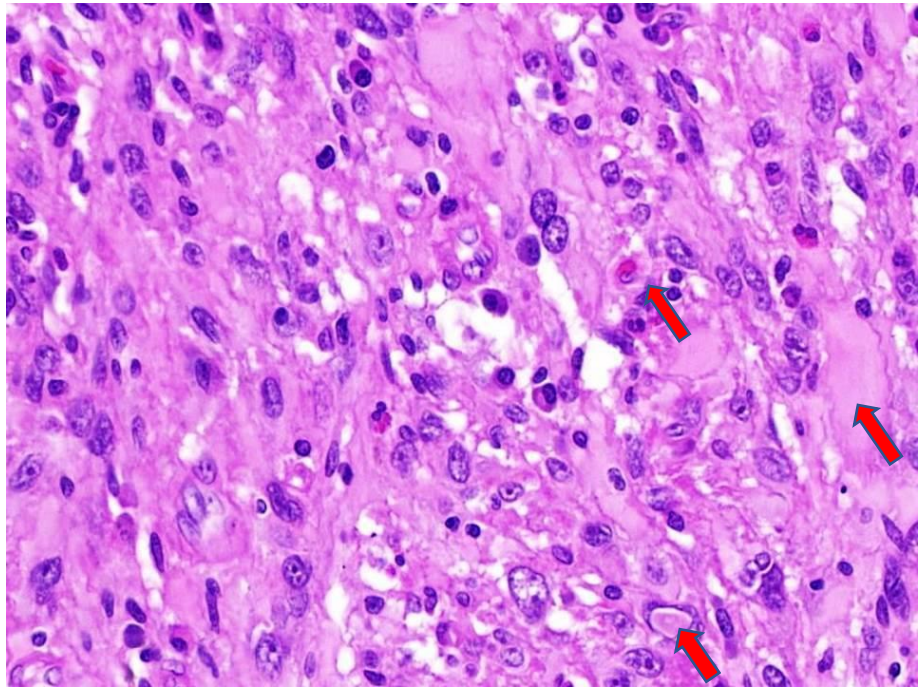
- ***Desirable Criteria (in selected cases)****: EWSR1-SMAD3* fusion (if available).



Superficial CD34-positive fibroblastic tumour

- Distinctive superficial low-grade neoplasm (skin and subcutis)
- Lower extremity, arm, shoulder, buttock
- Spindle cells with abundant granular to glassy eosinophilic cytoplasm arranged in sheets and fascicles with marked pleomorphism and essentially no mitotic activity
- **Uniform CD34 expression** and **frequent aberrant keratin expression**
- PRDM10 gene rearrangements in some cases
- Excellent prognosis (no local recurrence and only one case with lymph node metastasis)





Histology:
Relatively circumscribed, but at least partially infiltrative

Cellular fascicles and sheets of spindled to epithelioid cells

Abundant granular or glassy cytoplasm

Bizarre pleomorphism

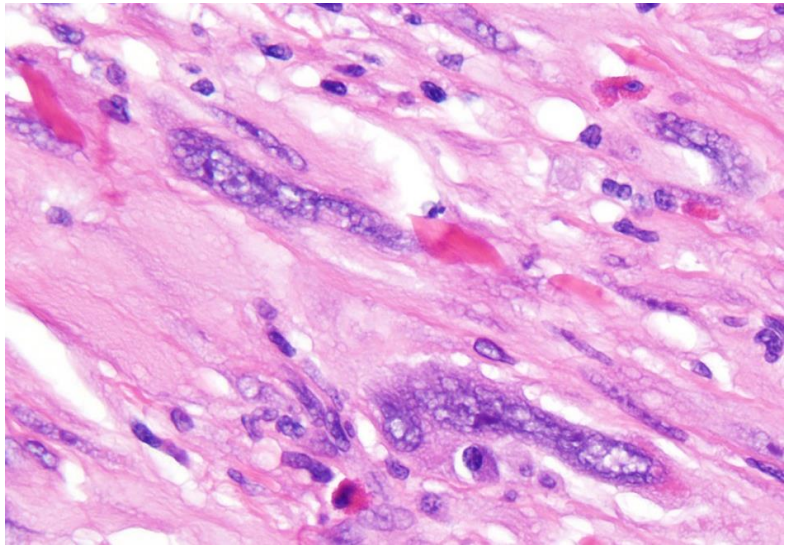
Intranuclear pseudoinclusions

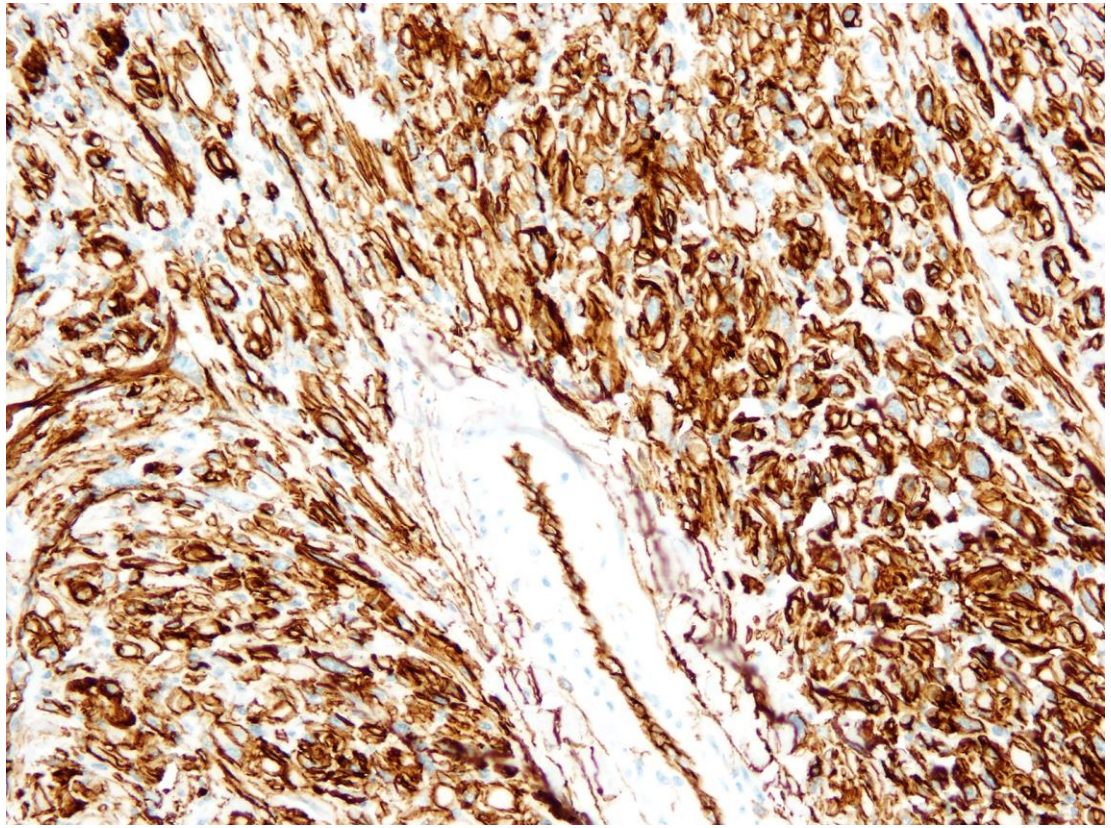
Inflammatory infiltrate with **eosinophils**

Occasional **lipidized cells.**

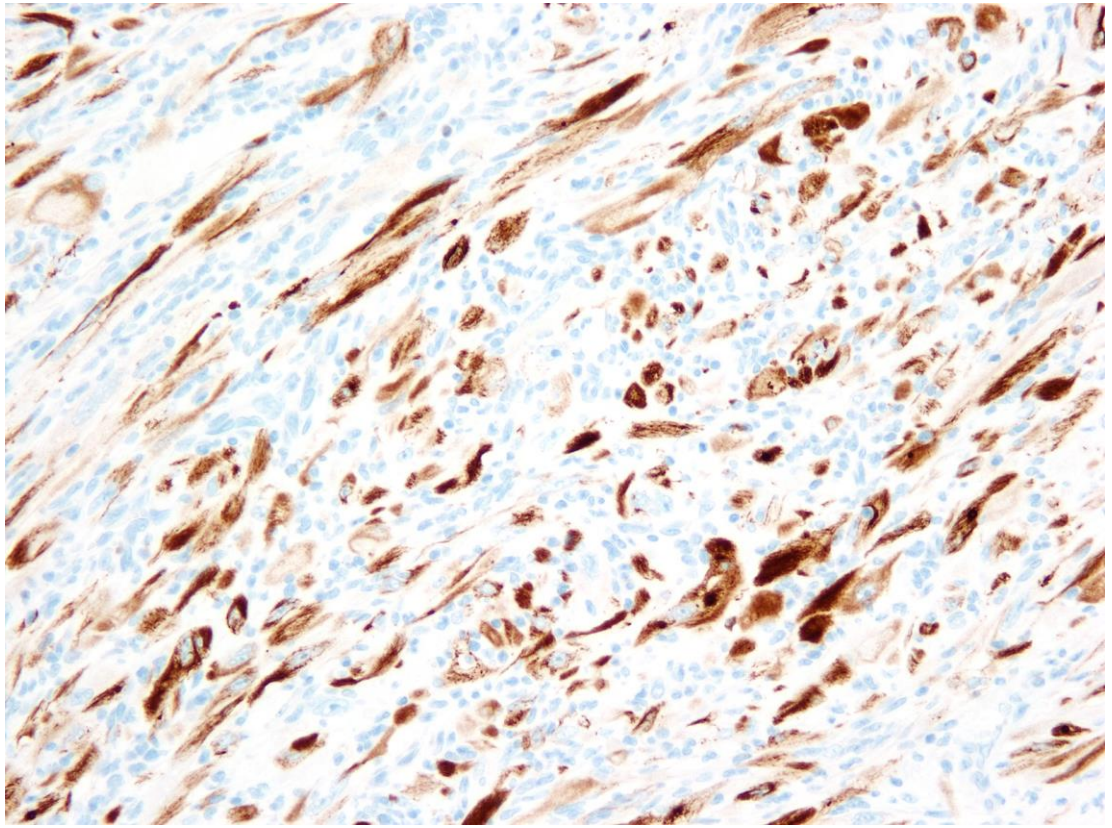
Essentially no mitotic activity

Necrosis is rarely seen.





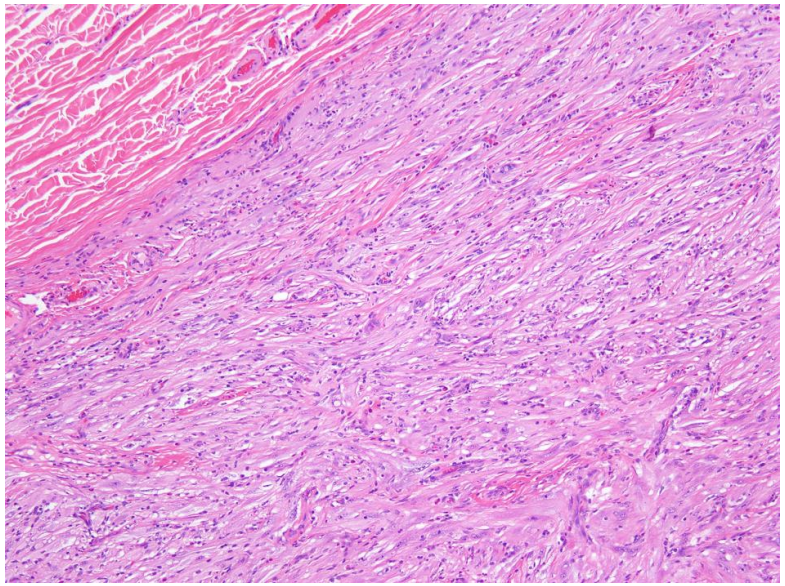
Uniformly **strong CD34 expression**.



Patchy moderate to strong AE1/AE3 keratin expression.

Superficial CD34-positive fibroblastic tumour

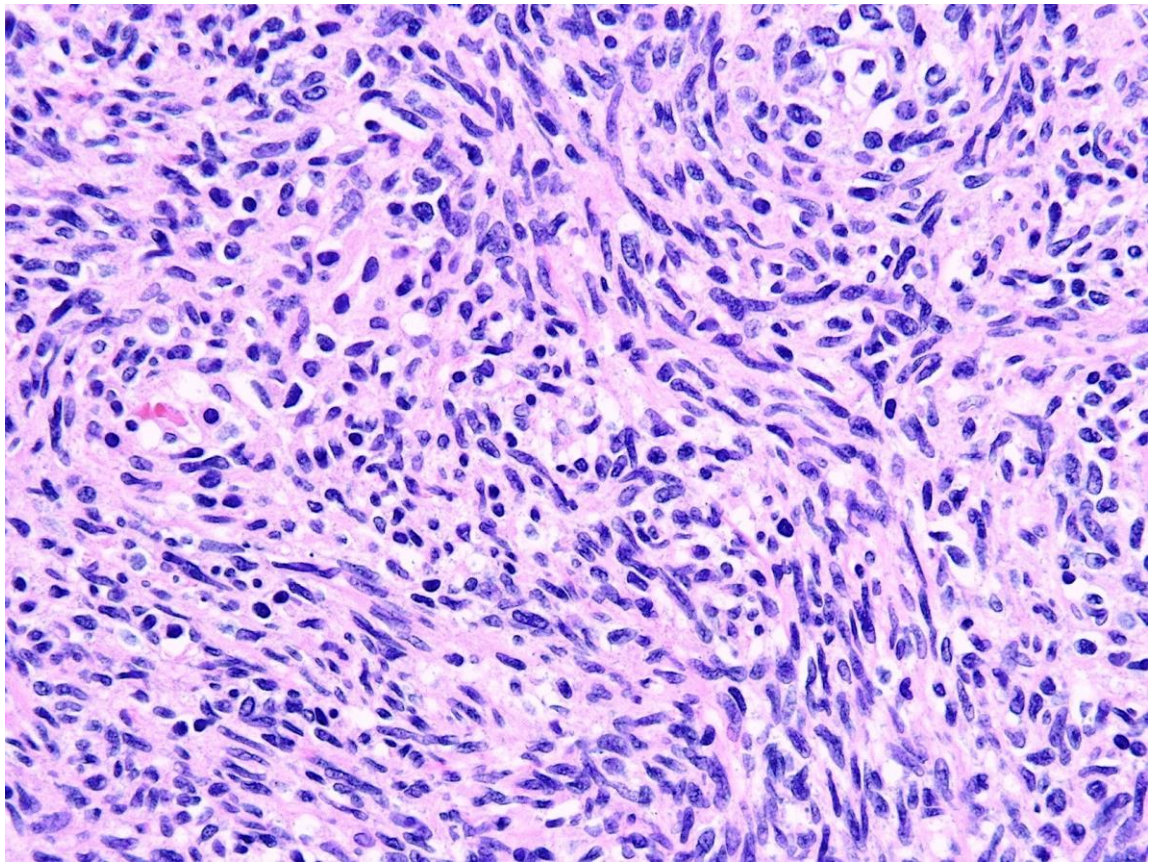
- ***Essential Criteria:*** superficial location; large eosinophilic cells with granular to glassy cytoplasm; marked nuclear pleomorphism but a **very low mitotic count**; diffuse **CD34** expression and frequent **keratin** immunoreactivity.

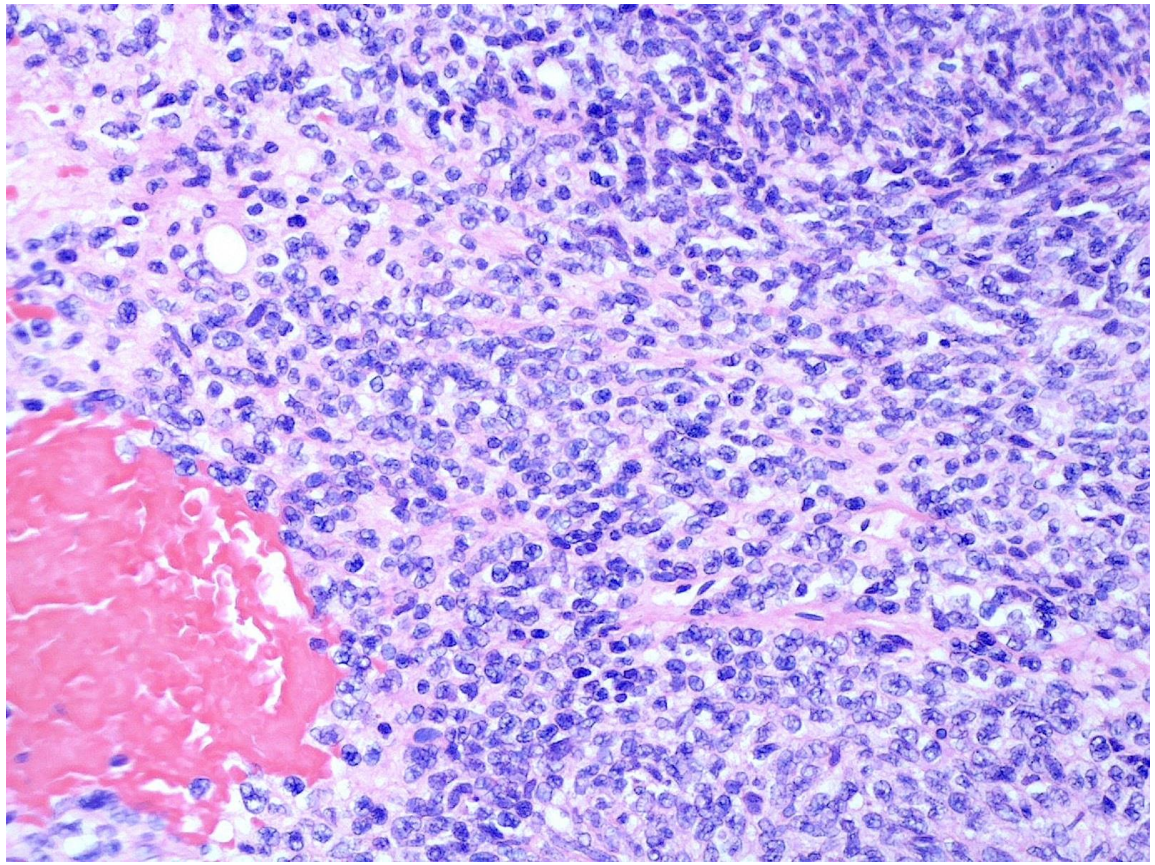


EBV-associated smooth muscle tumour

Definition:

- **Smooth muscle tumour associated with EBV infection**
- Most often in association with **immunosuppression (primary immunodeficiency, post-transplant, HIV, immunosuppressive tx)**
- Presents almost anywhere (skin, soft tissue, organs, CNS)
- HIV associated most common in CNS
- Post-transplant most common in liver (56%), lungs (31%), GI tract (15%)
- Smooth muscle cells or primitive smooth muscle cells and occasional HPC vascular pattern
- **Actin and caldesmon positive** but often desmin negative
- **EBER positive**
- CNS involvement associated with adverse prognosis
- Some post-transplant cases respond to reduction in immunosuppression
- Rarely metastsizes





Intersecting **fascicles of spindled cells** with ample eosinophilic cytoplasm and elongated nuclei

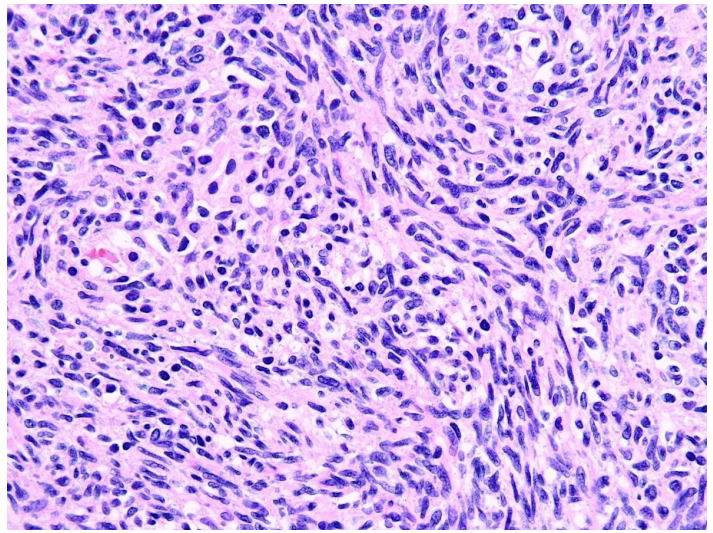
May have HPC-like vascular pattern.

Cytological atypia is usually mild to moderate but can be marked in HIV-positive patients

In about **half of cases, a second population of round, more primitive-appearing smooth muscle cells** is seen.

EBV-associated smooth muscle tumour

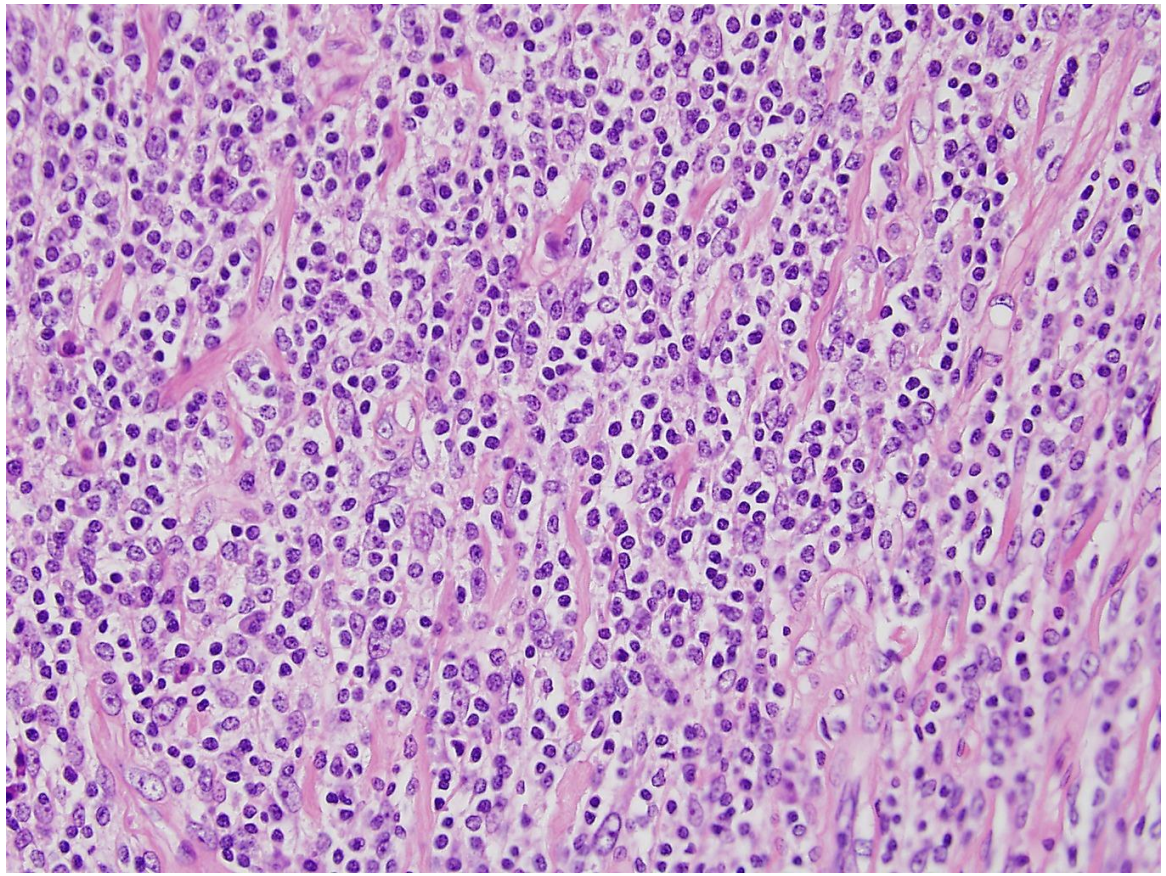
- ***Essential Criteria:*** clinical history of immunosuppression; neoplasm with smooth muscle differentiation; positivity for EBER transcripts by in situ hybridization.



Inflammatory leiomyosarcoma

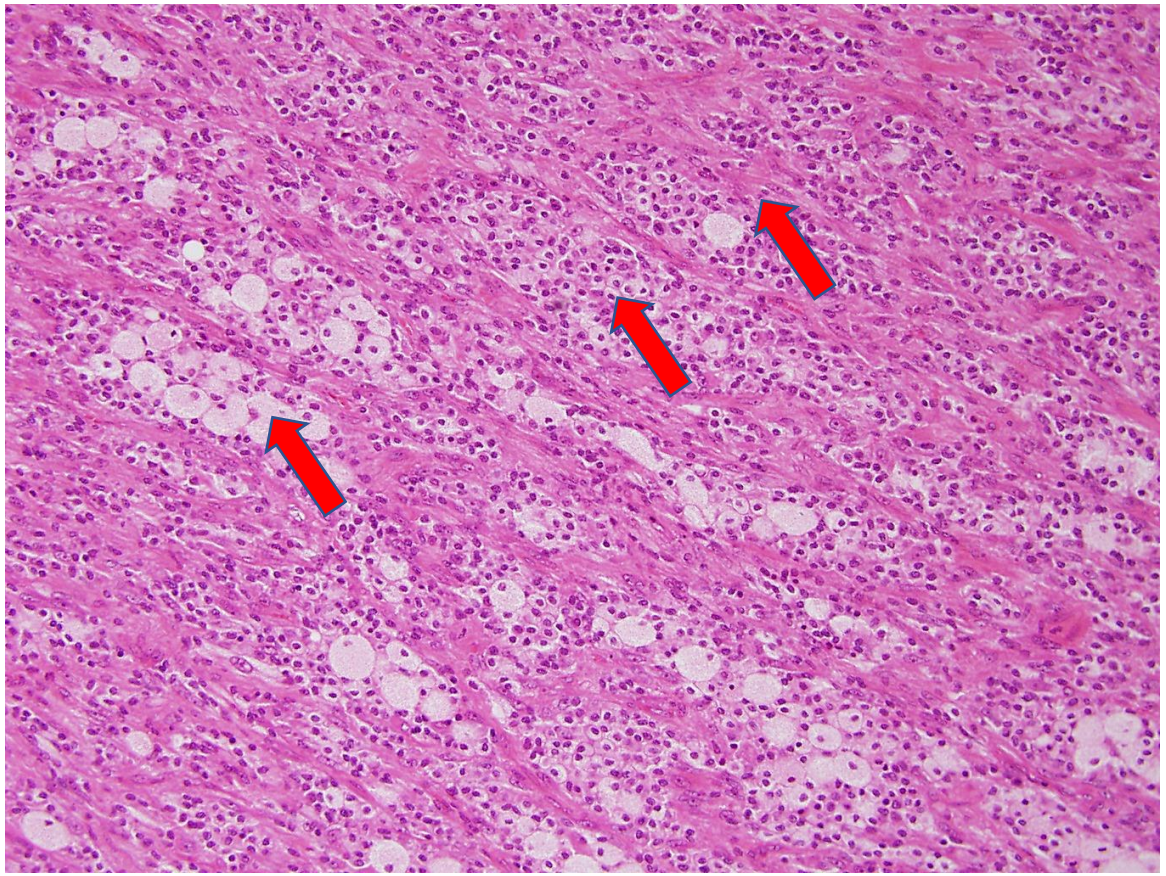
Definition:

- Rare malignant neoplasm showing **smooth muscle differentiation**, a **prominent inflammatory infiltrate**, and **near-haploidization**.
- Deep soft tissue
- Atypical spindle cells with blunt-ended nuclei arranged in fascicles and storiform configurations
- **Neoplastic cells obscured by inflammatory infiltrate (lymphocytes and plasma cells)**
- **Clusters of foamy cells** and **psammomatous calcifications**
- Low metastatic potential and fairly good prognosis



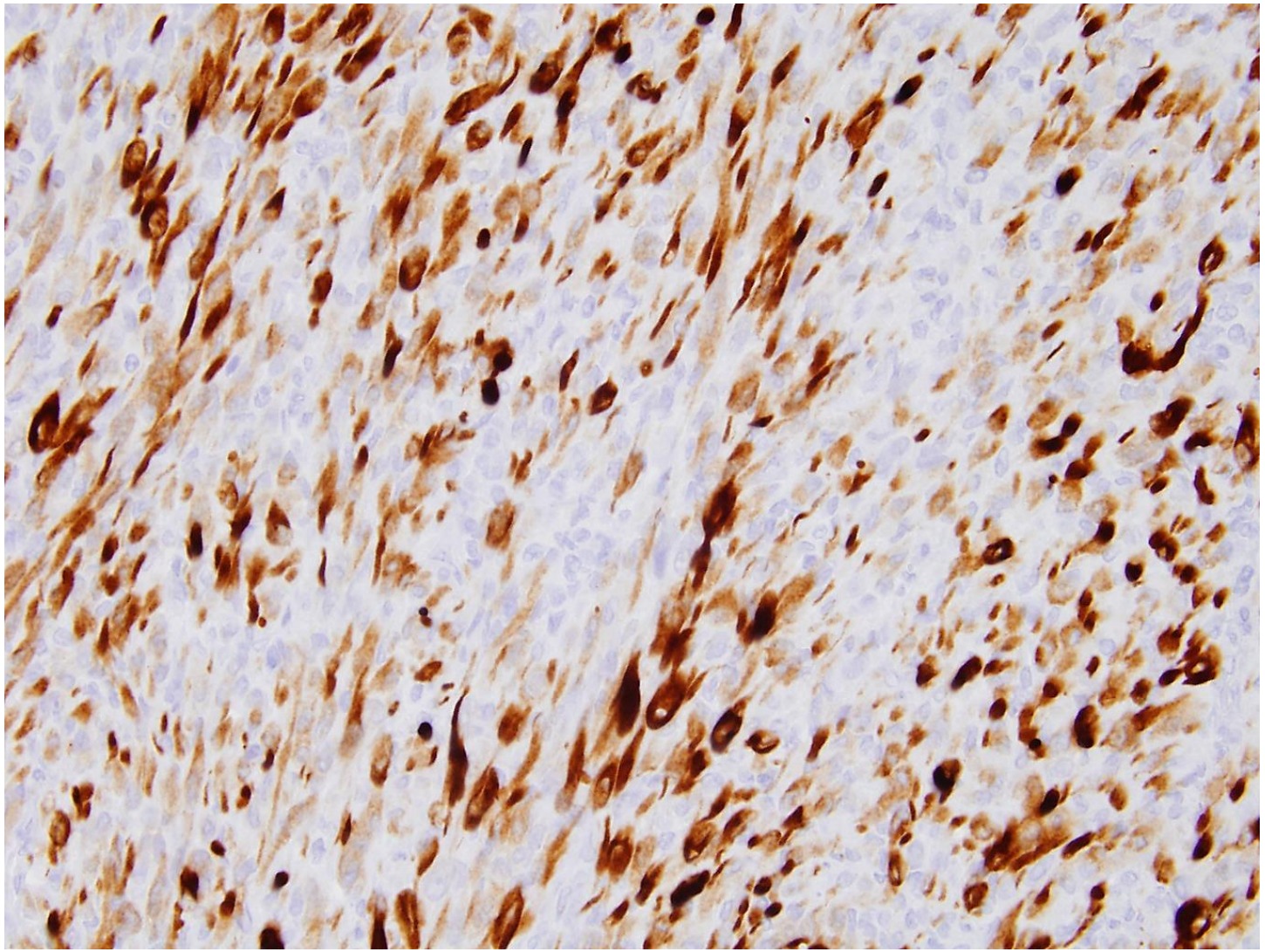
Circumscribed neoplasm composed of **eosinophilic spindle cells with blunt-ended elongated nuclei, arranged in fascicles or storiform fashion**.

Variable cytological atypia and mitotic activity



Prominent, usually diffuse, inflammatory infiltrate (lymphocytes, plasma cells) obscures the neoplastic spindle cell population.

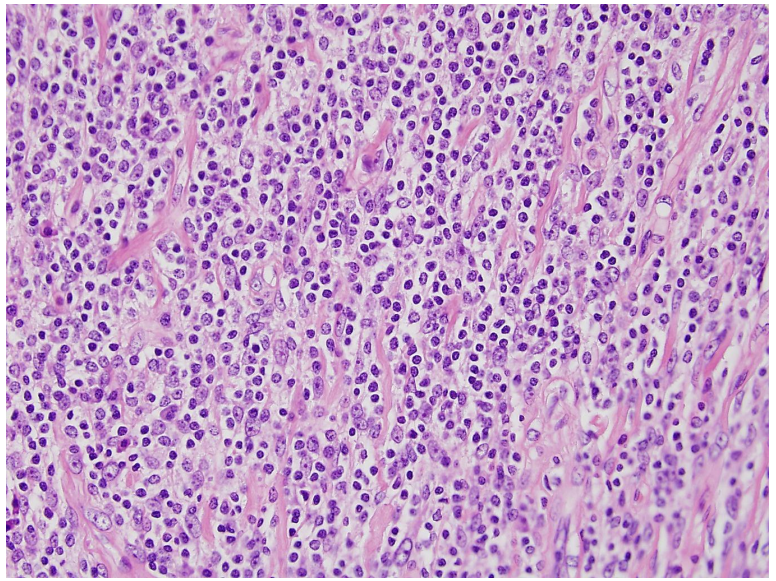
Clusters of **foamy histiocytes**



The neoplastic spindle cells are highlighted by **desmin**

Inflammatory leiomyosarcoma

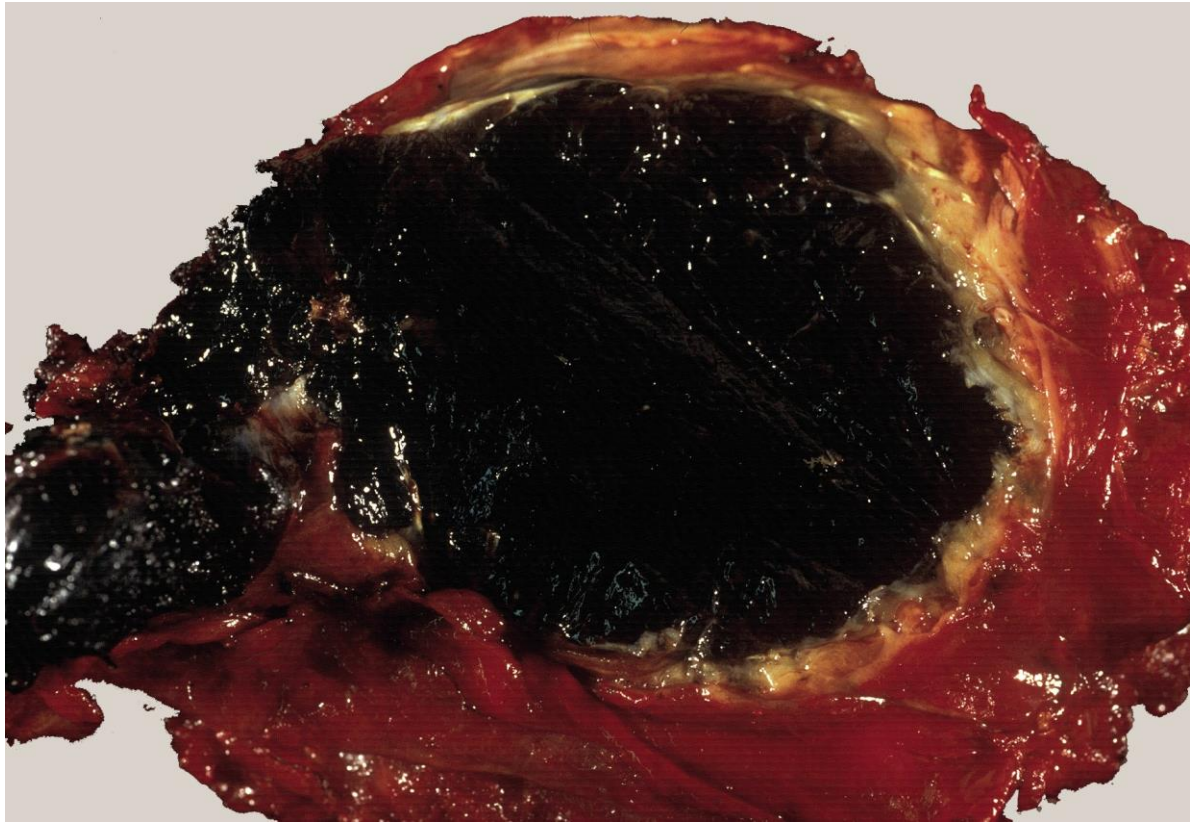
- ***Essential Criteria:*** fascicular proliferation of variably atypical eosinophilic spindle cells, which show mitotic activity; dense inflammatory infiltrate, most often lymphoid or histiocytic/xanthomatous, but the composition is variable; immunopositivity for smooth muscle antigens.

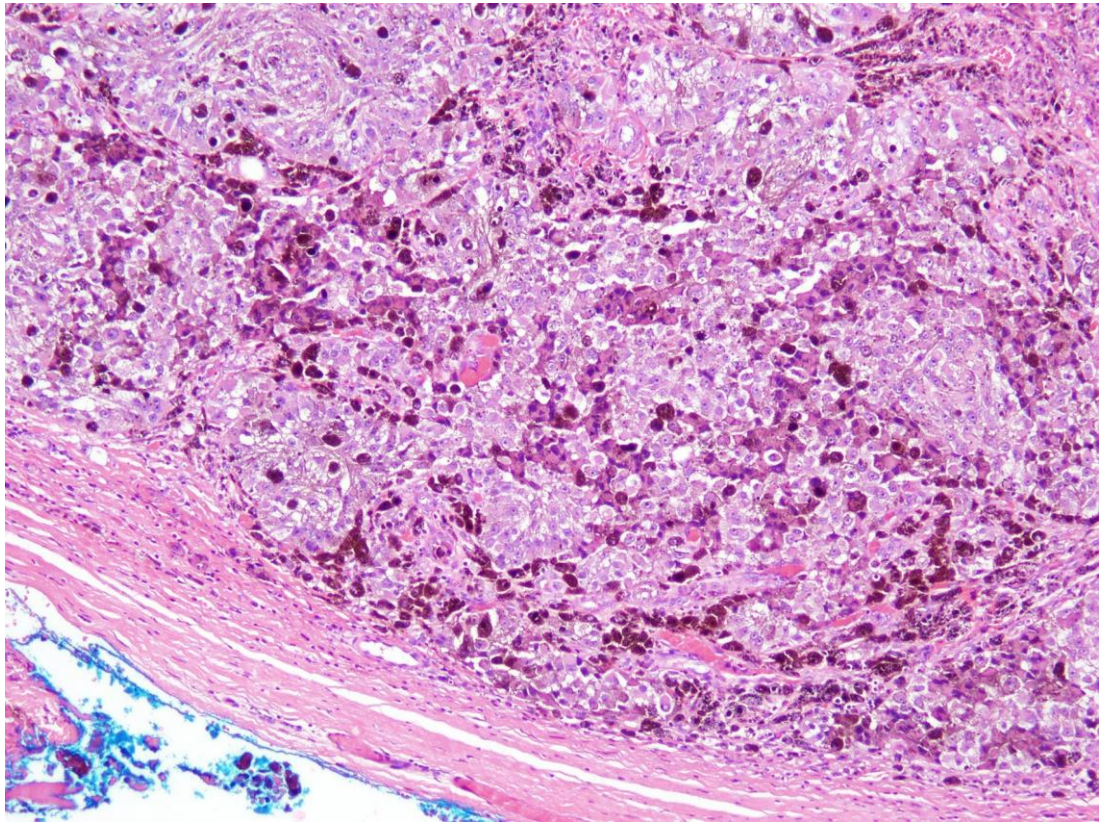


Malignant melanotic nerve sheath tumour

Definition:

- Rare **peripheral nerve sheath tumour composed uniformly of Schwann cells showing melanocytic differentiation**
- Usually arising in association with **spinal or autonomic nerves**.
- Variably associated with **Carney complex and mostly presents in adults**
- *PRKAR1A* mutations and **loss of PRKAR1A protein expression are seen in the overwhelming majority of cases.**
- **Strongly expression of S100, SOX10, HMB45, melan-A, and tyrosinase**.
- **PRKAR1A expression is typically lost.**
- **Originally thought to be benign (melanotic schwannoma)**
- **Now known to exhibit aggressive behaviour, with a local recurrence rate and metastatic risk of 26–44%**





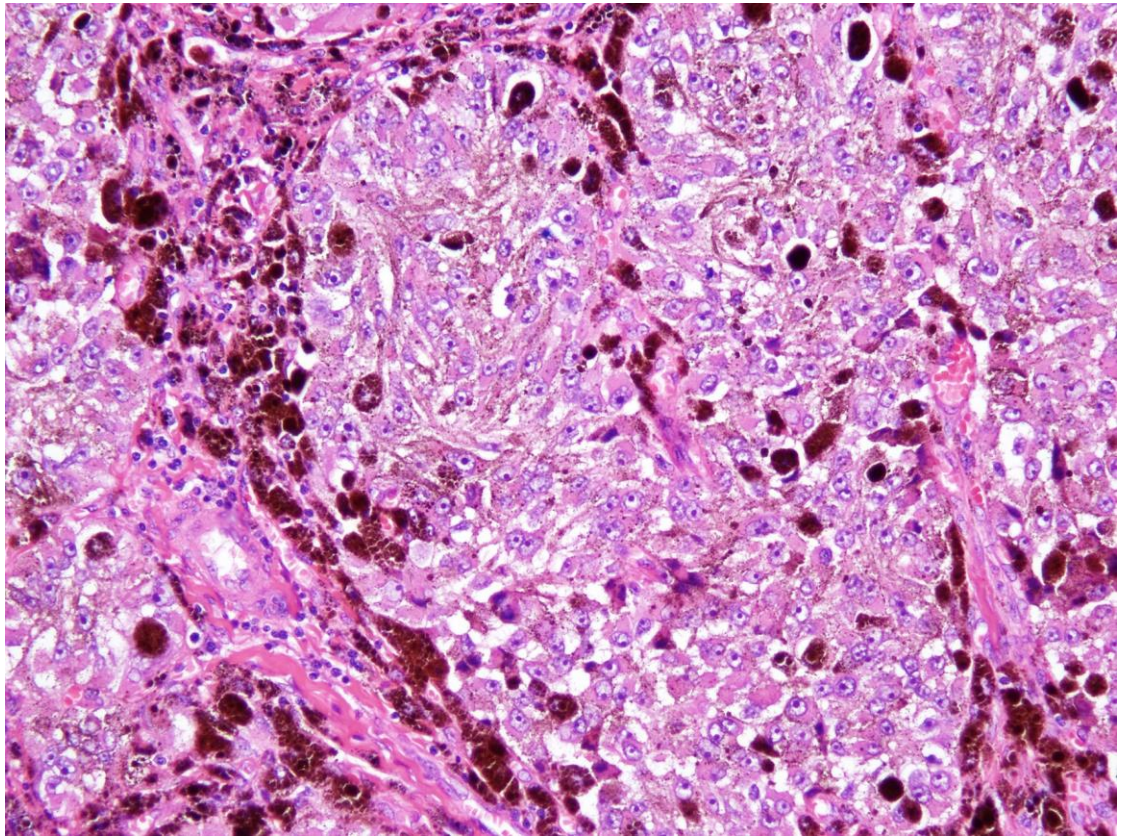
The tumours **appear circumscribed or partially encapsulated**

Often heavily pigmented, with the appearance of dried tar.

Previously called melanotic schwannomas.

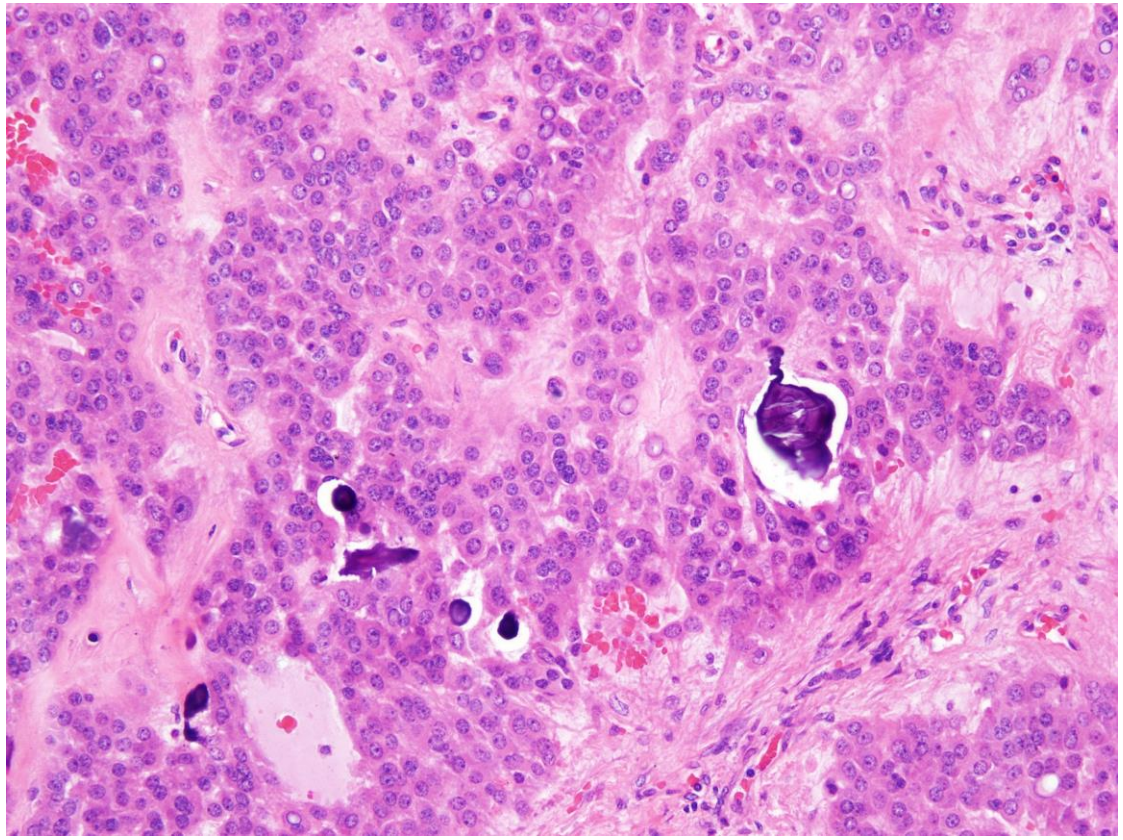
Encapsulated mass composed of **polygonal to spindled cells** arranged in **short fascicles or sheets** (syncytial appearance) and associated with coarsely clumped or finely granular **melanin pigment**.

Mitoses and necrosis can be present, but they are not clearly associated with outcome.



Polygonal to spindled cells with eosinophilic to amphophilic cytoplasm**, round to ovoid nuclei (often with nuclear grooves and pseudoinclusions),** and small nucleoli.

Occasional tumours show marked **nuclear hyperchromatism** with **prominent macronucleoli**.



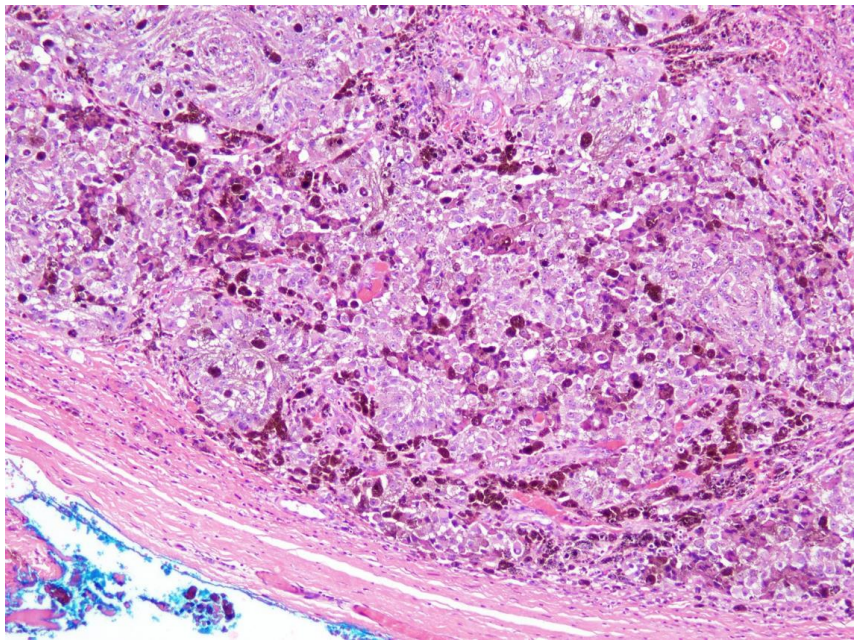
Some areas with epithelioid morphology.

Psammoma bodies are present in roughly 50% of cases, although extensive sampling may be required to identify them.

Malignant melanotic nerve sheath tumour

- ***Essential Criteria:*** frequent origin from paraspinal or visceral autonomic nerves; fascicular to sheet-like proliferation of heavily pigmented, relatively uniform plump spindled cells; coexpression of S100/SOX10 and melanocytic markers (e.g. HMB45, melan-A).

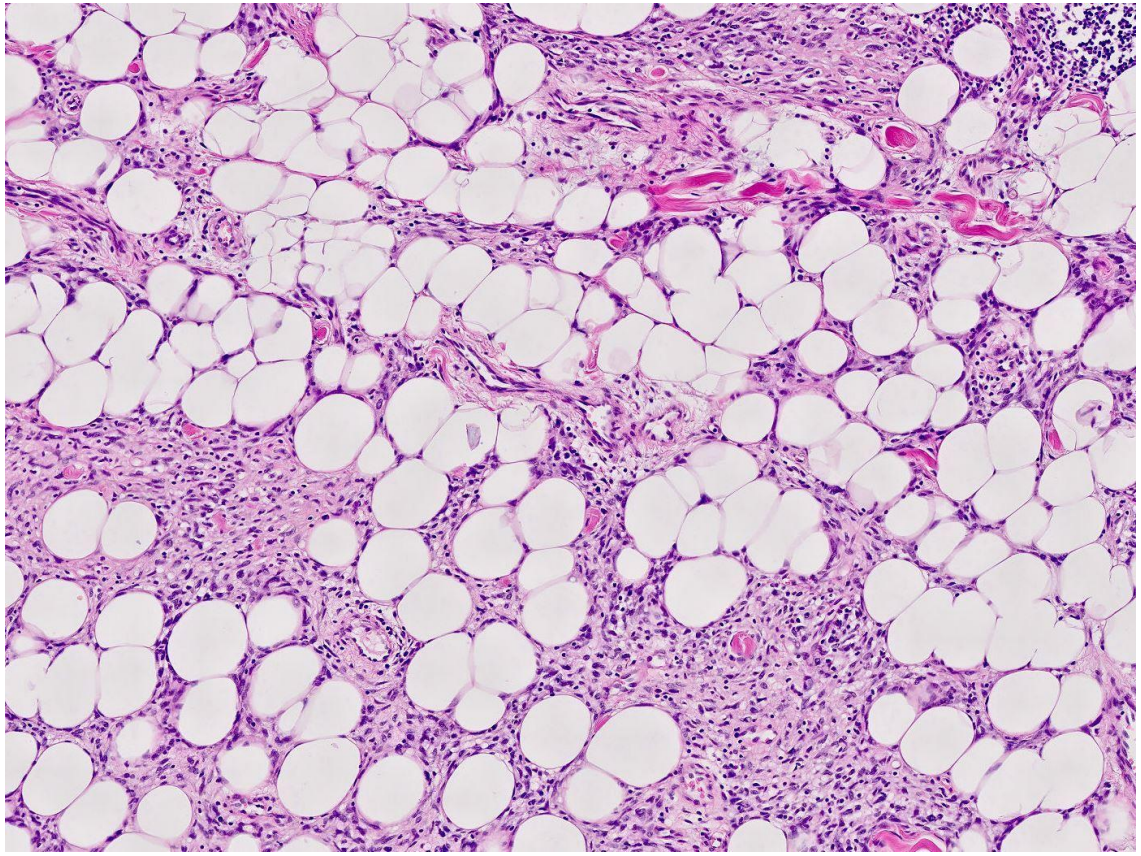
- ***Desirable Criteria:*** loss of PRKAR1A expression.

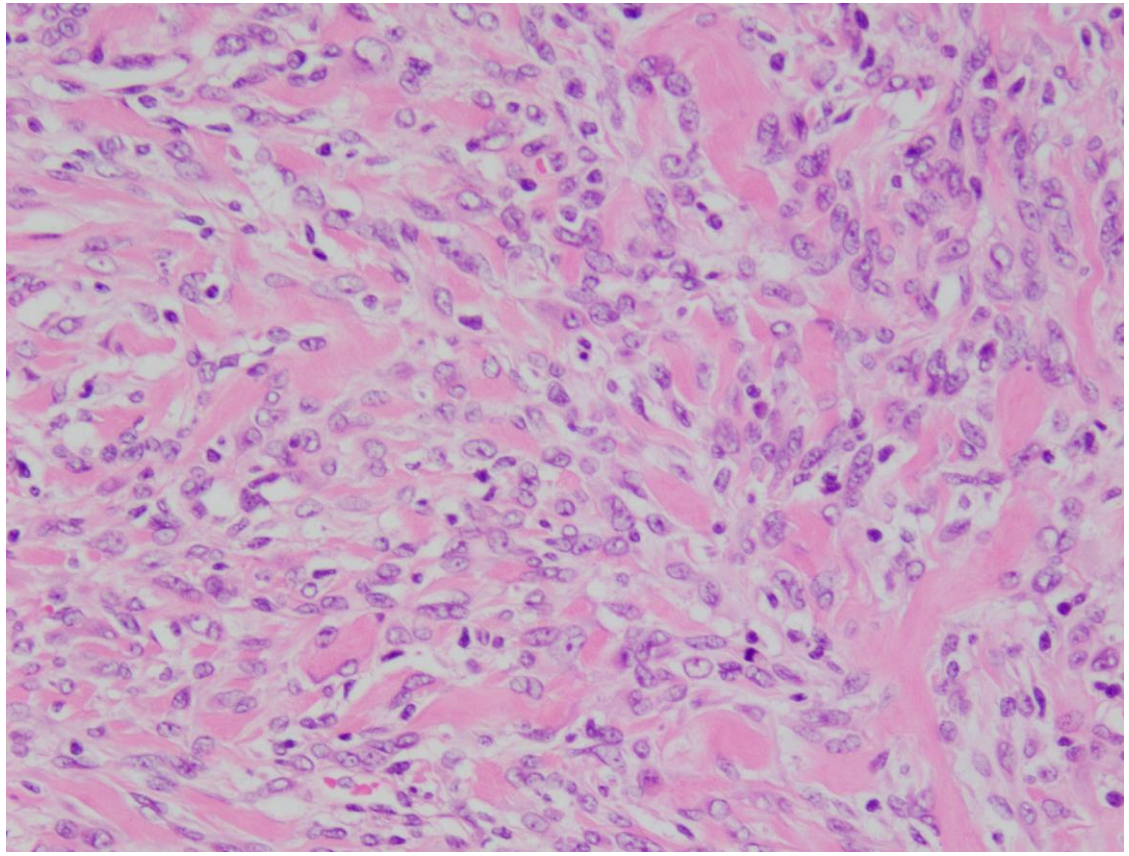


NTRK-rearranged spindle cell neoplasm (emerging)

Definition:

- **An emerging group of molecularly defined rare soft tissue tumours,** spanning a wide spectrum of morphologies and histological grades ranging from lipofibromatosis-like neural tumors to cellular variants resembling malignant peripheral nerve sheath tumor
- Superficial or deep
- Most common in first two decades of life
- Frequently coexpress **S100 and CD34 in the absence of SOX10**
- Expresses **pan-TRK**
- ***NTRK1* gene most commonly involved (rarely NTRK2 and NTRK3)**
- **Prognosis depends on histological grade (lower grades characterized by local recurrence and higher grades characterized by aggressive behavior and metastasis)**
- **Molecular confirmation of *NTRK* fusion required for targeted therapy**

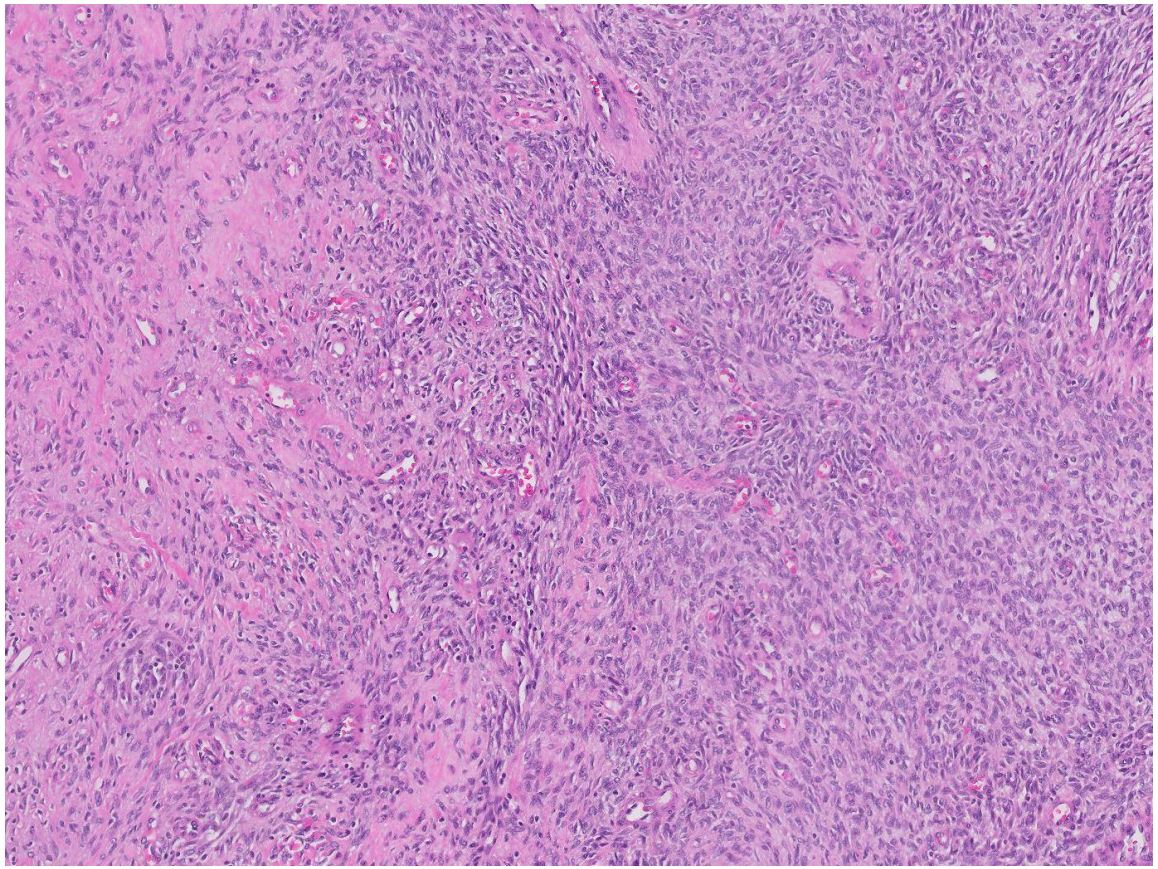




L**ipofibromatosis-like neural tumor** is characterized by haphazardly arranged monomorphic spindle cells, with tapering nuclei and indistinct cytoplasm, infiltrating fat with a **reticular pattern resembling lipofibromatosis**.

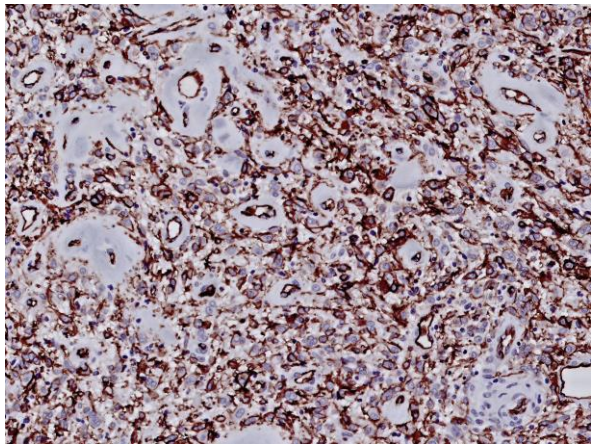
The **mitotic rate is low and there is no necrosis.**

Another subset shows **increased cellularity with solid and patternless growth patterns, keloid collagen, and prominent perivascular hyalinized collagen.**

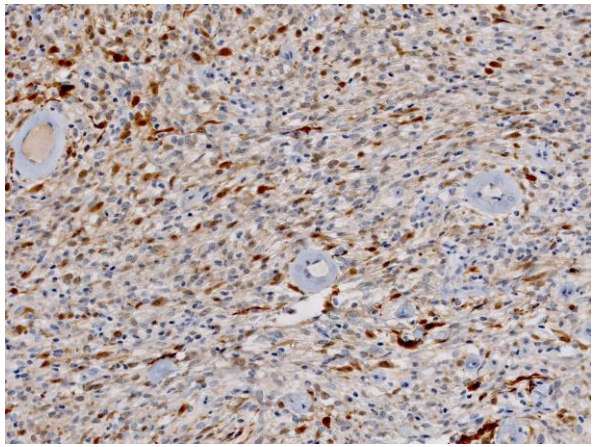


At the extreme, tumors resemble MPNST with increased mitotic rate and necrosis. These tumors may have a **zoned appearance with cellular** areas merging with **paucicellular** zones and perivascular hyalinized collagen. Rarely, tumors may have a **myopericytoma-like architecture**

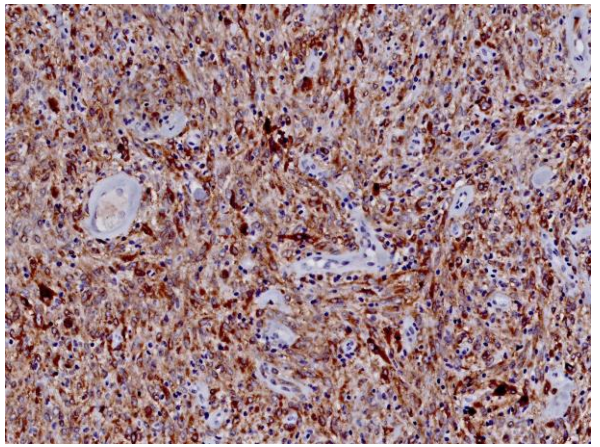
CD34 +



S100 +
SOX10 -

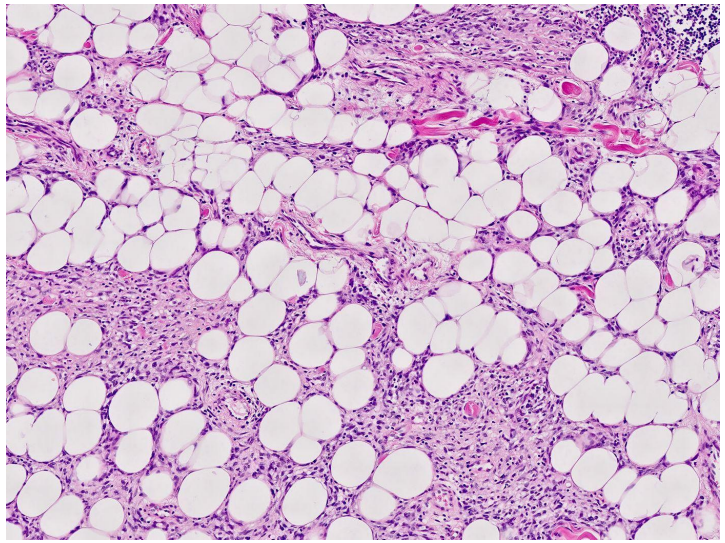


Pan-TRK +



NTRK-rearranged spindle cell neoplasm (emerging)

- ***Essential Criteria:*** tumours span a **wide spectrum of morphologies** and histological grades; characterized by haphazardly arranged monomorphic spindle cells; infiltrative growth within fat resembling lipofibromatosis; distinctive stromal and perivascular keloid collagen; immunohistochemically tumours are **positive for S100 and CD34** in many cases, whereas **SOX10 is negative**; tumours with *NTRK1* fusions will show **NTRK1 immunoreactivity**.

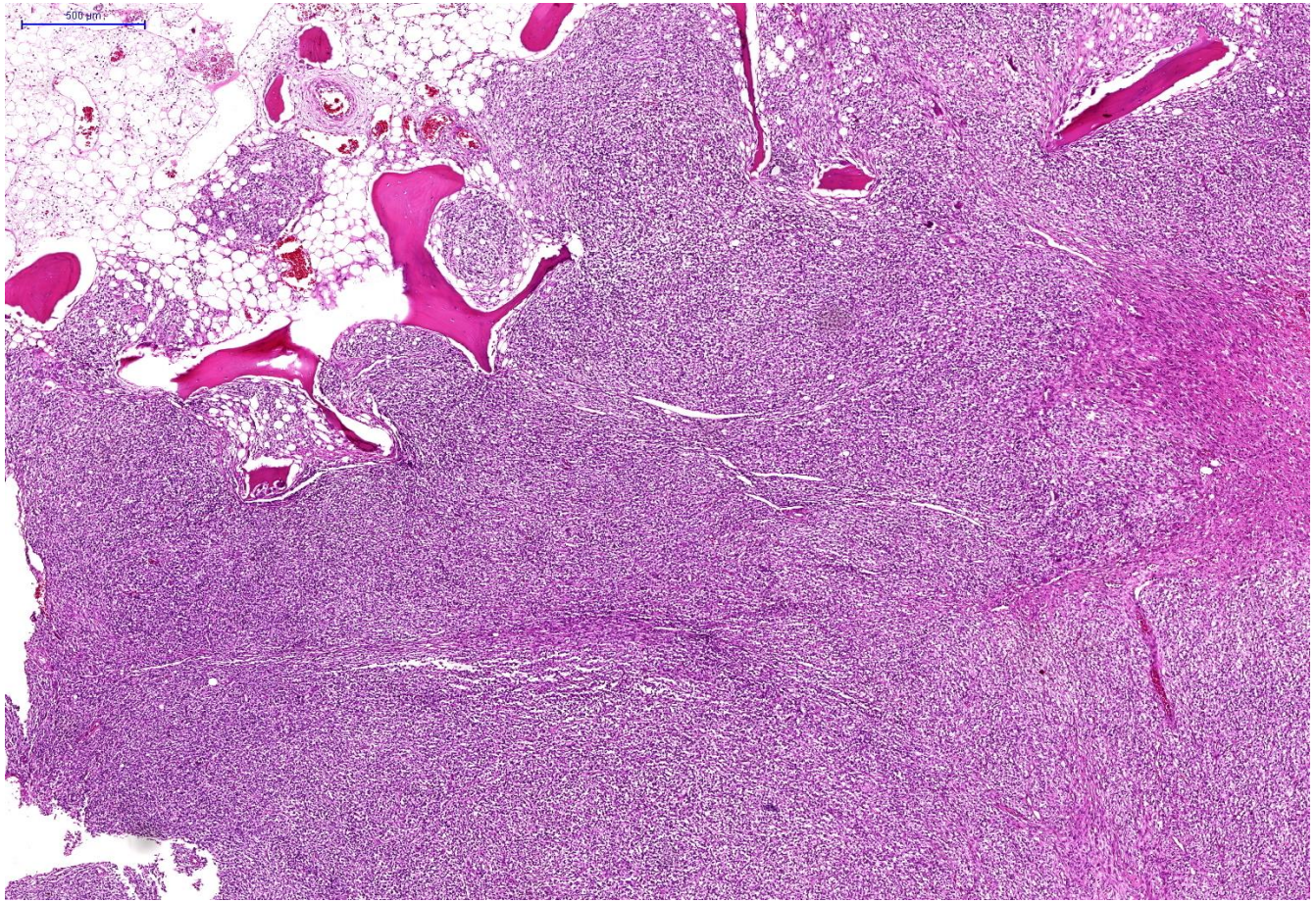


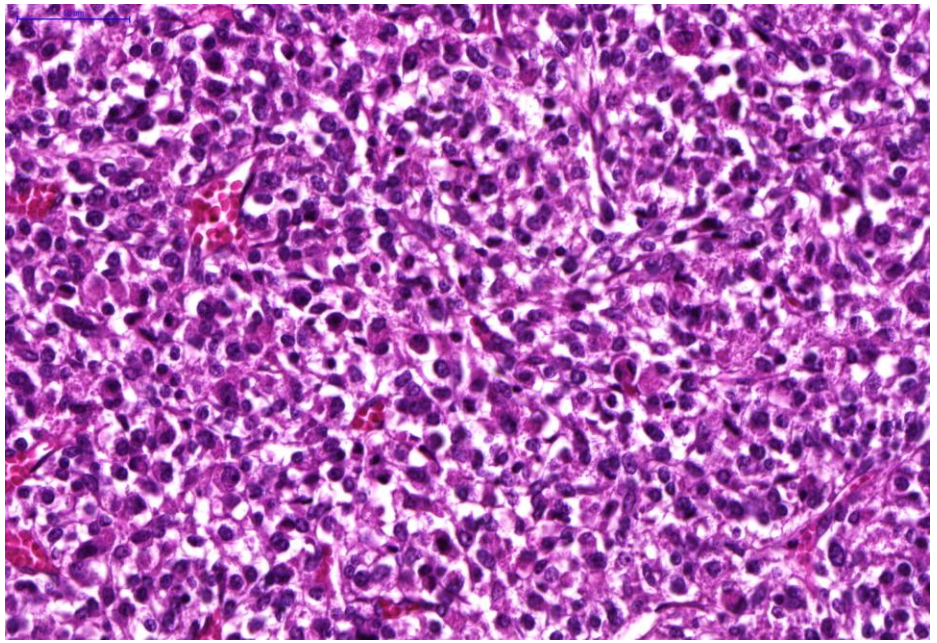
- ***Desirable Criteria:*** detection of NTRK fusions is usually required for determination of therapy.

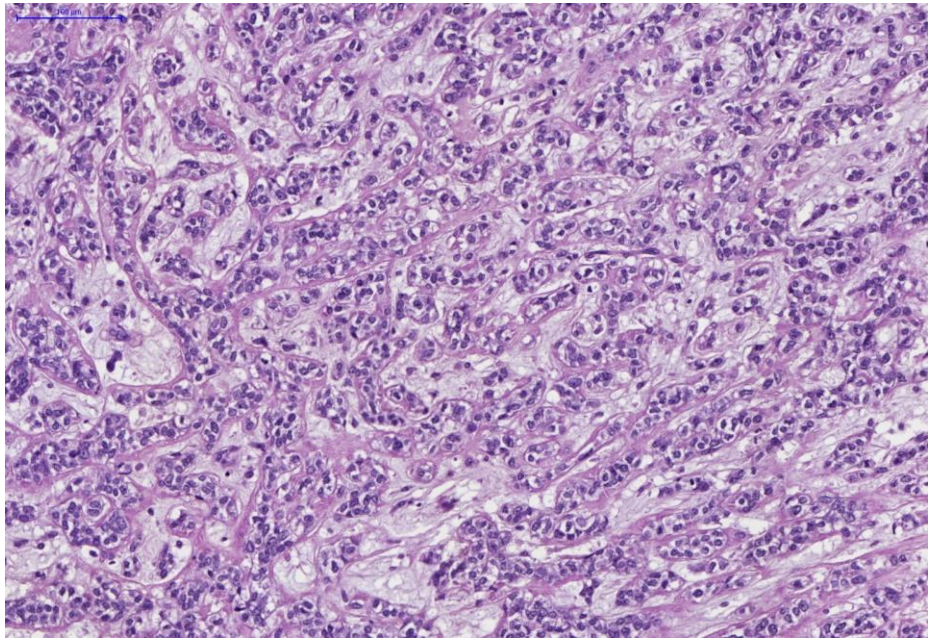
Round cell sarcoma with EWSR1-non-ETS fusions

Definition:

- Round cell or spindle cell sarcomas with *EWSR1 or FUS* fusions involving partners unrelated to the ETS gene family
- Formerly called Ewing-like sarcoma
- Any age (pediatric and adult)
- ***EWSR1-NFATC2* sarcomas arise in bone and occasionally soft tissue**
- ***FUS-NFATC2* tumors** are reported exclusively in **long bones**
- ***EWSR1-PATZ1* sarcomas** arise in **deep soft tissue** (mostly **chest wall and abdomen** / rarely extremity and head & neck) or **CNS**
- **Aggressive tumors** with little or **no response to chemotherapy** and propensity for local recurrence and distant metastasis



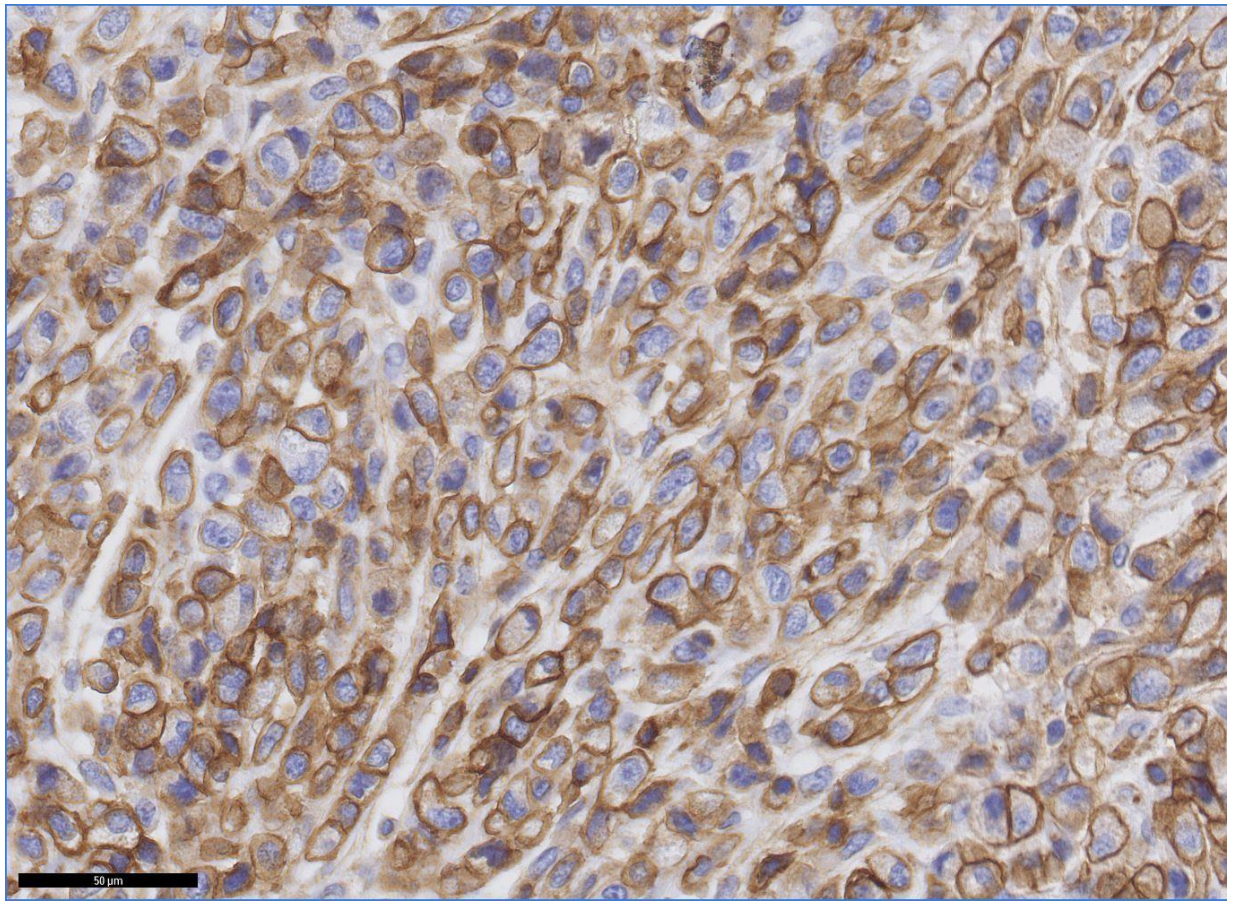




EWSR1-NFATC2 sarcoma with spindled to round cells infiltrating bone

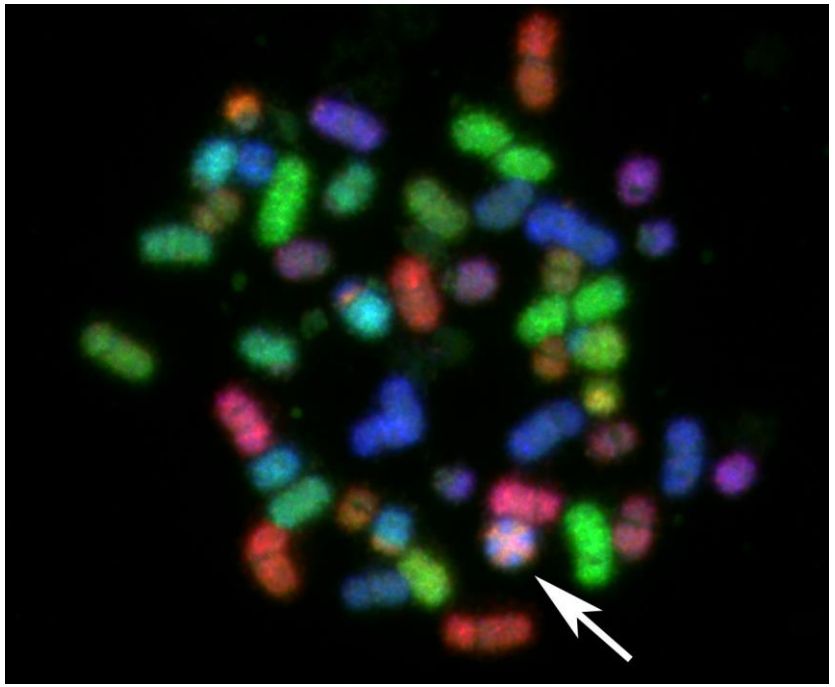
Spindled to round primitive cells with scant cytoplasm

May have nested pattern in myxohyaline stroma

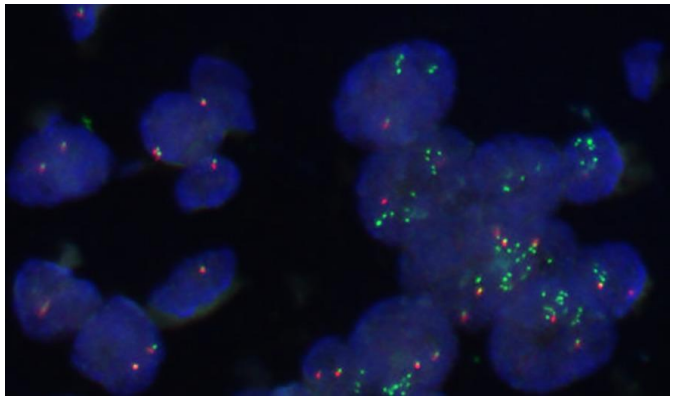


EWSR1-NFATC2 sarcoma demonstrates membranous CD99 and may have dot-like keratin expression

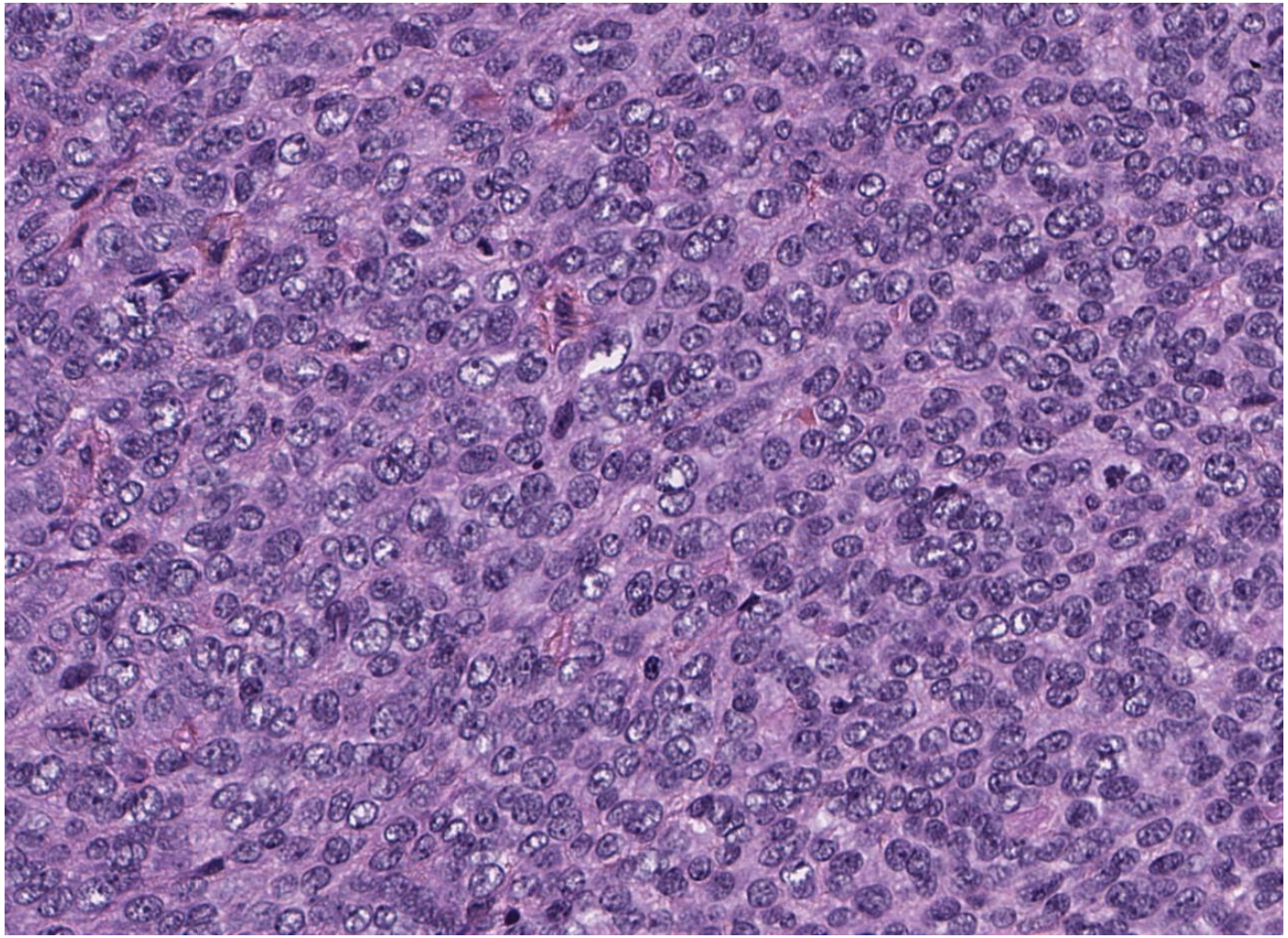
The translocation event resulting in fusion of *EWSR1* (22q12.2) and *NFATC2* (20q13.2) genes typically arises within a derivative 22 ring chromosome as unbalanced and amplified.



Multicolour FISH shows a **ring chromosome derived from multiple alternating segments of chromosomes 20 and 22 (arrow).**



***EWSR1* break-apart shows split signals with amplification of the telomeric probe (green)**



EWSR1-PATZ1 sarcoma with **small to medium sized cells**, **round to ovoid nuclei, and fine granular chromatin**

***EWSR1-PATZ1* IHC**

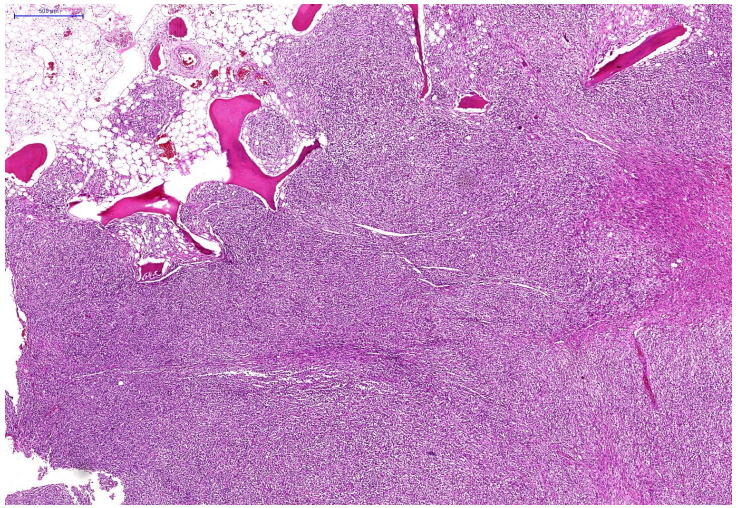
- Coexpresses myogenic markers (desmin, myogenin, MYOD1) and neurogenic markers (S100P, SOX10, MITF, GFAP)
- CD34 can be positive
- CD99 is not consistently expressed.

***EWSR1-PATZ1* Molecular**

- Poor sensitivity of *EWSR1* break-apart probe due to short genomic distance between *PATZ1* and *EWSR1* on 22q12.2
- Best detected by PCR or NGS fusion panel

Round cell sarcoma with EWSR1-non-ETS fusions

- ***Essential Criteria:*** spindled to rounded cytomorphology; mostly low-grade features, but high-grade cases are reported; fibrohyaline stromal changes are common; *EWSR1* break-apart FISH shows amplification of the 5′ probe in *EWSR1-NFATC2*–rearranged sarcomas; identification of the fusion transcript remains the gold standard.

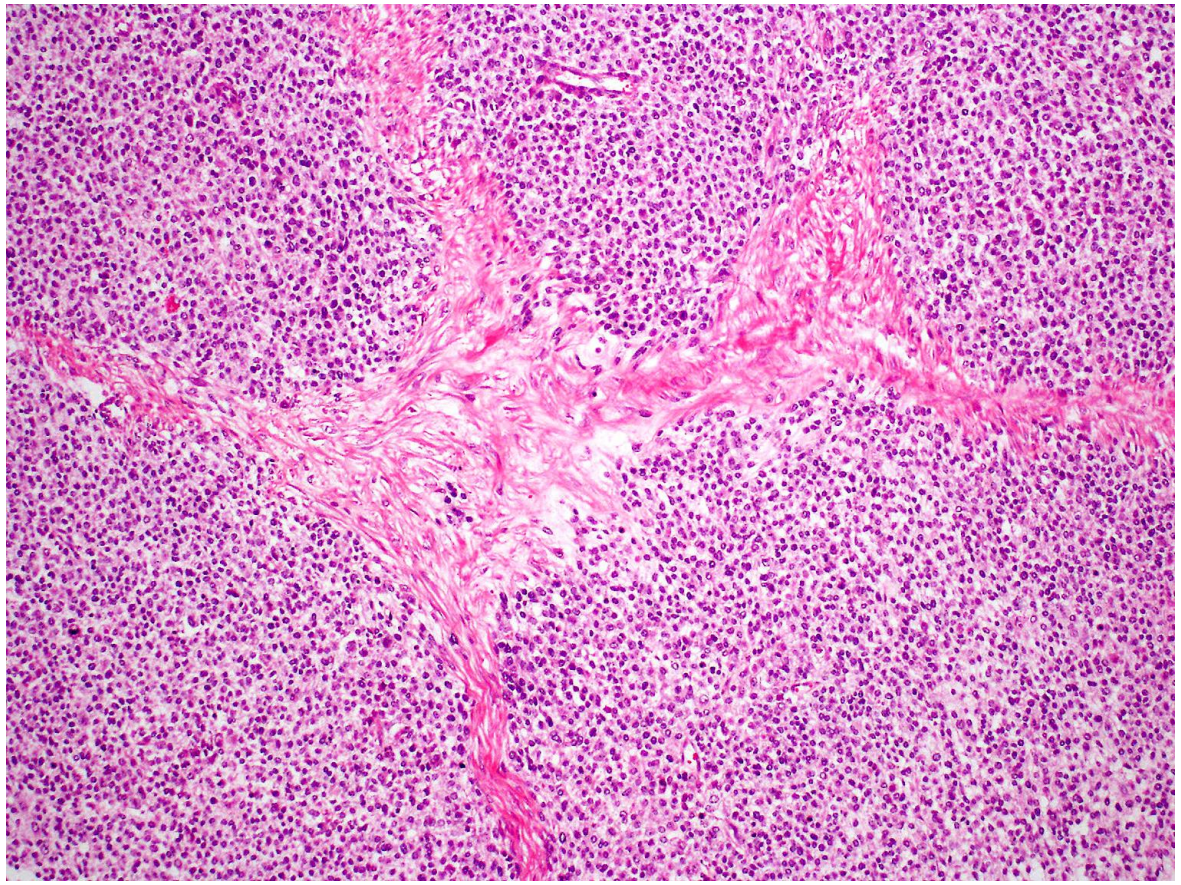


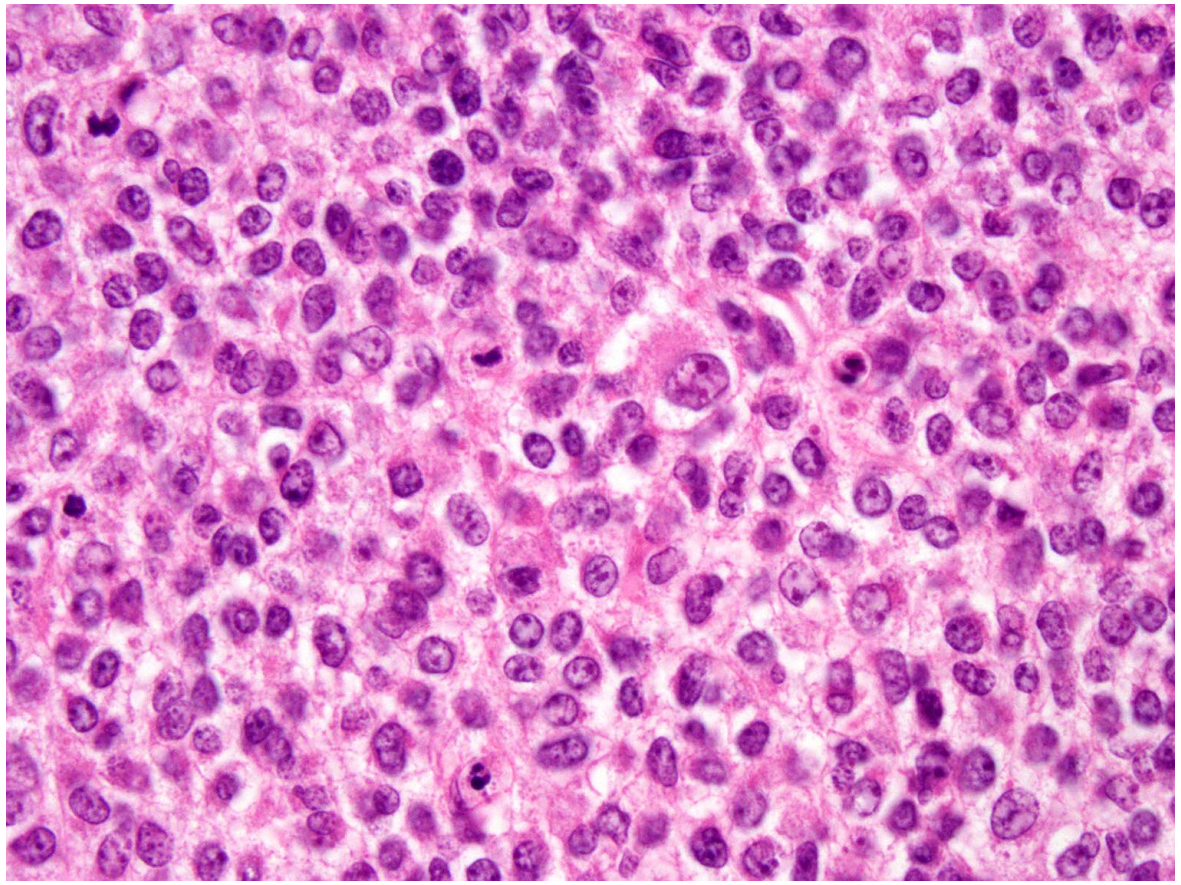
- ***Desirable Criteria:*** most *NFATC2*-rearranged tumours are located in long bone; *PATZ1*-rearranged sarcomas: round to spindled cells with divergent phenotype, both myogenic and neurogenic.

CIC-rearranged sarcoma

Definition:

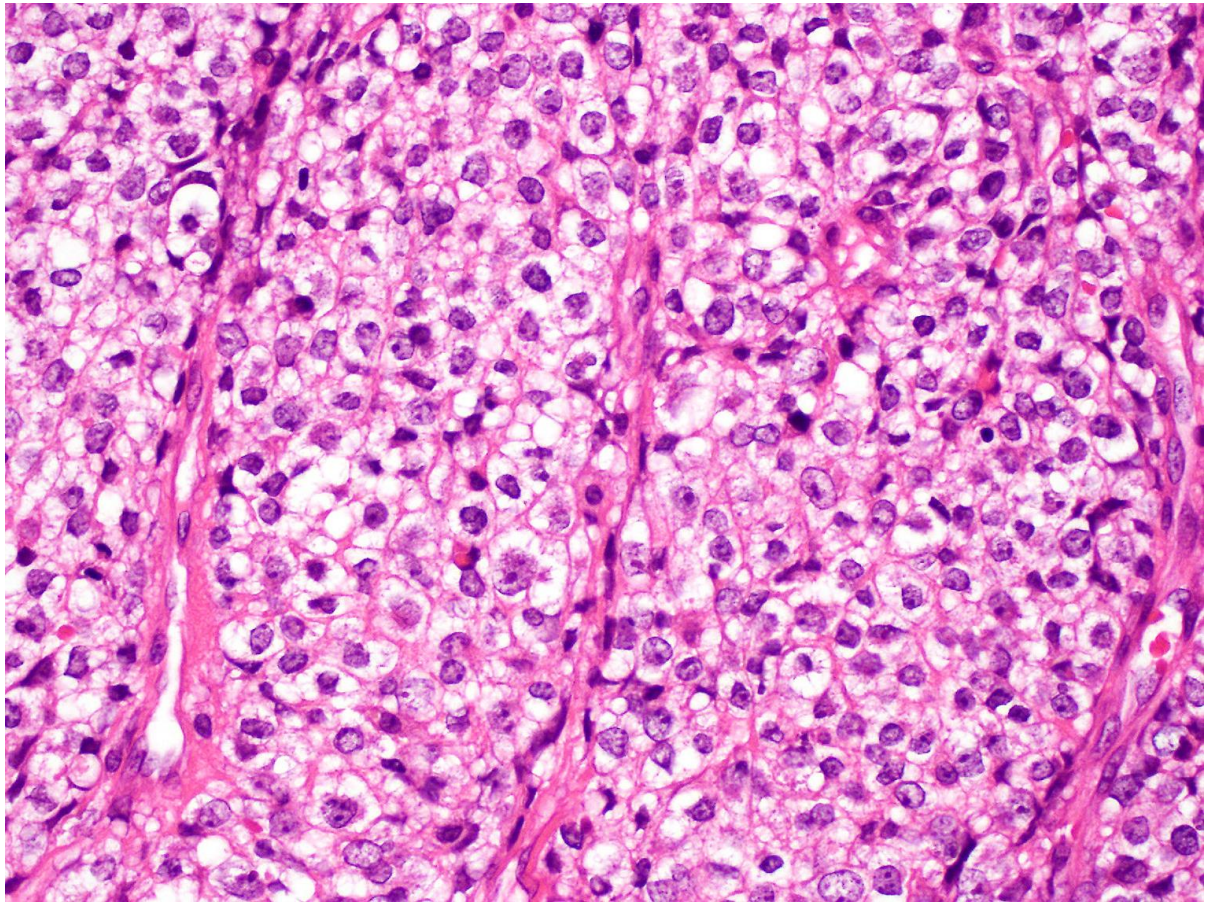
- *CIC*-rearranged sarcoma is a **high-grade round cell undifferentiated sarcoma defined by *CIC*-related gene fusions (**most often *CIC-DUX4)*
- **Most common in deep soft tissues of the limbs or trunk** (10% visceral, less common head & neck, retroperitoneum, pelvis)
- **Any age (children to elderly adults) but with striking predilection for young adults** (**25–35 years)**
- A ***CIC-DUX4* fusion is present in 95% of cases, resulting from either a t(4;19)(q35;q13) or a t(10;19)(q26;q13) translocation**; however**, rare examples are associated with non-*DUX4* partner genes, including *FOXO4*, *LEUTX*, *NUTM1*, and *NUTM2A***.
- **Highly aggressive course with frequent metastases, most commonly to the lung**.
- Significantly worse prognosis than Ewing sarcoma.
- **Chemotherapy response to Ewing sarcoma regimens has been dismal**

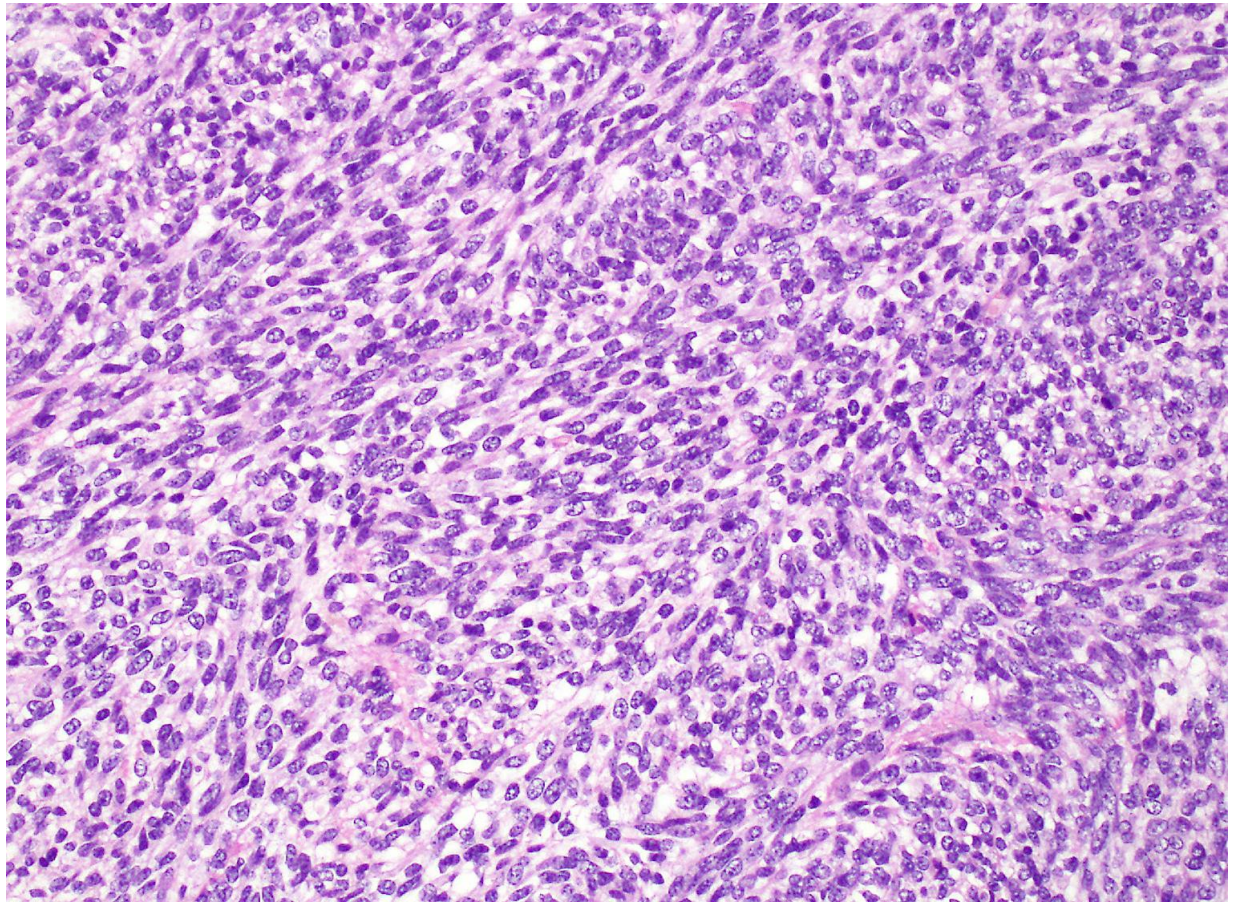




Histopathology:

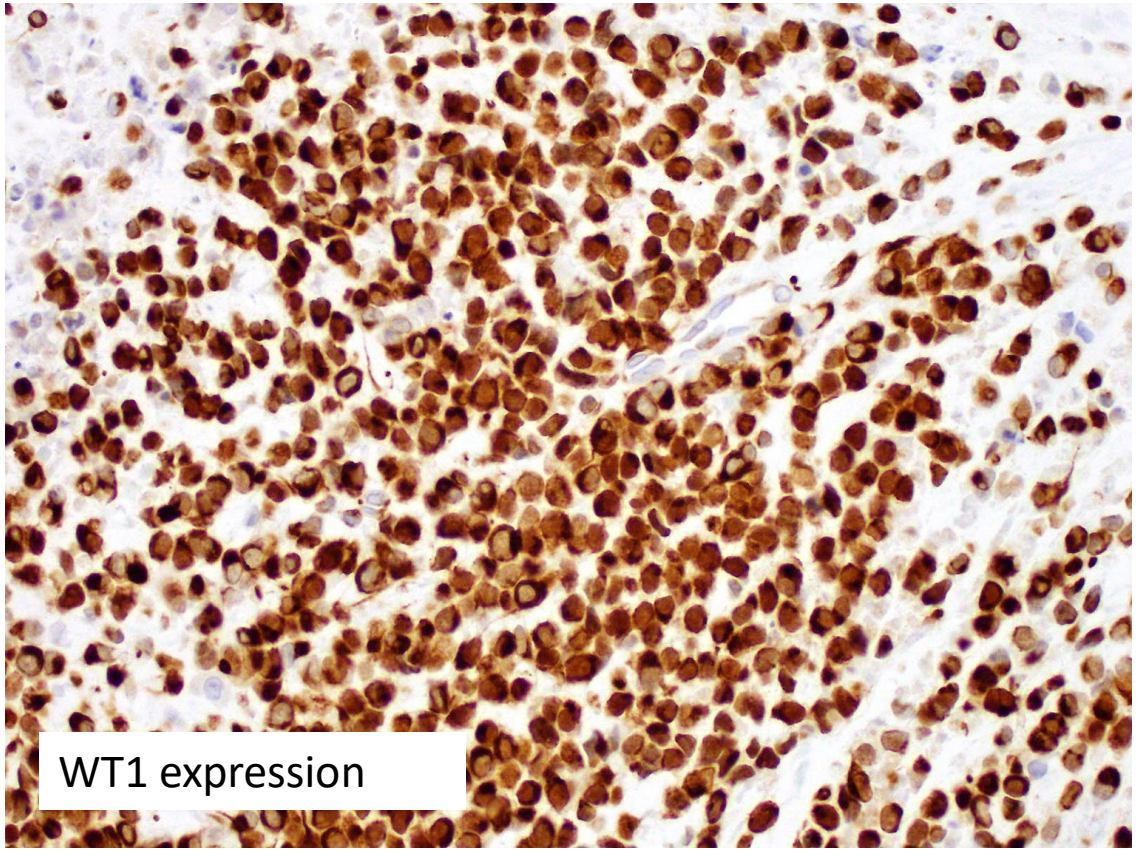
- Sheets of **undifferentiated round cells** arranged in lobules delineated by **fibrous septa**.
- Minor component of **spindled or epithelioid** cells
- Focal **myxoid** change with **reticular or pseudoacinar** patterns
- **Necrosis** is common and **mitotic activity is brisk**.
- Cells are relatively **monomorphic and primitive with scattered enlarged cells showing mild nuclear pleomorphism**

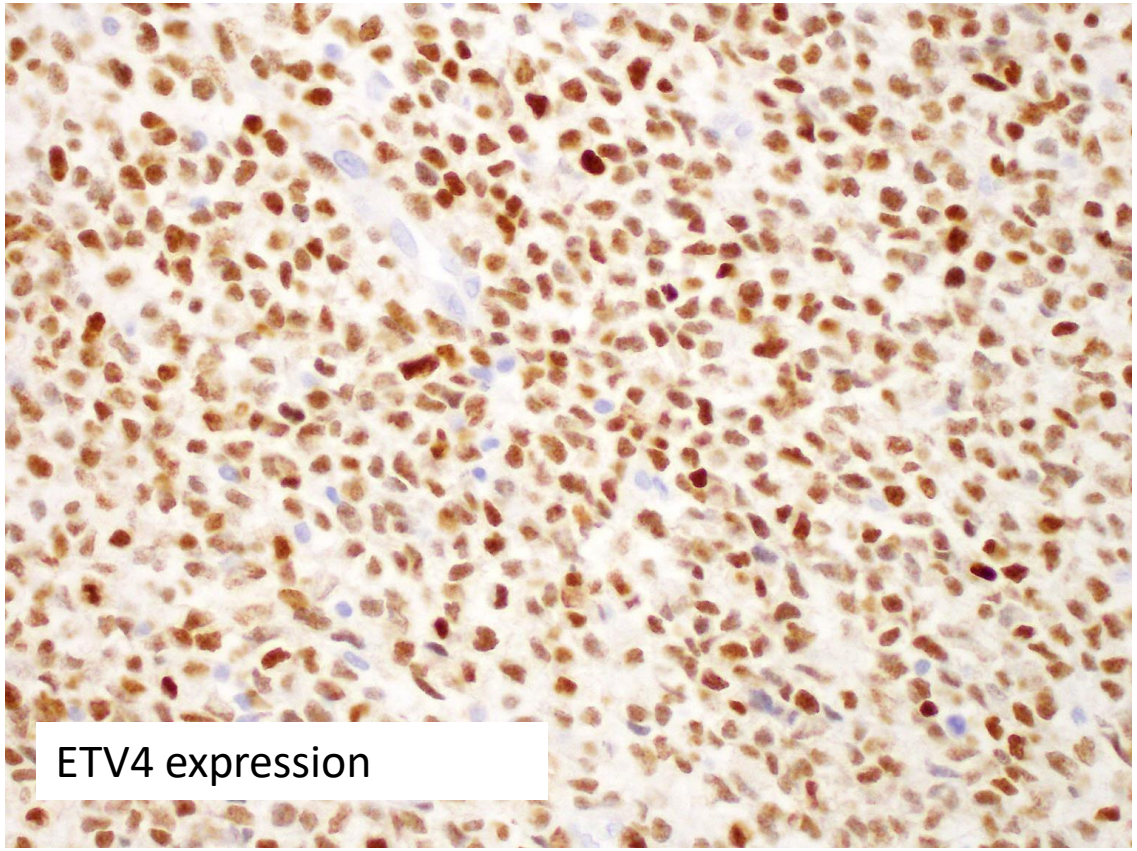




- Sheets of epithelioid cells with moderate amount of **pale eosinophilic to clear cytoplasm** and **distinct cell membranes.**
- The **chromatin is vesicular and the nucleoli are prominent.**

A minor component may show spindle cells arranged in short fascicles and some storiform configurations

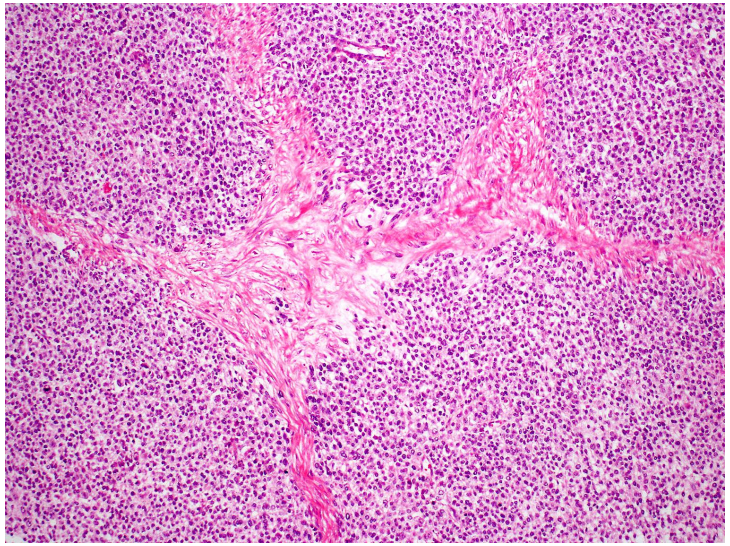




- **WT1 (90–95%)** and **ETV4 (95–100%)** are frequently positive and represent useful ancillary markers.
- NKX2-2 is typically negative. Sarcomas with *CIC-NUTM1* fusions express NUT protein.
- Keratin, S100, and myogenic markers are rarely expressed.
- Variable staining with CD99
- **Calretinin and ERG can be positive**

CIC-rearranged sarcoma

- ***Essential Criteria:*** predominant round cell phenotype; mild nuclear pleomorphism; epithelioid and/or spindle cell components; variably myxoid stroma; immunoprofile shows **variable CD99 staining, with frequent WT1 and ETV4 positivity.**



- ***Desirable Criteria:*** *CIC* gene rearrangement (in selected cases).

Sarcoma with BCOR genetic alterations

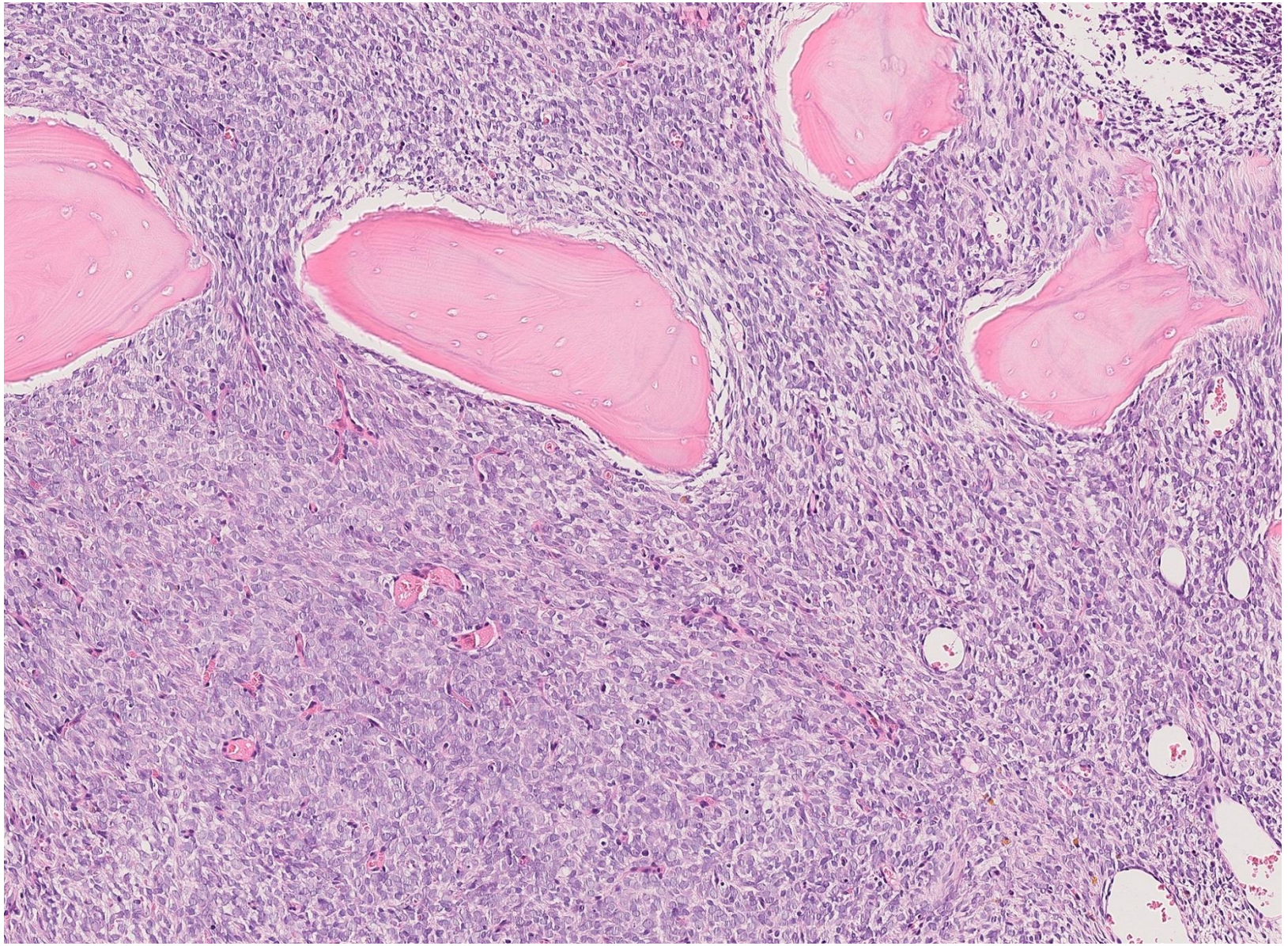
Definition:

- **Several groups of primitive round cell sarcomas show *BCOR* genetic alterations, resulting in oncogenic activation and BCOR overexpression.**
- **They differ in clinical presentation but overlap with regard to morphology, immunoprofile, and gene expression**
- **First group** is characterized by sarcomas with ***BCOR*-related gene fusions**, most frequently ***BCOR-CCNB3***.
- **Second group** shows **internal tandem duplication (*BCOR*-ITD)**, which has been described in **infantile undifferentiated round cell sarcomas and primitive myxoid mesenchymal tumours of infancy**.

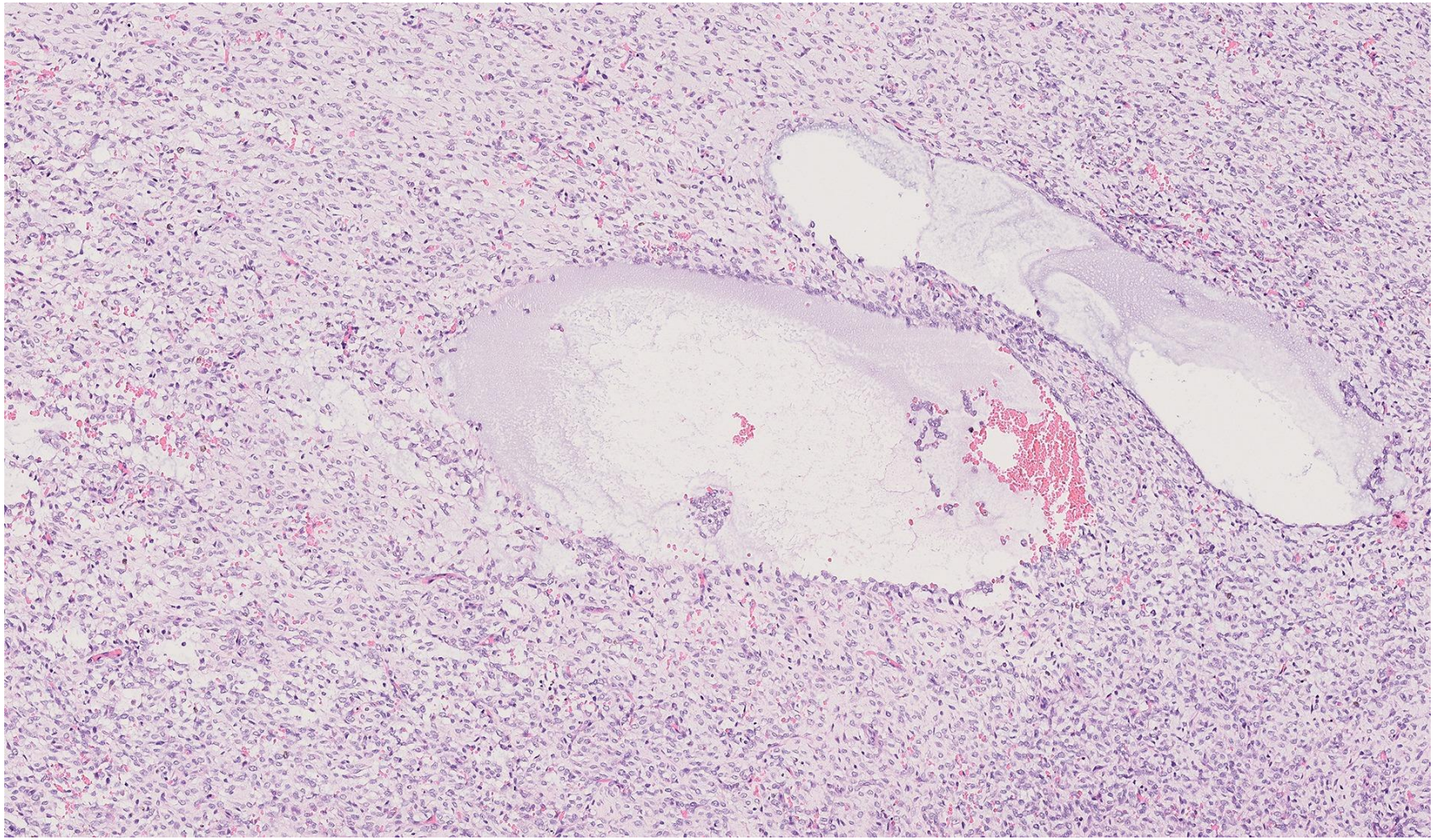
Sarcoma with BCOR genetic alterations

***BCOR*-related gene fusions**

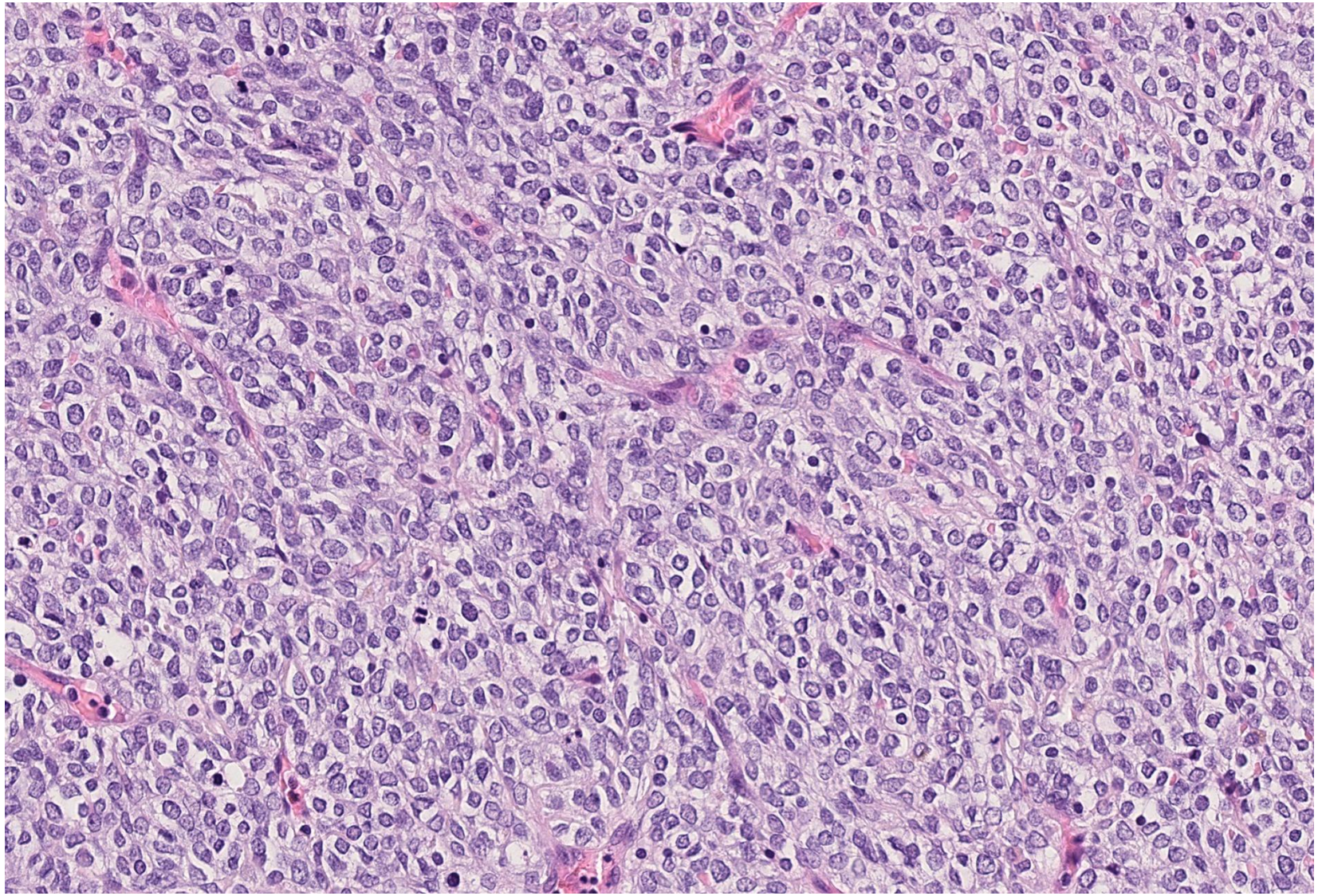
- ***BCOR-CCNB3* sarcomas have striking predilection for children** (< 20 years and male predominance (4.5:1)
- **Alternative *BCOR*-related gene rearrangements are seen in a wider age range**.
- Arise in **bone** or **soft tissue** (1.5:1)
- Predilection for **pelvis, lower extremity, and paraspinal** region (rare head & neck region, lung, and kidney)
- **Emerging data suggests *BCOR-CCNB3* sarcoma has 5-year survival rates similar to Ewing sarcoma (72–80%) and shows histological response to Ewing sarcoma–based treatment regimens.**



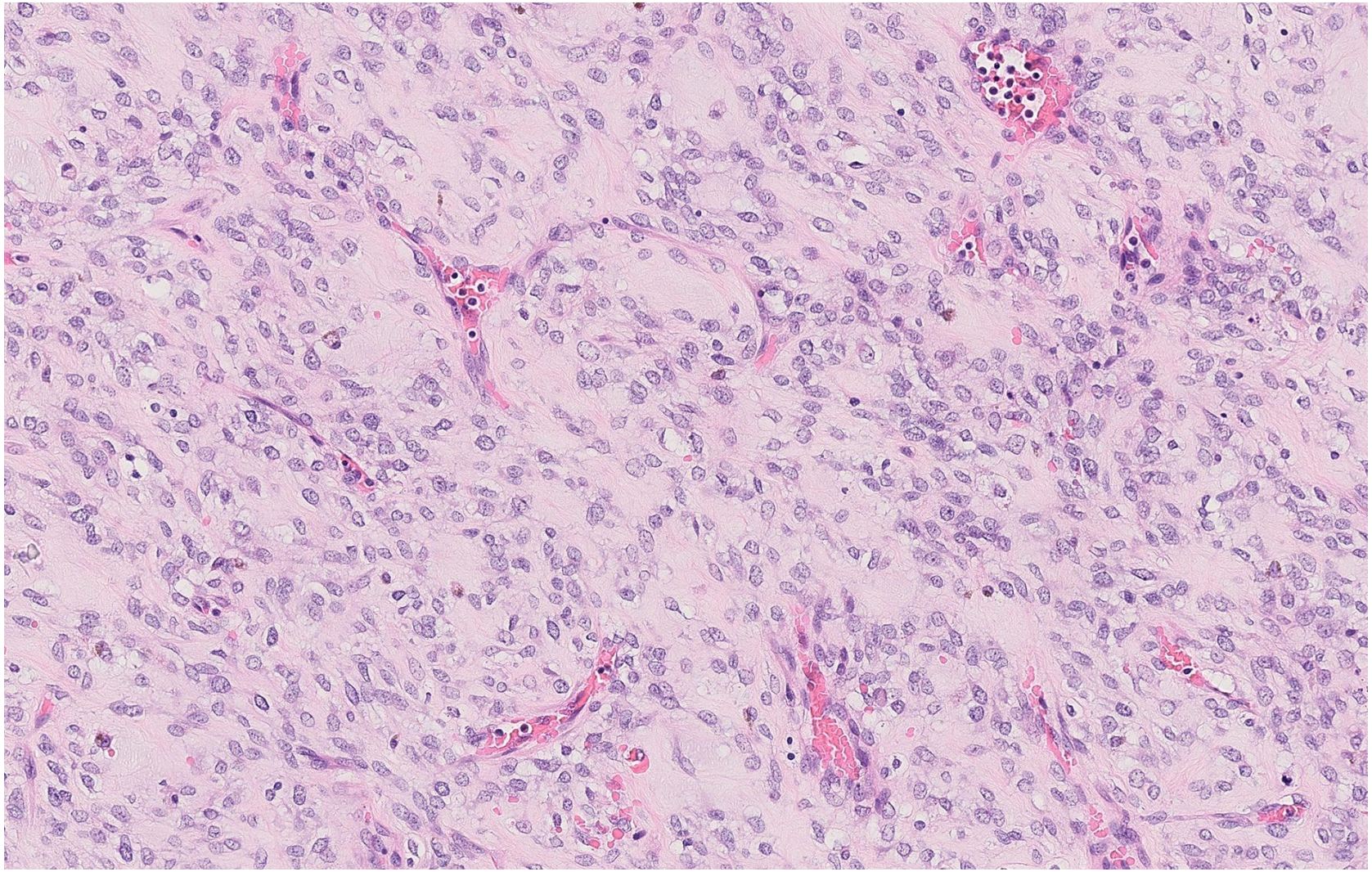
BCOR-CCNB3 sarcoma: A **primitive round to spindle cell proliferation arranged in sheets and vague fascicles**, involving the marrow spaces of a long bone (and **resembling poorly differentiated synovial sarcoma**.



BCOR-CCNB3 sarcoma:
Some tumours show **lower cellularity with tumour cells embedded in a loose fibromyxoid stroma with microcystic changes and rich vascularity**



BCOR-CCNB3 sarcoma: **Solid sheets of undifferentiated round to ovoid cells** with light eosinophilic to clear cytoplasm and round nuclei with fine chromatin and scattered mitotic figures.

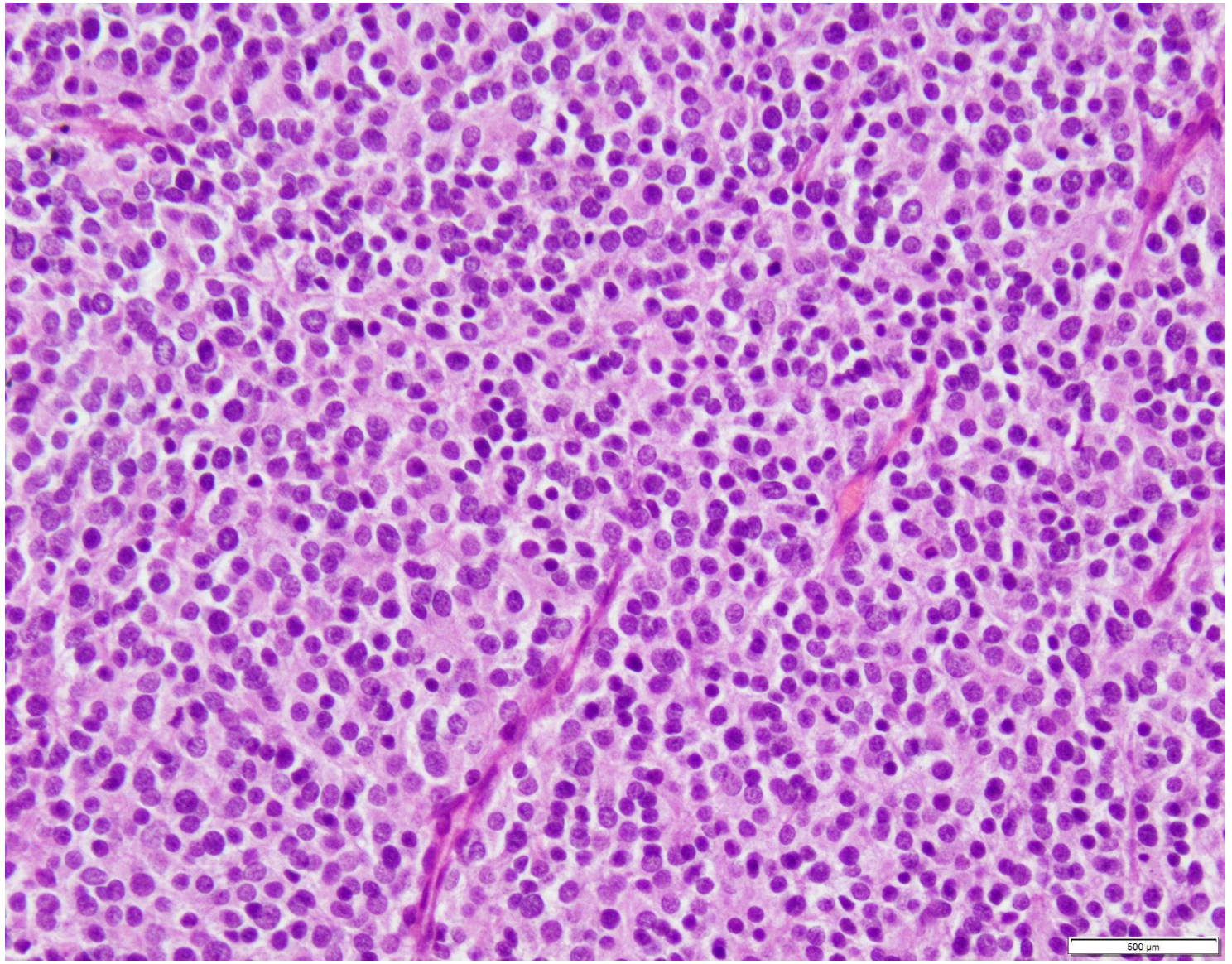


BCOR-CCNB3 sarcoma:
Deceptively bland ovoid to short spindle cells arranged in a streaming pattern in a fibrotic background with a rich vascular network.

Sarcoma with BCOR genetic alterations

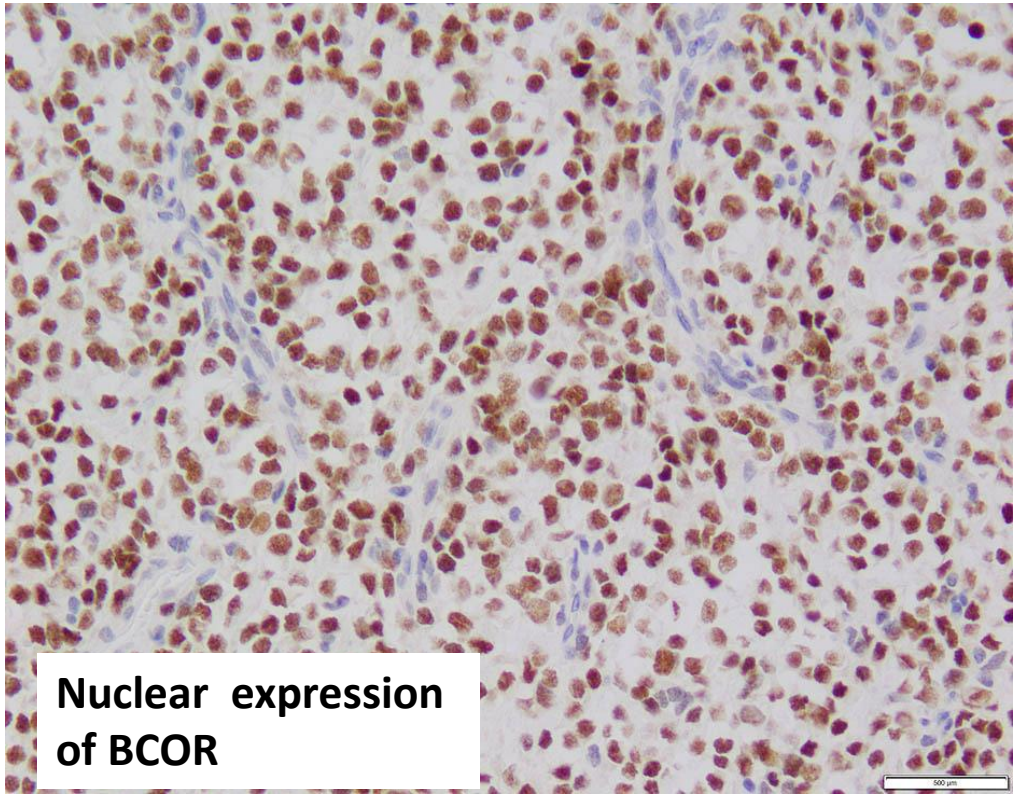
Sarcoma with *BCOR*-ITD and primitive myxoid mesenchymal tumour of infancy

- Occur within the **first year of life** or **may be present at birth**
- Occur mainly in the **soft tissues of the trunk, retroperitoneum, and head and neck** (typically **spares extremities**)
- Prognosis, therapy response, and outcome not well defined

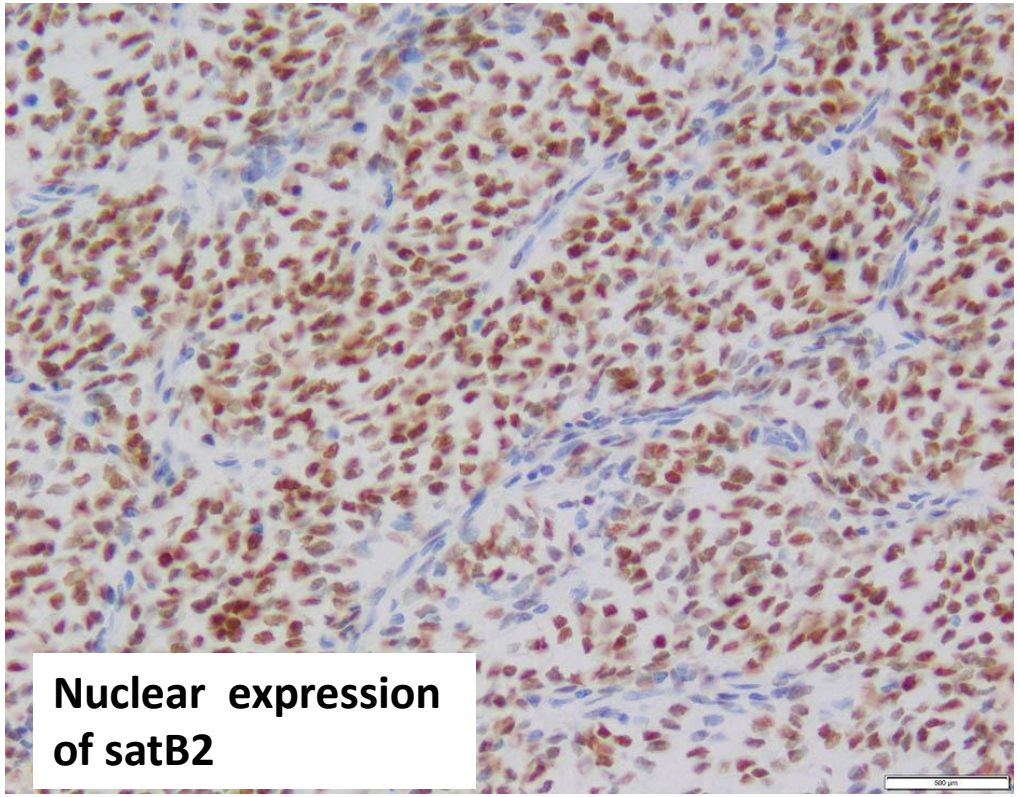


BCOR-ITD sarcoma: This spectrum of tumours shows variable degrees of cellularity**, ranging from solid sheets of small primitive cells to hypocellular areas of dispersed spindle cells, within a myxoid matrix and delicate vessels.**

This picture shows **solid sheets of monomorphic round cells with scant eosinophilic cytoplasm and round nuclei, separated by thin septa with delicate capillaries, from an infant patient.**



Nuclear expression of BCOR



Nuclear expression of satB2

Immunohistochemistry:

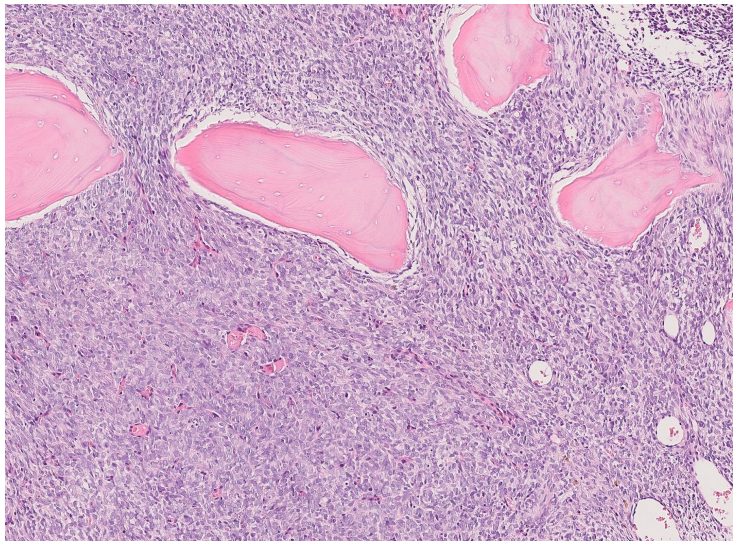
- All tumours with various *BCOR* gene alterations show strong and diffuse **nuclear BCOR** positivity and in most cases also **express SATB2, TLE1, and cyclin D1**.
- **CD99 is positive** in approximately 50% of cases.
- **BCOR expression is not specific and, for example, is often observed in synovial sarcoma**.
- *BCOR-CCNB3* sarcomas also express cyclin B3, which is not seen in other *BCOR* family tumours

Diagnostic Molecular Pathology:

- ***BCOR* gene rearrangements and *BCOR*-ITD detected by various molecular approaches (ie. NGS fusion panel)**.

Sarcoma with BCOR genetic alterations

- ***Essential Criteria:*** primitive round to spindle cells arranged in nests, sheets, or fascicular growth; variably myxoid stroma with delicate vasculature; immunohistochemical positivity for BCOR, SATB2, and cyclin D1.



- ***Desirable Criteria (in selected cases):*** molecular confirmation of *BCOR* genetic abnormality (*BCOR* fusion, *BCOR*-ITD).

Educational Objectives

- List the various categories in the classification of soft tissue tumours
- List new entities in each category
- List main distinguishing features (essential and desired criteria) of new entities

The End