CLASSIFICATION AND HISTPATHOLOGY OF SARCOMAS

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PROF AND HOD

SGRD AMRITSAR

INTRODUCTION

SARCOMAS AND THE PATHOLOGIST

- Sarcomas - diverse group of malignant tumors arising from mesenchymal tissues
- Soft tissue sarcomas arise from non-epithelial tissues, including muscles, fat, blood vessels, nerves, and connective tissues.
- One of the most challenging field of diagnostic pathology due to complexity of histopathological features and diversity of overlapping IHC markers and scarcity of molecular signatures.
- Constantly revising classification schemes plays a key role in improving the quality of pathologic diagnosis and choosing most suitable therapeutic options

CHALLENGES IN DIAGNOSIS

- Rarity -
  - incidence of approximately 5 cases/100,000 thus matching the formal definition of a rare tumor
  - May not be encountered in low-volume centers for years
- Intrinsic complexity
- Technological complexity: Diagnosis requires a complex combination of conventional microscopy, IHC and molecular genetics often requiring state of the art molecular technology such as Next Generation Sequencing approaches

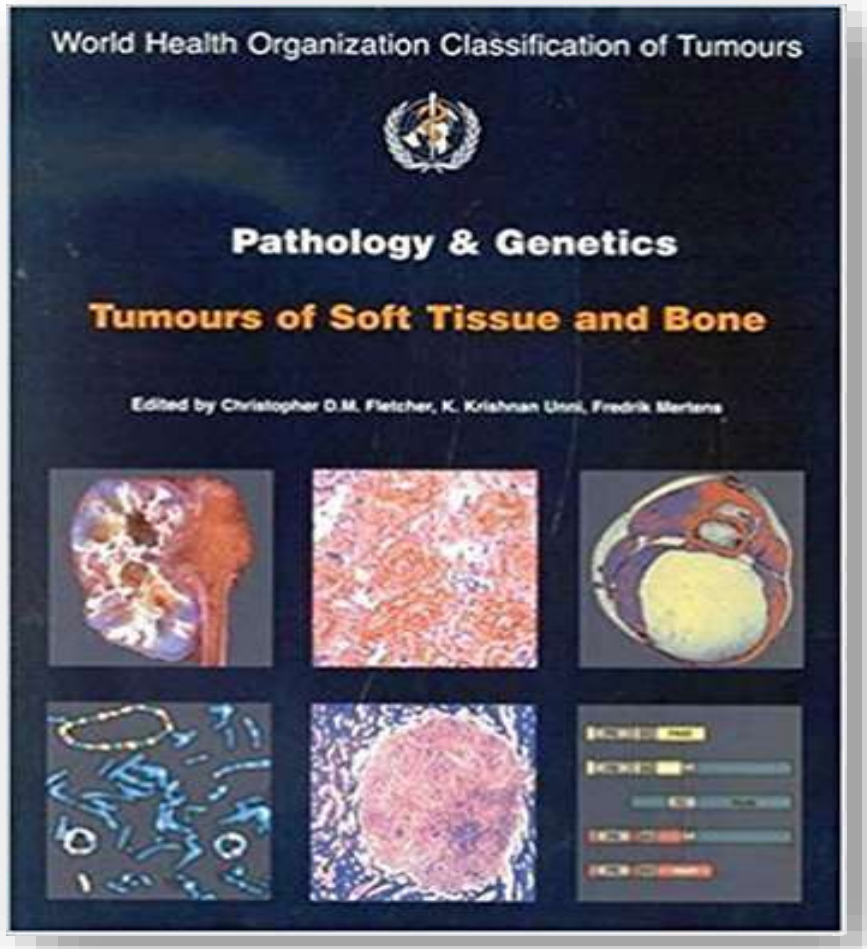
WHO CLASSIFICATION

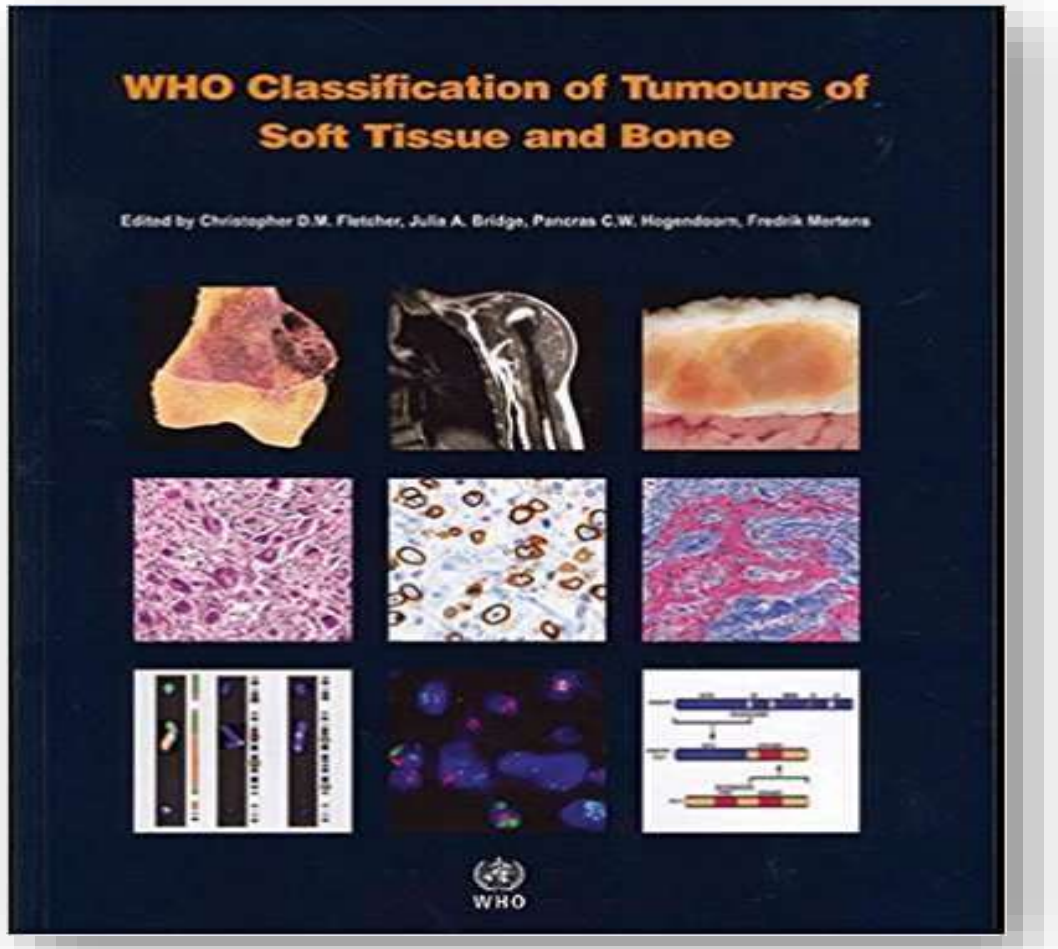
World Health Organization 2020-classification based on lineage/ histogenesis

1. Adipocytic
2. Fibroblastic and myofibroblastic tumours
3. So called fibrohistiocytic tumors
4. Vascular tumors
5. Pericytic (perivascular)
6. Smooth muscle
7. Skeletal muscle
8. Gastrointestinal stromal tumour
9. Chondro-osseous tumours
10. Peripheral nerve sheath tumours
11. Tumors of uncertain differentiation
12. **Undifferentiated small round cell sarcoma of bone and soft tissue**

Tumour behaviour is classified as:

1. **Benign**
2. **Intermediate (locally aggressive)**
3. **Intermediate (rarely metastasizing)**
4. **Malignant**





3 new chapters: Gastrointestinal stromal tumours
Nerve sheath tumours
Undifferentiated/unclassified sarcomas

Approach to Diagnosis

Differential Diagnosis by Histologic Pattern

- Adipocytic
- Spindle cell
- Myxoid
- Round cell
- Epithelioid
- Pleomorphic

HISTOPATHOLOGY OF SARCOMAS

MAJOR ENTITIES TO BE DISCUSSED

ADIPOCYTIC TUMORS

- Well differentiated liposarcoma
- Dedifferentiated liposarcoma
- Myxoid liposarcoma
- Pleomorphic liposarcoma

Fibroblastic/myofibroblastic tumors

- Solitary fibrous tumour, malignant
- Fibrosarcoma NOS
- Myxofibrosarcoma

So-called fibrohistiocytic tumours.

- Malignant tenosynovial giant cell tumor

Vascular tumours

- Epithelioid haemangioendothelioma
- Angiosarcoma

Pericytic (perivascular) tumours.

- Glomus tumour, malignant

Smooth muscle tumours.

- Leiomyosarcoma

Skeletal muscle tumours.

- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma

Gastrointestinal stromal tumours.

Osteosarcoma, extraskeletal

Peripheral nerve sheath tumours.

- Malignant peripheral nerve sheath tumour
- Melanotic malignant nerve sheath tumour

Undifferentiated small round cell sarcomas of bone and soft tissue.

- EWING'S SAROMA

MAJOR ENTITIES TO BE DISCUSSED - CONTD

Tumors of uncertain differentiation	
Synovial sarcoma	Epithelioid sarcoma: proximal and classic variant
Alveolar soft part sarcoma	Clear cell sarcoma
Extraskeletal myxoid chondrosarcoma	Desmoplastic small round cell tumor
Rhabdoid tumor	Perivascular epithelioid tumor, malignant
Myoepithelial carcinoma	Pleomorphic sarcoma, undifferentiated

IDENTIFY THIS HISTORIC EDUCATIONAL INSTIUTION

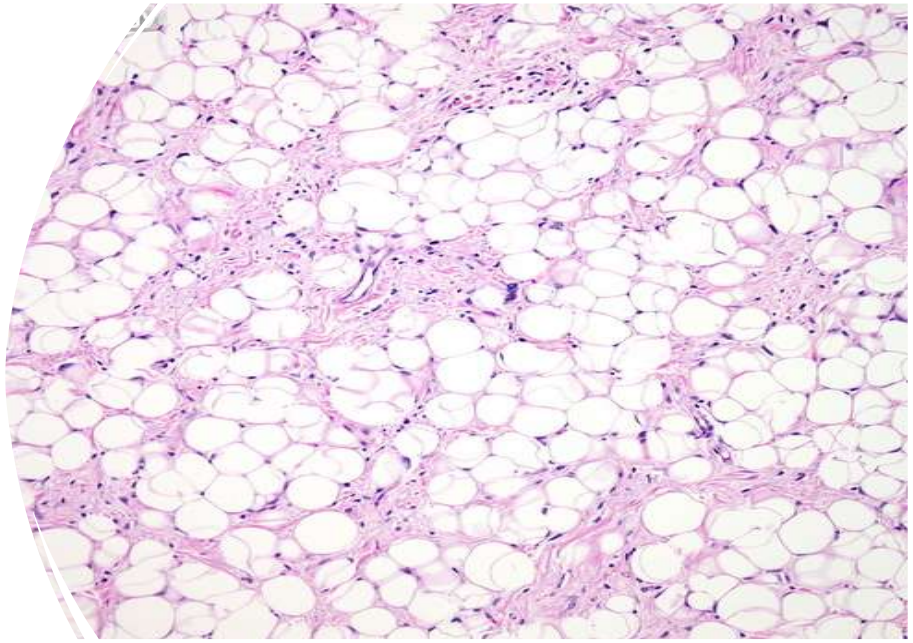
KHALSA COLLEGE – AMRITSAR

- FOUNDED IN 1892
- LEADING EDUCATIONAL INSTITUTIONS
- ARCHITECTURE IS A MIX OF BRITISH, MUGHAL AND SIKH DESIGNS

ADIPOCYTIC TUMORS
Well differentiated liposarcoma
Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma

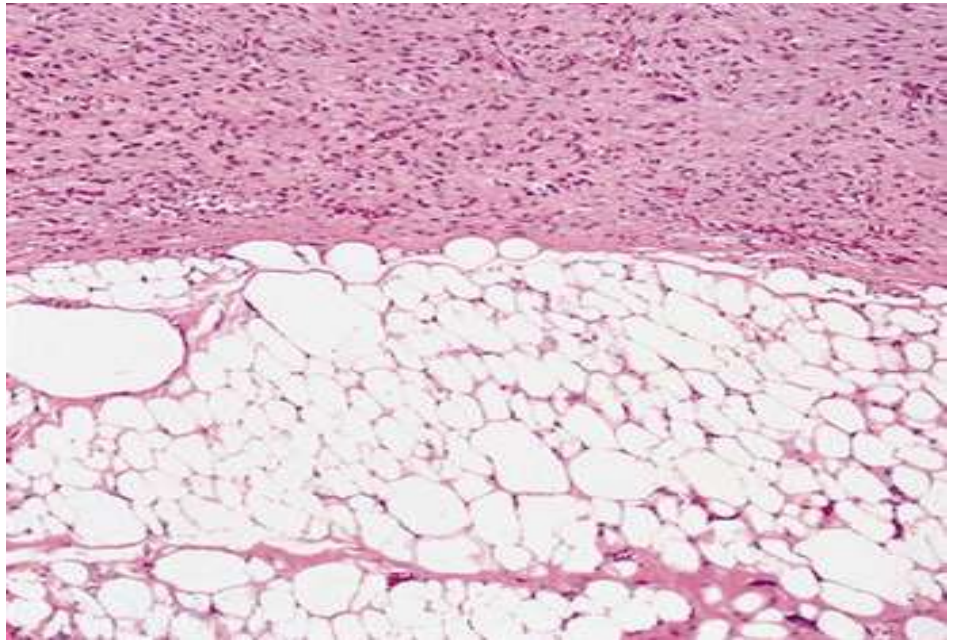
• Well differentiated liposarcoma

- **Most common histologic subtype**
- Mature adipocytes, atypical spindle cells and multivacuolated lipoblasts embedded in a loose myxoid to dense fibrous stroma
- Atypical lipoblasts and multinucleated giant cells are frequently found
- IHC: MDM2, CDK4 (usually negative in myxoid / round cell and spindle subtypes) and S – 100



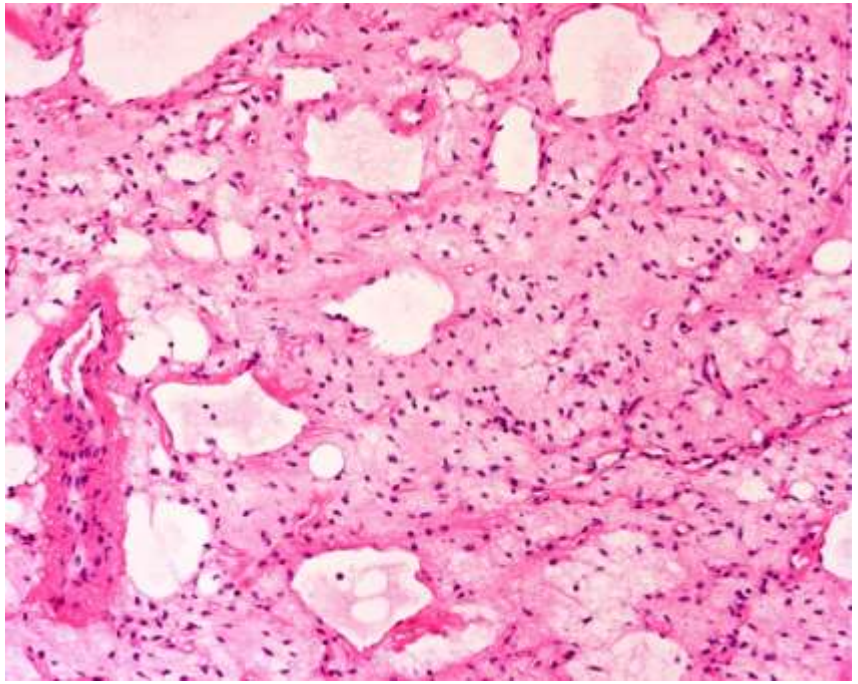
• Dedifferentiated liposarcoma

- Well differentiated and dedifferentiated components often both present
- Dedifferentiated component is a cellular sarcoma with significant pleomorphism
- Often resembles malignant fibrous histiocytoma (MFH) with pleomorphic spindle cells



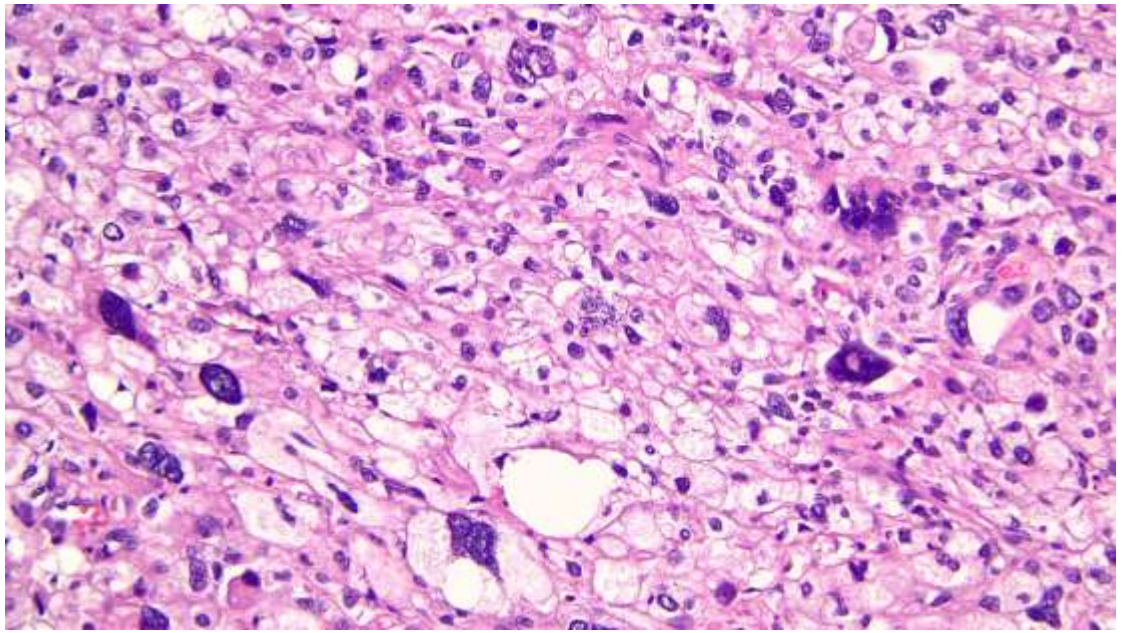
Myxoid liposarcoma

- Paucicellular with monomorphic, stellate or fusiform shaped cells without atypia
- Prominent plexiform vasculature (chicken wire fencing)
- Numerous signet ring lipoblasts
- Mucoid matrix is rich in hyaluronic acid that may form large mucoid pools
- IHC: Positive for Vimentin, S – 100, DDIT3 and SOX 11



Pleomorphic liposarcoma

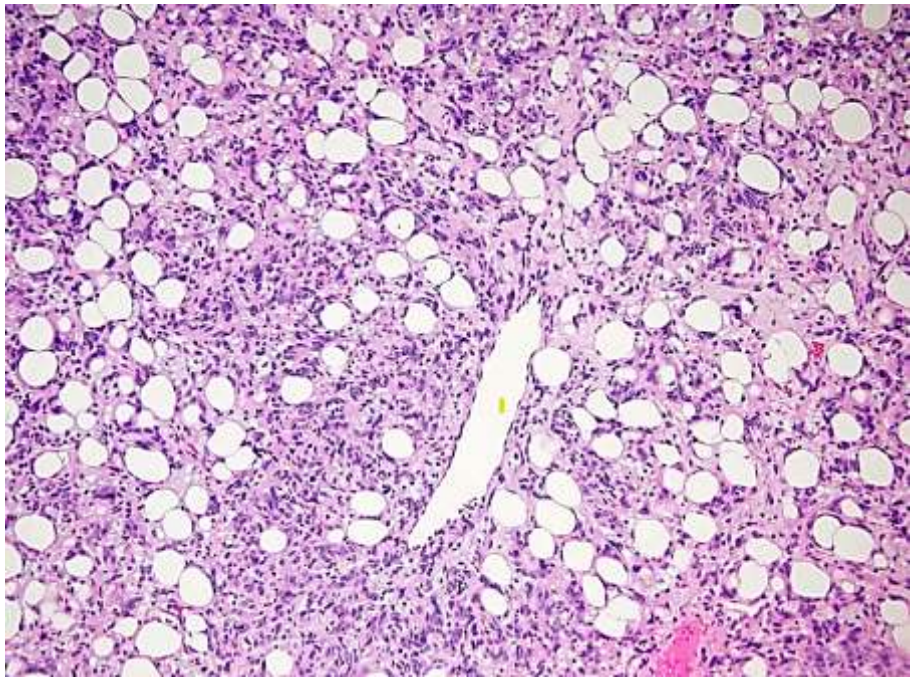
- Varying proportion of pleomorphic lipoblasts in a background of a high grade, usually pleomorphic, undifferentiated sarcoma
- high grade cells with varying numbers of pleomorphic and often bizarre, multinucleated tumor cells
- Signet ring lipoblasts
- IHC: Positive for Vimentin, S – 100, SMA, kerati, CD 34 and desmin



Fibroblastic/myofibroblastic tumors
Solitary fibrous tumor, malignant
Fibrosarcoma NOS
Myxofibrosarcoma

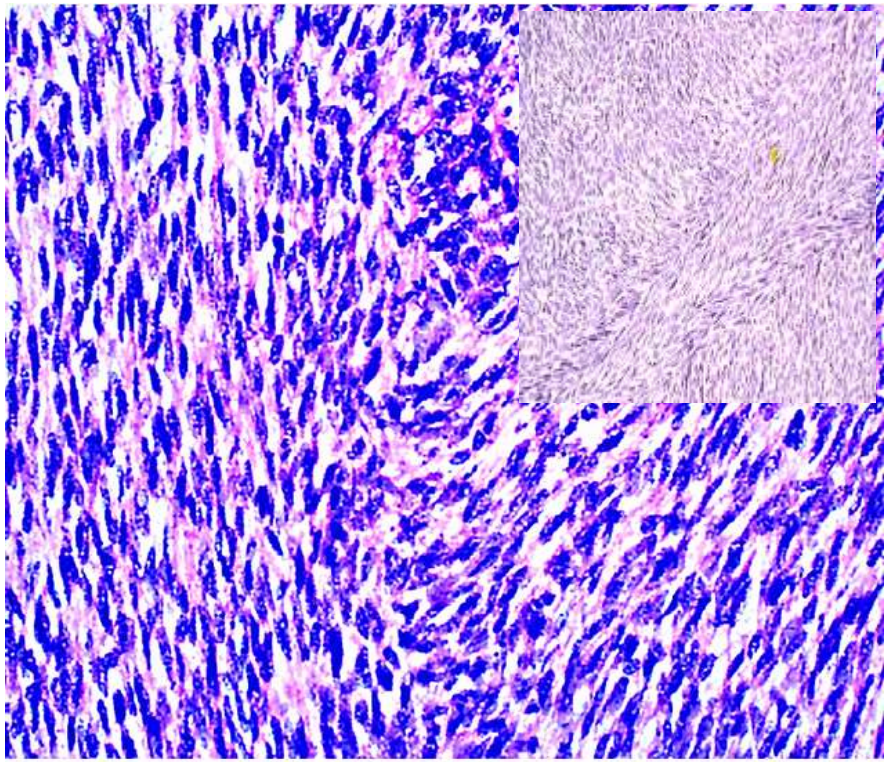
• Solitary fibrous tumor, malignant

- Ovoid to fusiform spindle cells with indistinct cell borders arranged in fascicles
- Dilated, branching, hyalinized staghorn-like (hemangiopericytoma-like) vasculature
- Hyalinized to collagenous stroma, sometimes with streaming of cells between collagen
- IHC: CD 34 Positive
- STAT 6 – Highly sensitive and specific



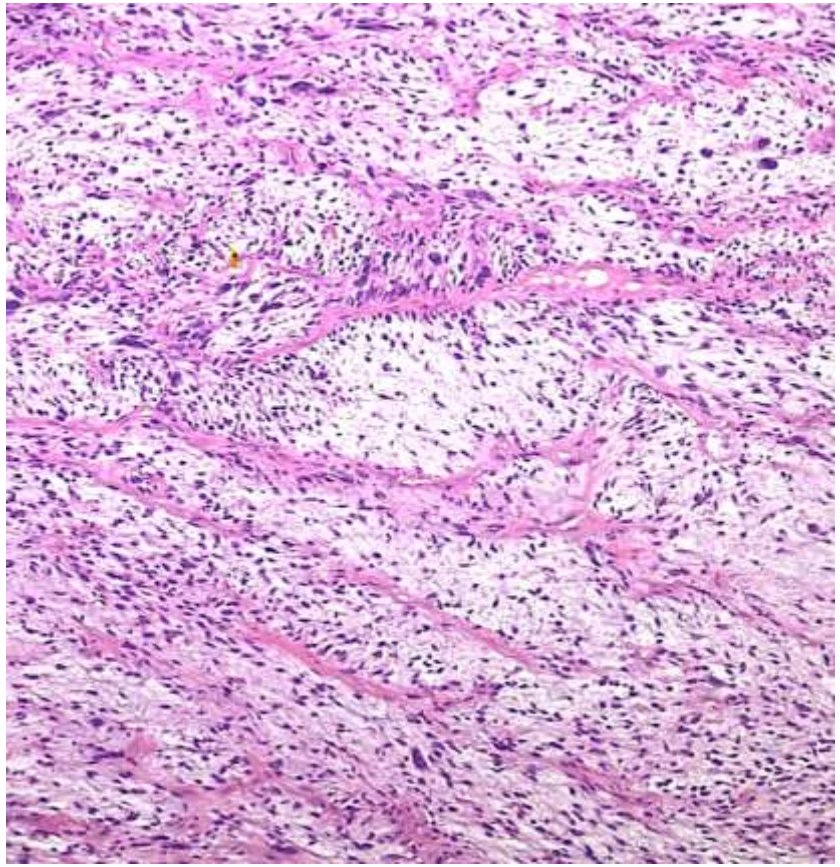
• Fibrosarcoma

- Highly cellular fibroblastic proliferation in herringbone pattern (cells in columns of short parallel lines with all the lines in one column sloping one way and lines in adjacent columns sloping the other way)
- Cells have scant cytoplasm, tapering elongated dark nuclei with increased granular chromatin, variable nucleoli
- Mitotic activity present, often with abnormal forms



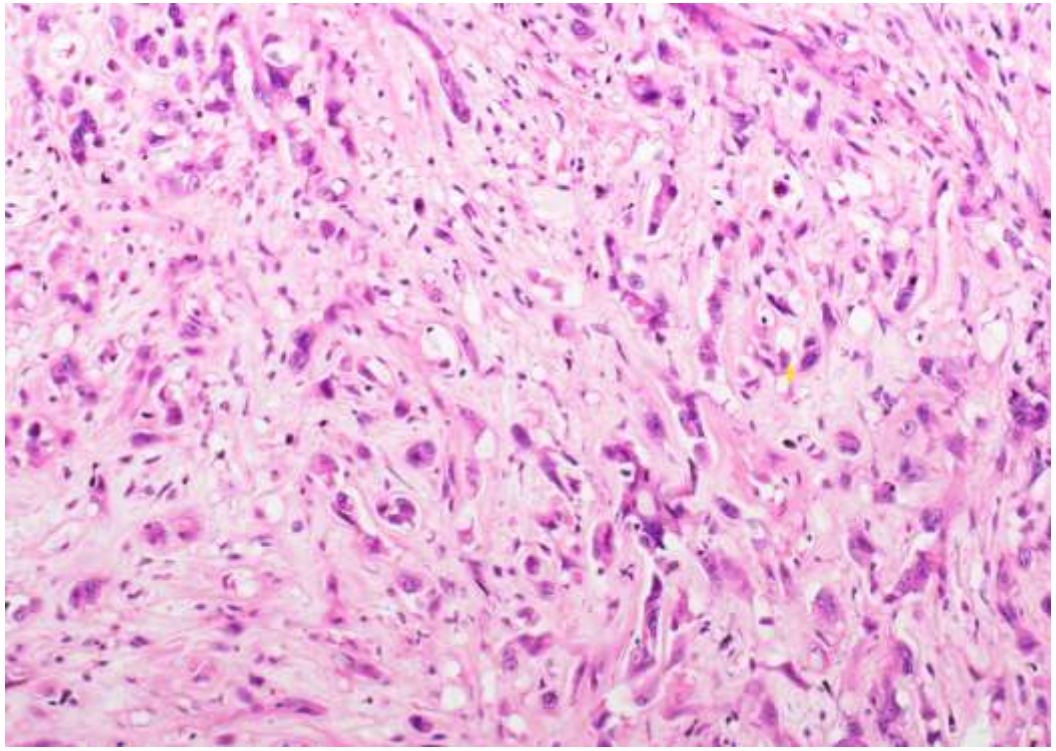
Myxofibrosarcoma

- Lobulated tumor with multinodular growth and incomplete fibrous septae
- Alternate hypocellular and hypercellular areas
- IHC: Positive for Vimentin, SMA, MSA and CD34

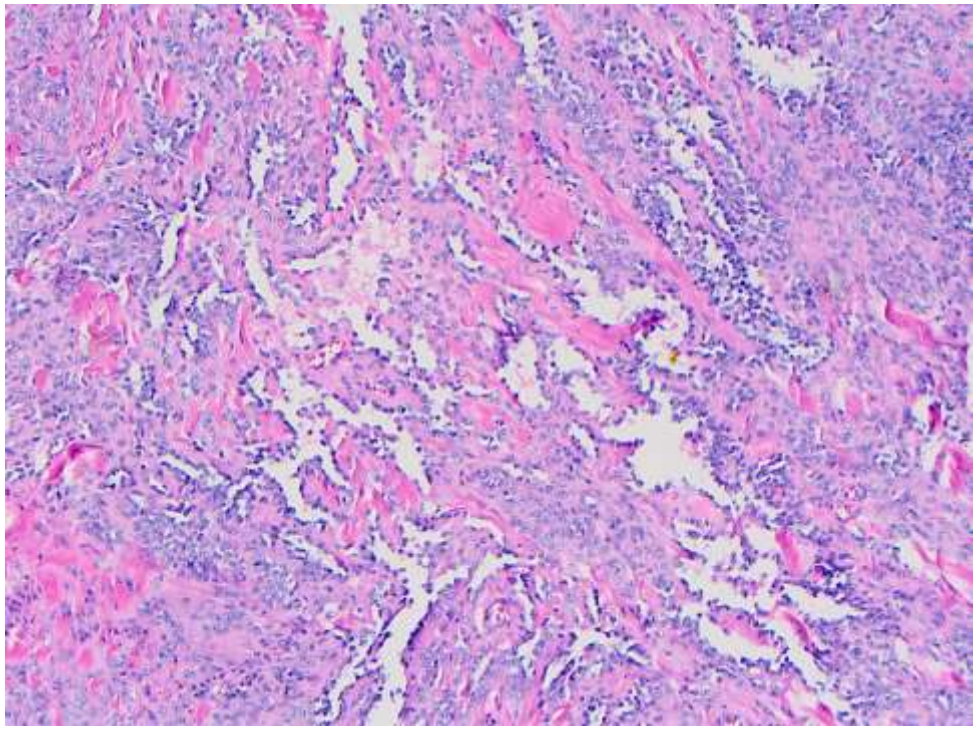


Vascular tumours

- **Epitheloid hemangioendithelioma**
  - **Cords, strands or small nests of large endothelial cells with abundant eosinophilic cytoplasm**
  - **Some tumor cells have intracytoplasmic, round, clear vacuoles representing small vascular lumina, which may contain erythrocytes**
  - **IHC: ERG, CD31, CD34, D2-40**

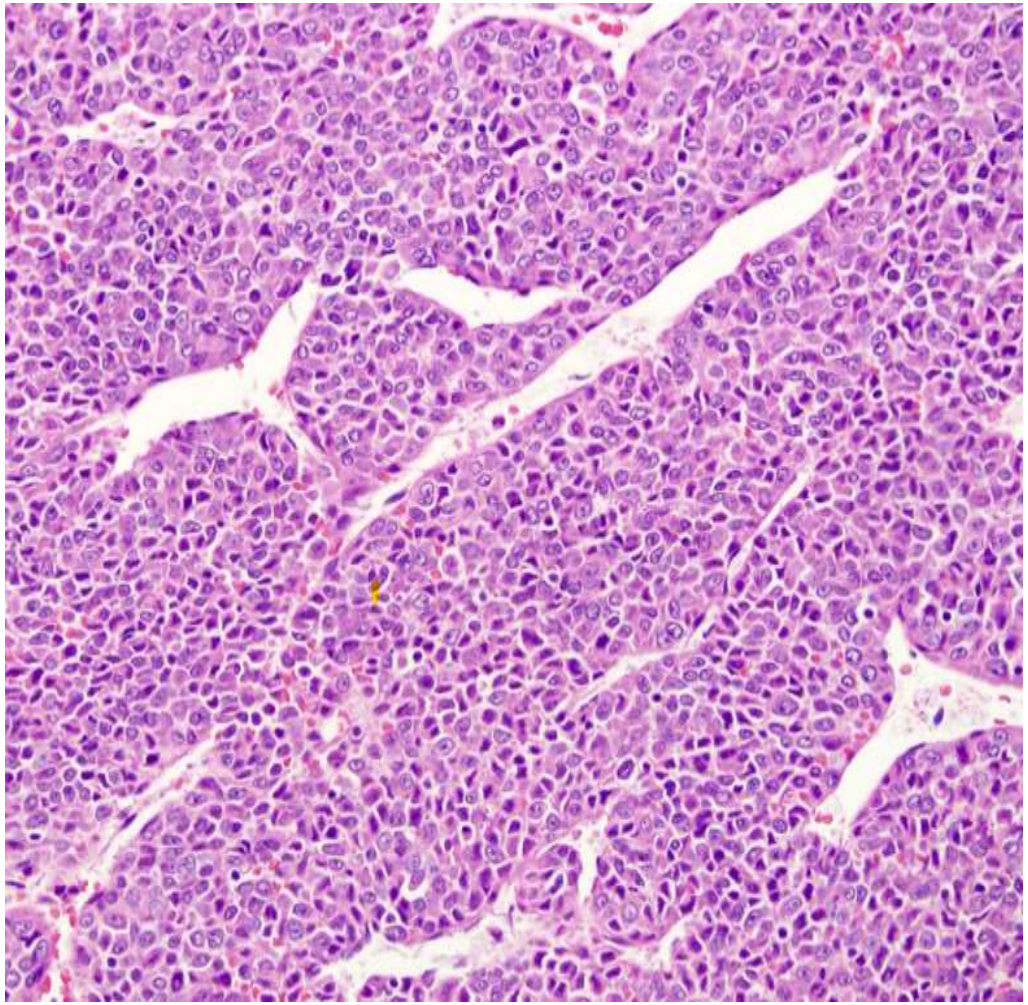


- **Angisarcoma**
  - Cytologically bland and vasoformative lesion to solid sheets of highly pleomorphic cells without definitive vasoformation
  - Numerous irregularly shaped anastomosing vascular channels lined by atypical endothelial cells with a highly infiltrative architecture and poor demarcation
  - **IHC**: endothelial cell markers, including CD31, CD34, ERG, FLI1, VEGF and factor VIII



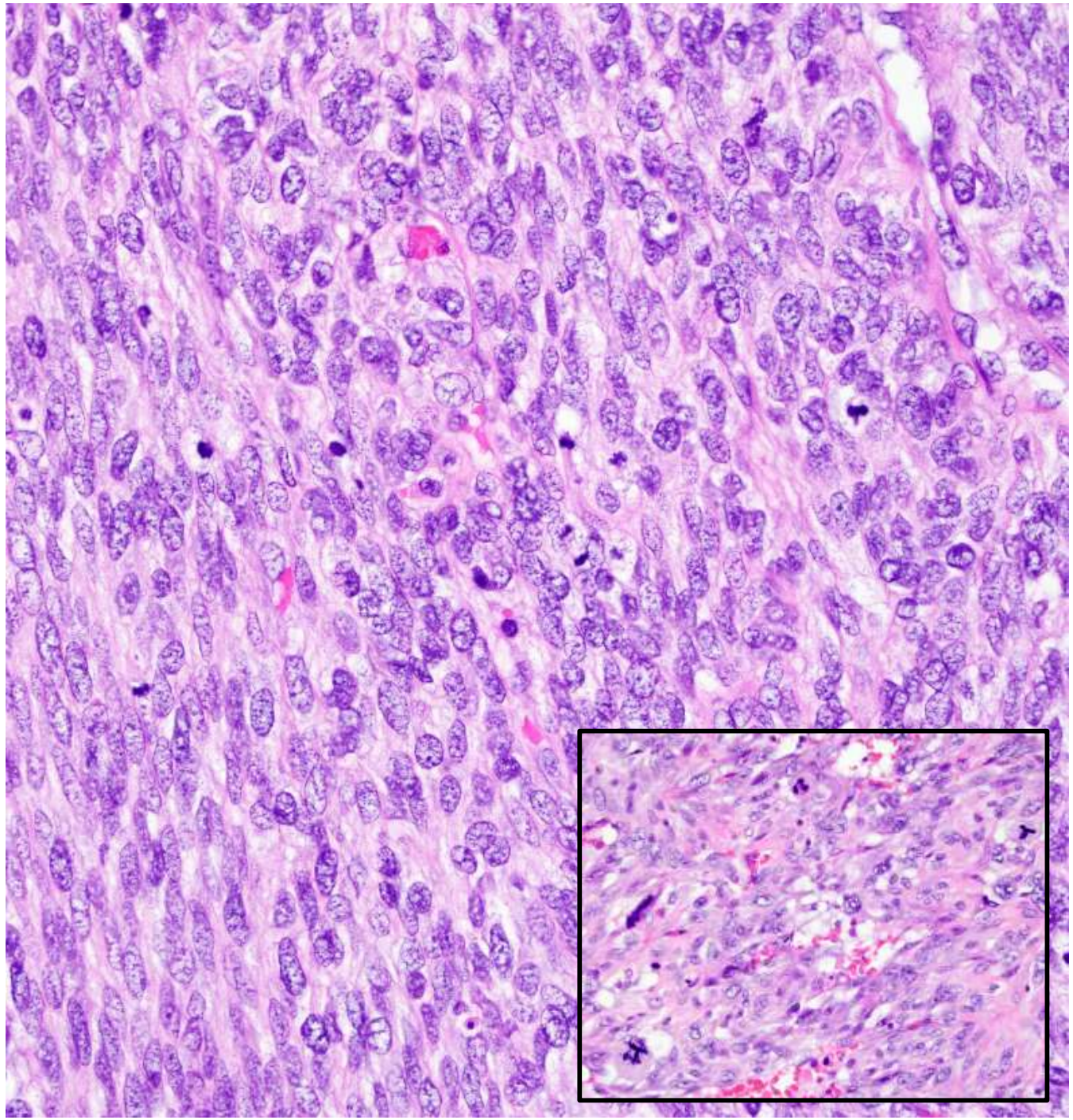
PERICYTIC (PERIVASCULAR) TUMORS: GLOMUS TUMOR MALIGNANT

- Diagnosis should be reserved for tumors showing marked nuclear atypia and any level of mitotic activity or atypical mitotic figures
- May be spindled and resemble leiomyosarcoma / fibrosarcoma
- Benign glomus tumor component can be found at the periphery
- IHC: Vimentin (100%), smooth muscle actin (99%), muscle specific actin (95%), calponin (80%), CD34 (32 - 53%)



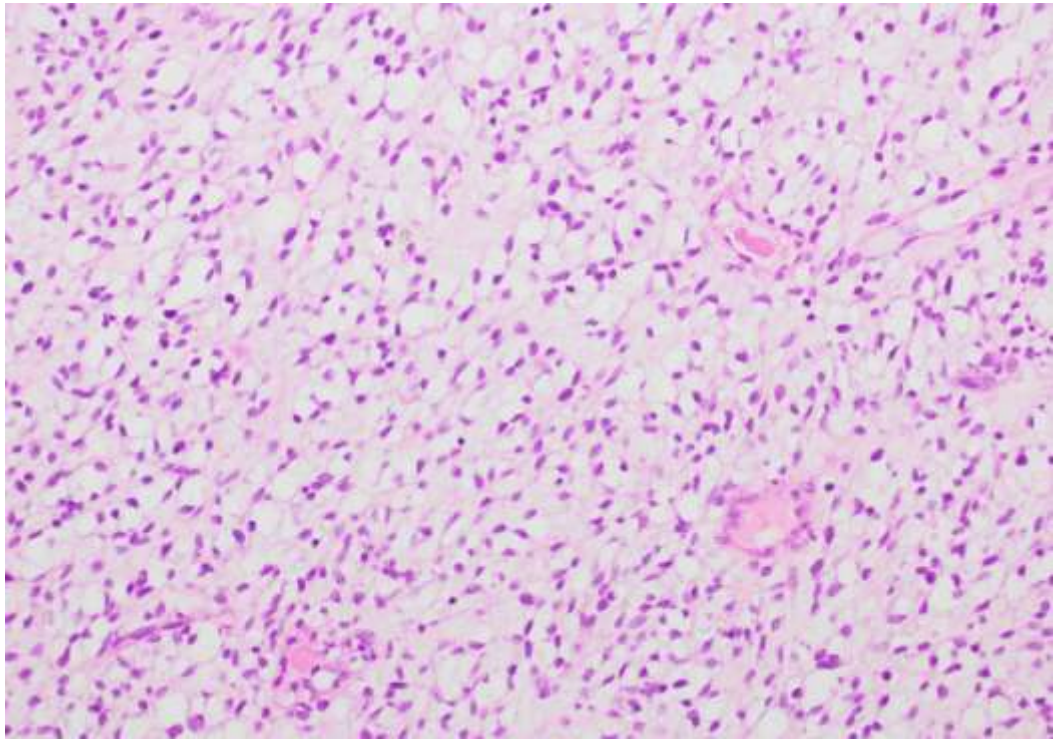
SMOOTH MUSCLE TUMORS: LEIOMYOSARCOMA

- Cellular tumor comprised of long intersecting or haphazard fascicles having infiltrative border
- Spindle cells with eosinophilic cytoplasm hyperchromatic nucleiwith moderate to severe nuclear pleomorphism and atypical mitoses
- Multinucleated and osteoclast-like giant cells may be seen
- IHC: Smooth muscle markers including h-caldesmon (more specific), desmin and SMA

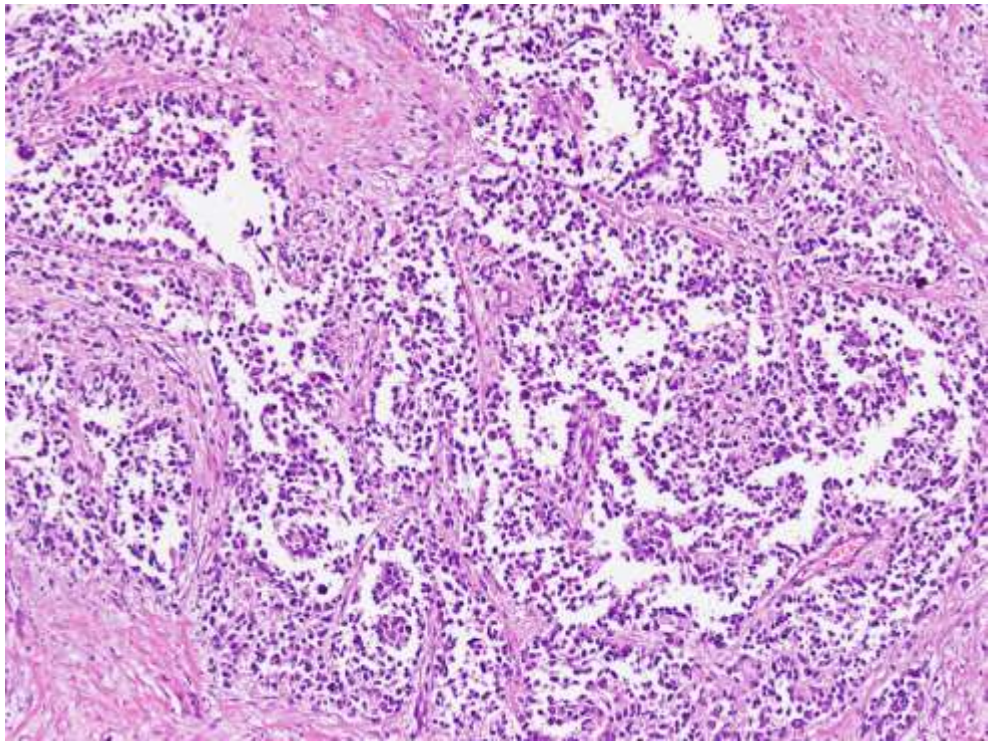


Skeletal muscle tumors
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma

- **EMBRYONAL RMS**
  - Primitive mesenchymal of skeletal muscle differentiation
  - Both hypocellularity and hypercellular areas with a loose, myxoid stroma
  - Strap and tadpole cells
  - Botryoid variant shows a cambium layer
  - IHC: Desmin, MyoD1 or myogenin, Vimentin actin myoglobin and myosin

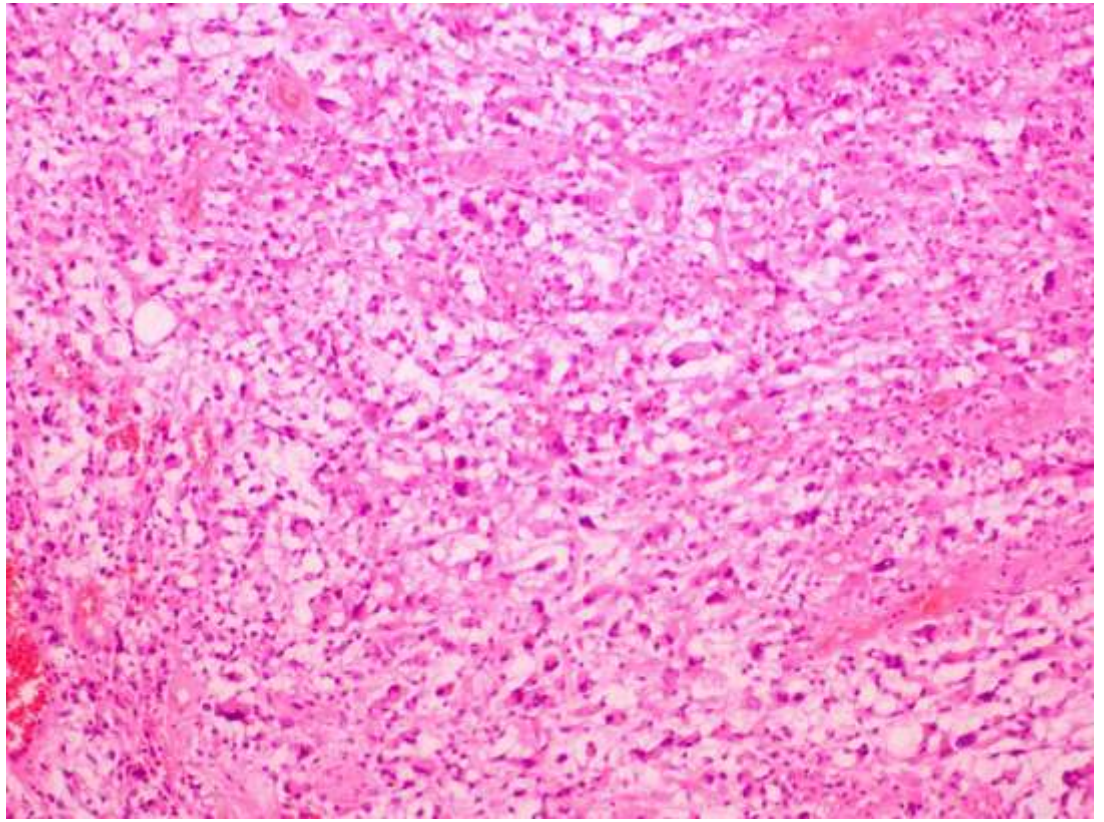


- **ALVEOLAR RMS**
  - Cellular round cell tumor
  - Large clusters, nests, cords and trabeculae of primitive round cells, separated by septa
  - Loss of cellular cohesion in the center forms alveolar-like appearance
  - Cells in the center have poor preservation and are necrotic; may appear floating
  - IHC: Desmin, myogenin, MyoD1, muscle specific actin



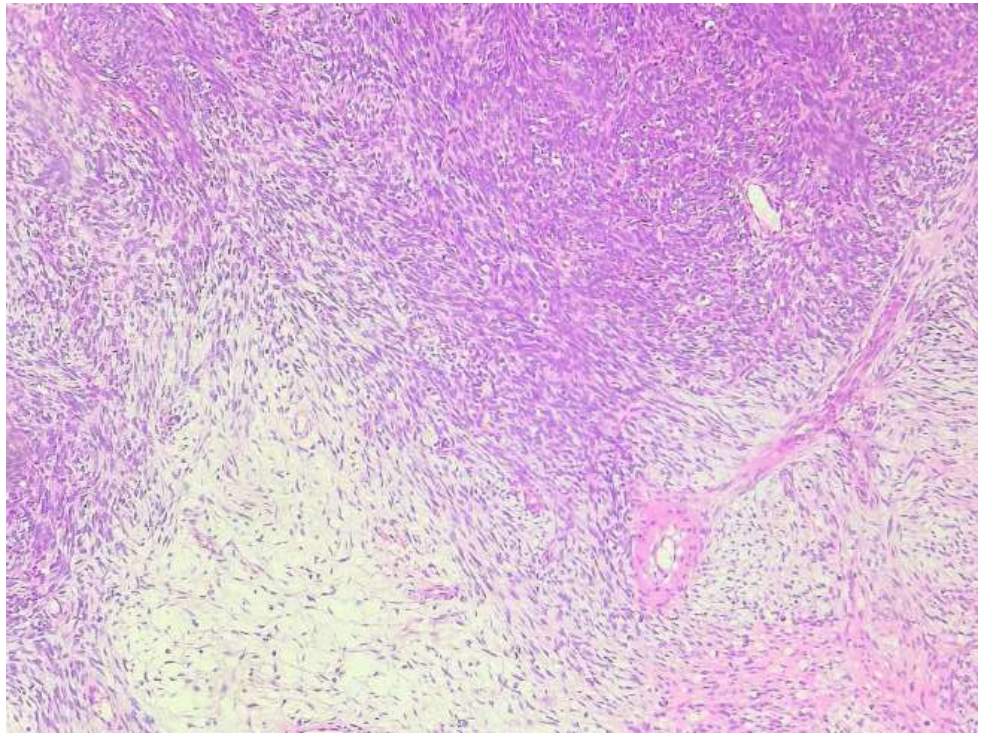
PLEOMORPHIC RHABDOMYOSARCOMA

- Sheets of large, atypical and frequently multinucleated polygonal, spindled or rhabdoid eosinophilic cells
- Cross striations are seldom detected
- IHC: Expresses desmin, MyoD1, skeletal muscle (fast) myosin and myogenin
- Desmin expression is usually strong, while myogenin and MyoD1 staining can be focal

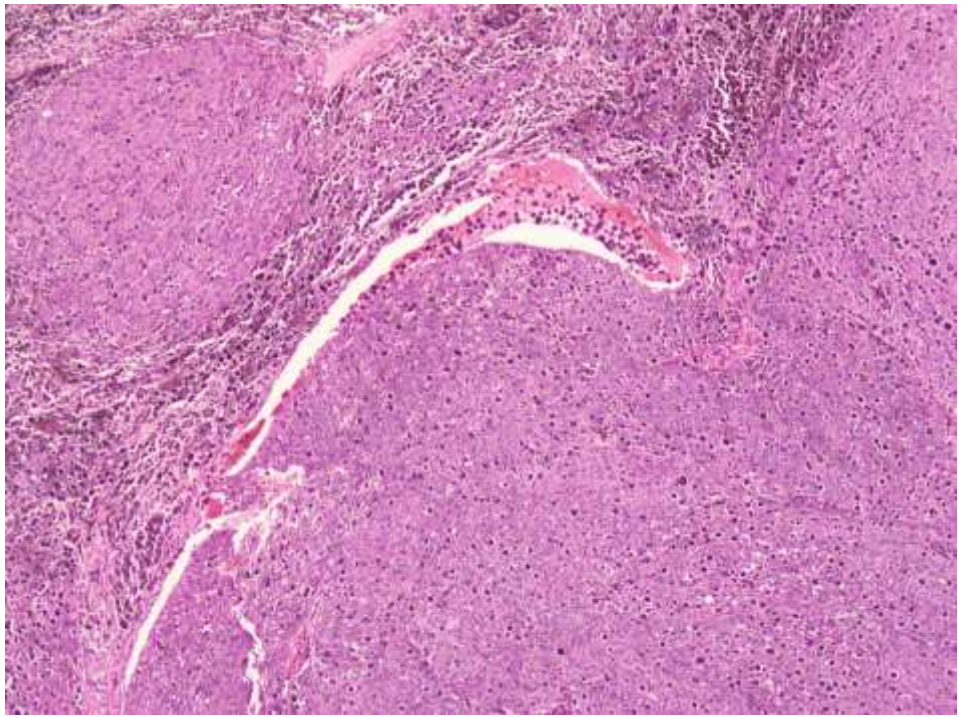


PERIPHERAL NERVE SHEATH TUMORS

- **MPNST**
- Low power: marbled appearance due to alternating hypocellular and hypercellular areas with perivascular accentuation
- Uniform spindle cells with hyperchromatic, thin, wavy, or focally buckled nuclei
- IHC: S100 and SOX10



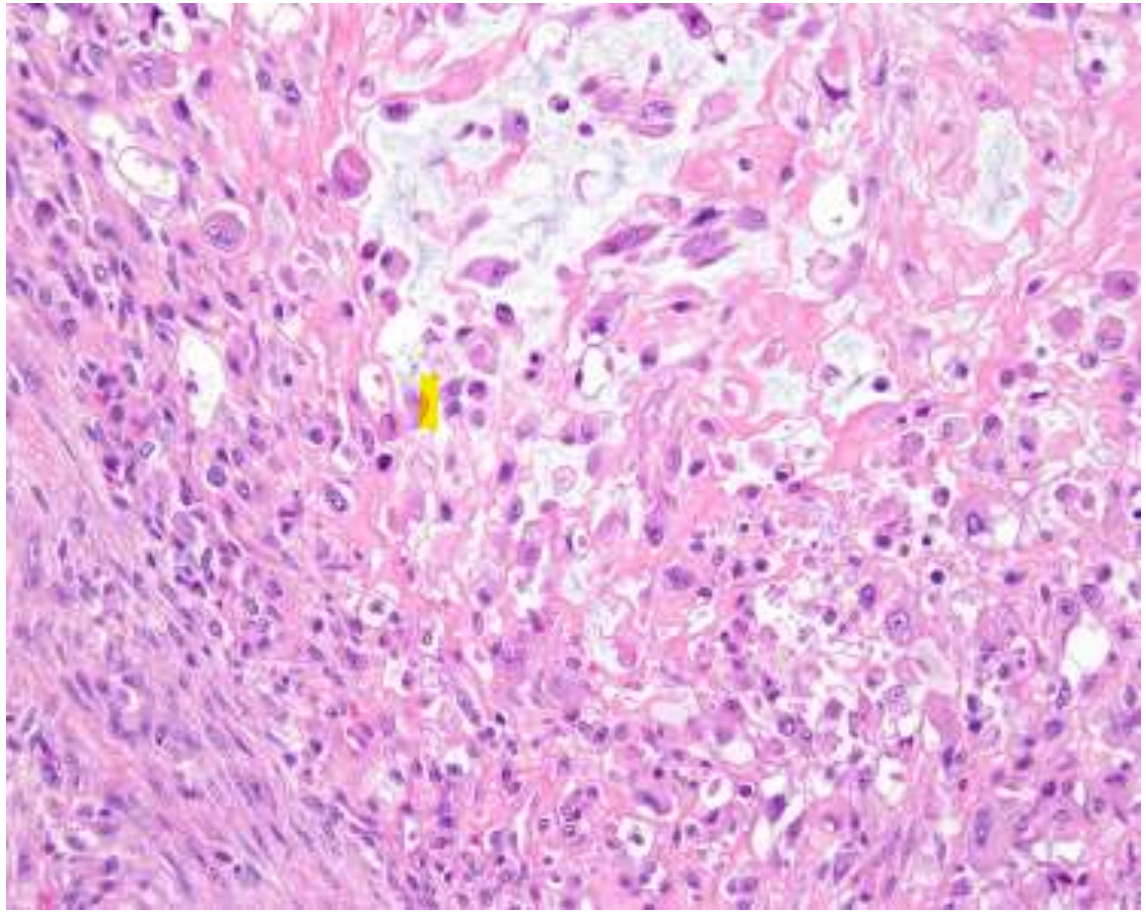
- **Melanotic malignant nerve sheath tumor**
- Circumscribed, unencapsulated lesion with plump spindle and epithelioid cells arranged in interlacing fascicles
- Accumulation of melanin in neoplastic cells and associated melanophages
- Round, ovoid or elongated nuclei with distinct nucleoli
- IHC: S100, SOX10, MelanA, HMB45, tyrosinase



MISCELLENEOUS ENTITIES

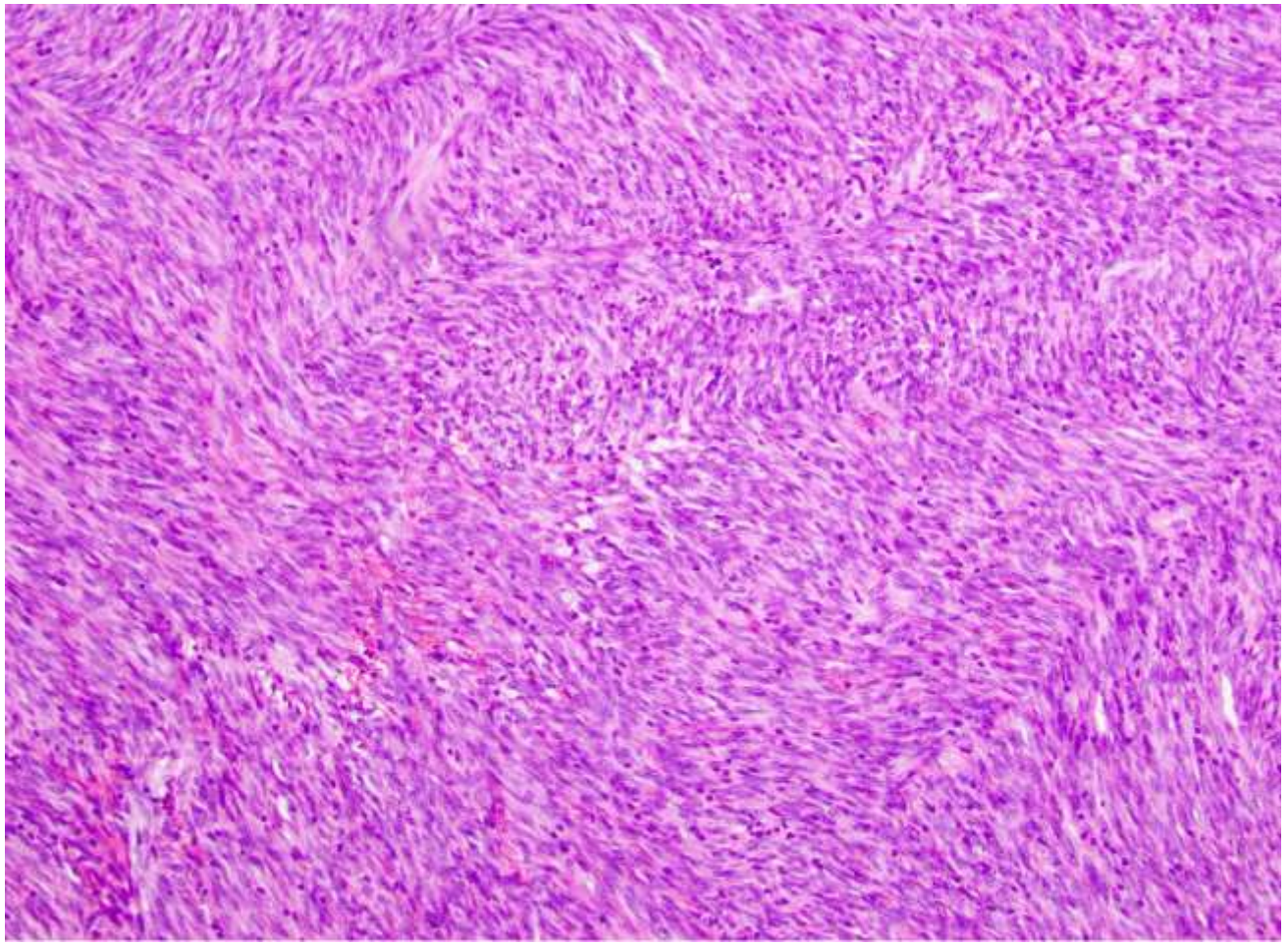
Malignant tenosynovial giant cell tumor

- Composed of sheets and nodules of enlarged mononuclear cells
- Significantly increased mitotic count, including atypical mitoses, necrosis, enlarged nuclei with nucleoli, spindling of mononucleated cells and myxoid changes
- May contain areas that resemble undifferentiated pleomorphic sarcoma or myxofibrosarcoma
- IHC: Positive for Clusterin, D2-40, CD68, p63, MDM2 and p16



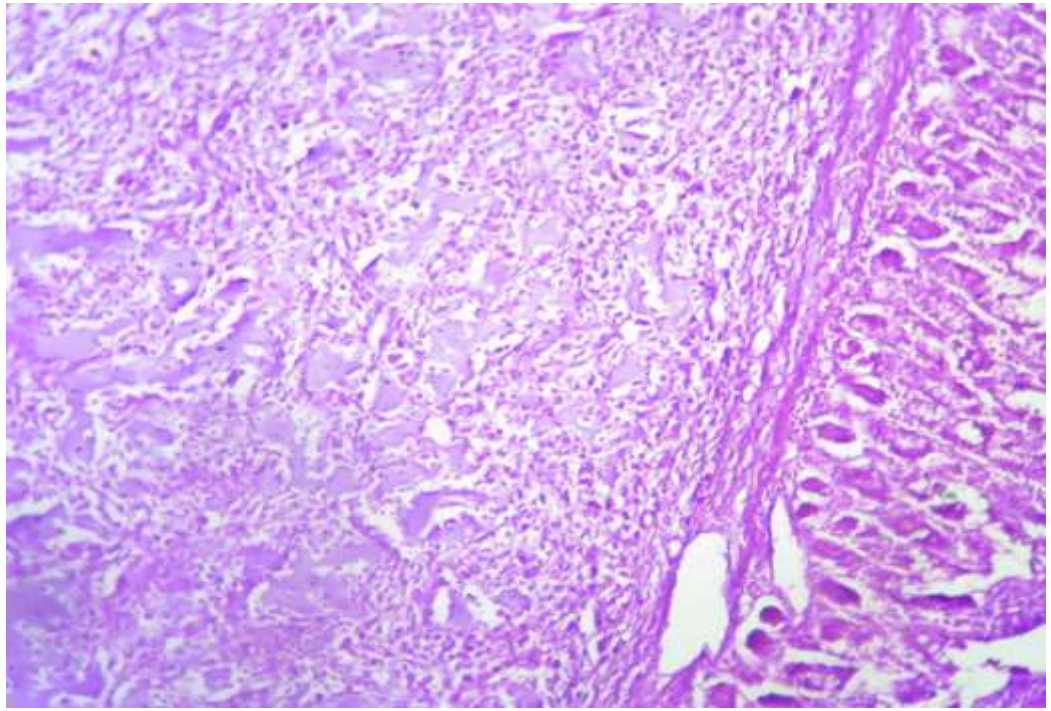
GASTROINTESTINAL STROMAL TUMOR

- 3 morphologic subtypes
- Spindle: bland spindle cells in syncytial pattern with paranuclear vacuoles
- Epithelioid: round cells in sheets or nest
- Mixed
- IHC: DOG 1, CD117



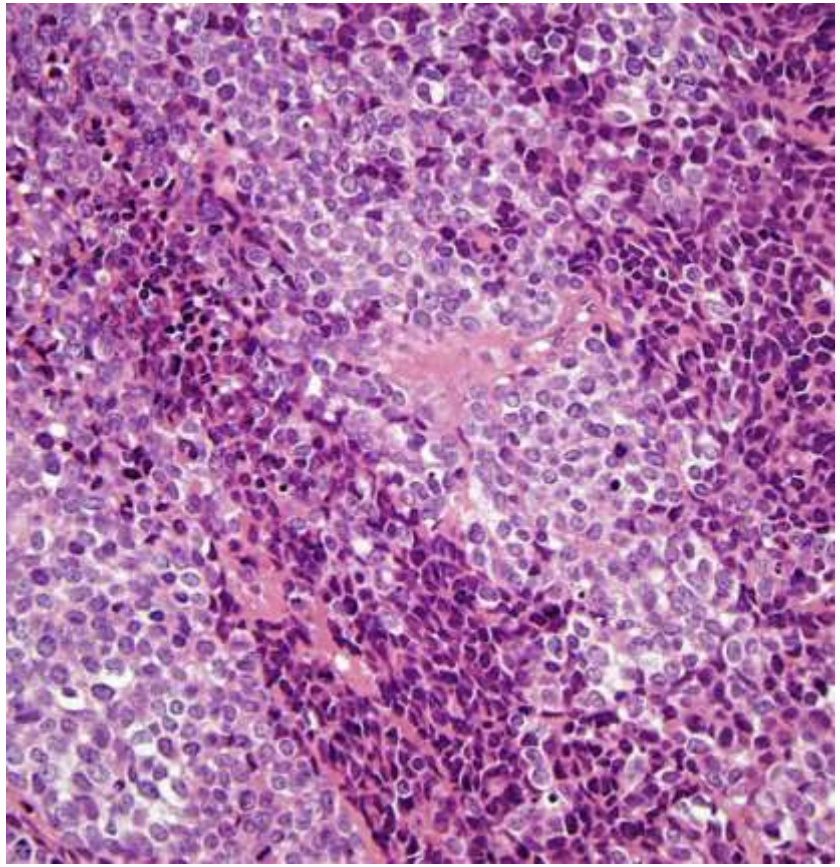
- **Extraskeletal Osteosarcoma**

- Osteoid and bone formation produced by tumor cells, without interposition of cartilage



Undifferentiated small round cell sarcomas of bone and soft tissue: Ewing's Sarcoma

- Uniform small round cells
- Tumor cells 1 - 2x size of lymphocytes with round nuclei
- Finely stippled chromatin, inconspicuous nucleoli
- Indistinct cytoplasmic membranes
- Sheet-like growth pattern
- Islands separated by dense fibrous tissue
- Subset with neuroectodermal differentiation (Homer-Wright pseudorosettes)
- IHC: CD99, NKX2.2, Vimentin, L11 and ERG



IDENTIFY THIS MEMORIAL

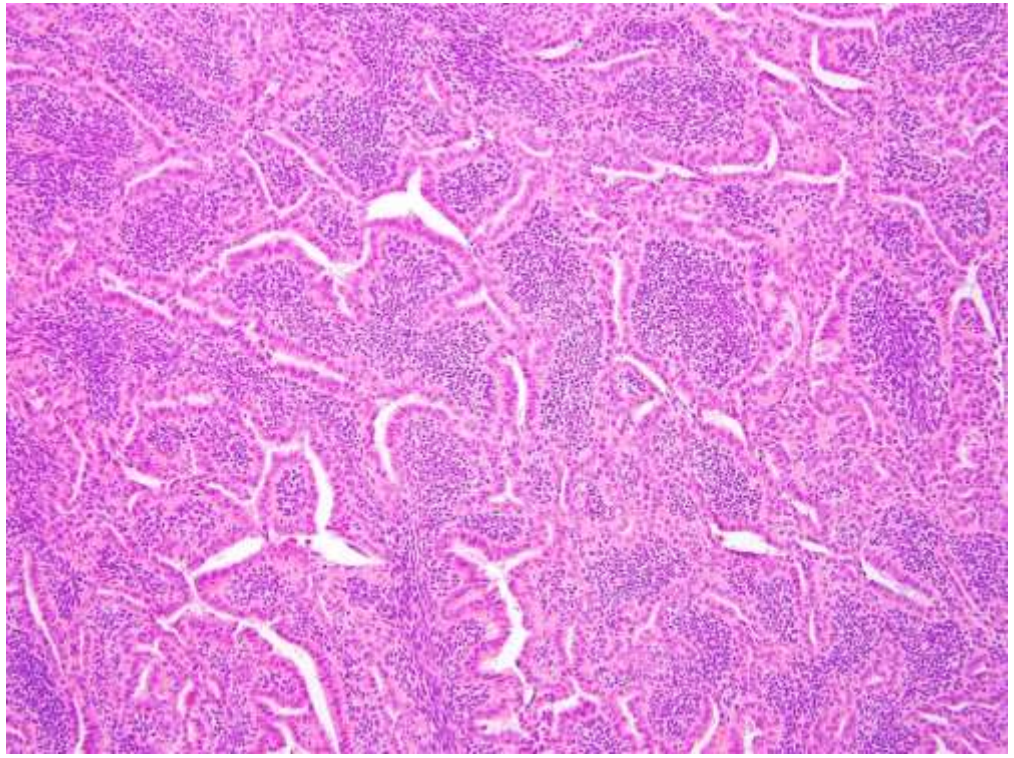
JALLIANWALAH BAGH MEMORIAL

- 13 APR 1919
- BRIGADIER GENERAL R E H DYER ORDERED SHOOTING OF PROTESTERS
- AROUND 1500 INNOCENT LIVES WERE LOST

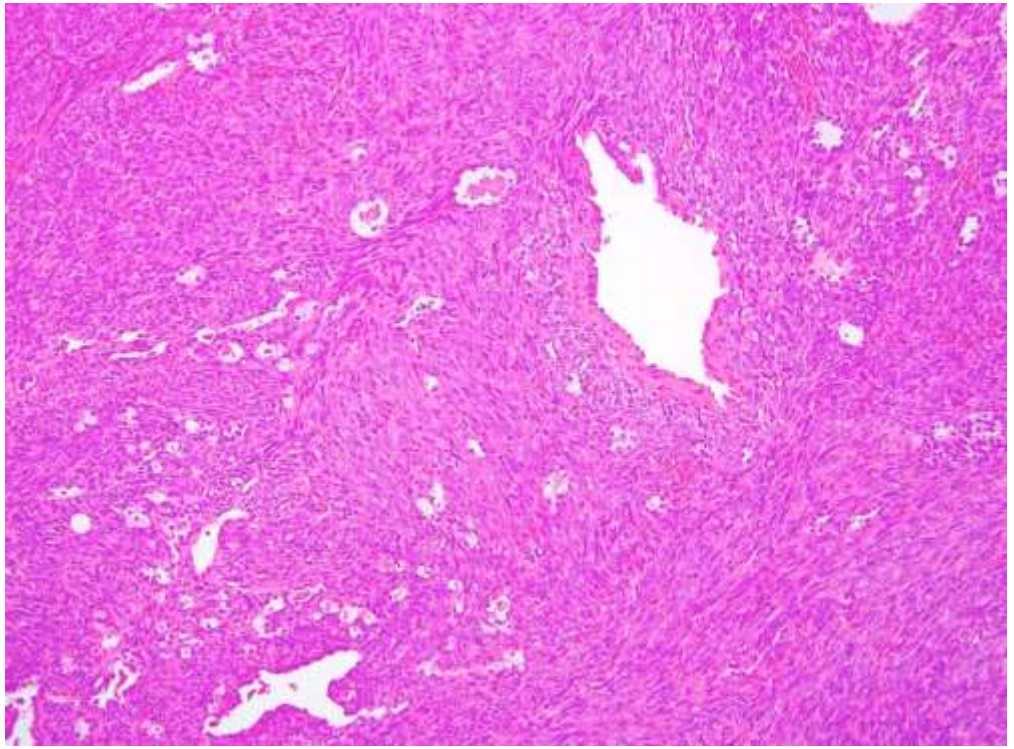
Tumors of uncertain differentiation	
Synovial sarcoma	Epithelioid sarcoma: proximal and classic variant
Alveolar soft part sarcoma	Clear cell sarcoma
Extraskeletal myxoid chondrosarcoma	Desmoplastic small round cell tumor
Rhabdoid tumor	Perivascular epithelioid tumor, malignant
Myoepithelial carcinoma	Pleomorphic sarcoma, undifferentiated

SYNOVIAL SARCOMA

- **BIPHASIC**
  - **Biphasic: 2 components: spindle cells and gland-like epithelial structures**
  - **Glandular lumina contain mucin**
  - **Epithelial component has moderate, distinct amphophilic cytoplasm with round to ovoid nuclei**
  - **IHC: TLE1, CKs, EMA and BCL2**

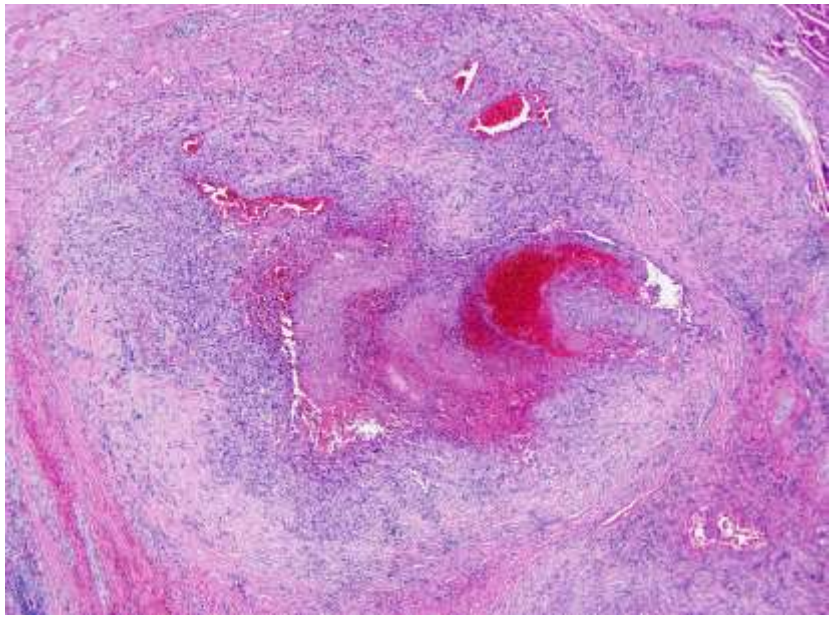


- **MONOPHASIC**
  - Infiltrative borders
  - Hypercellular fascicular architecture with little intervening stroma
  - Can rarely show hyalinization or myxoid change
  - Ill defined nuclear palisading may be seen

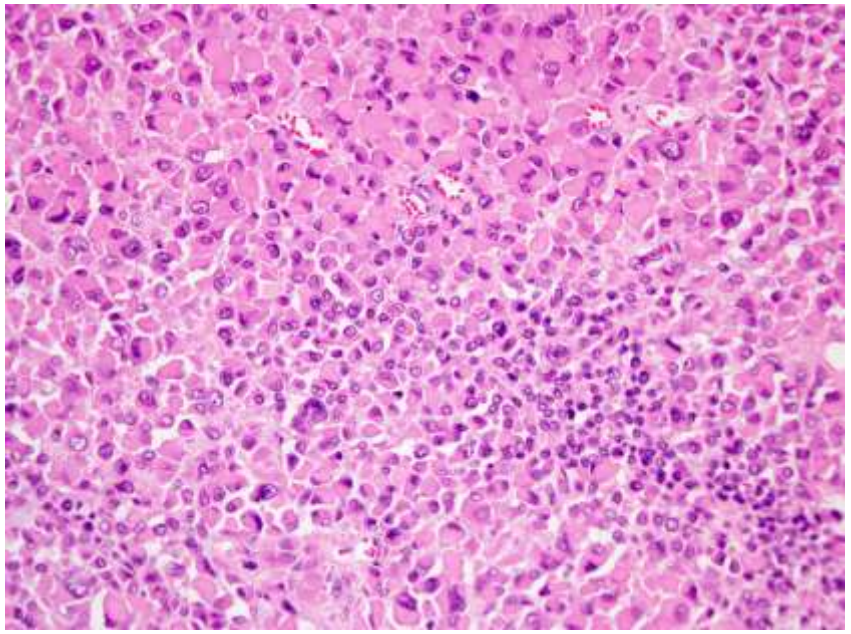


Epithelioid sarcoma: proximal and classic variant

- **CLASSIC**
  - Can mimic granulomatous process, with or without necrosis
  - Fairly uniform plump small to medium sized cells with eosinophilic cytoplasm
  - Mixed chronic inflammatory infiltrate common
  - Dystrophic calcification and metaplastic bone formation
  - IHC: Pancytokeratin, Vimentin and CD34

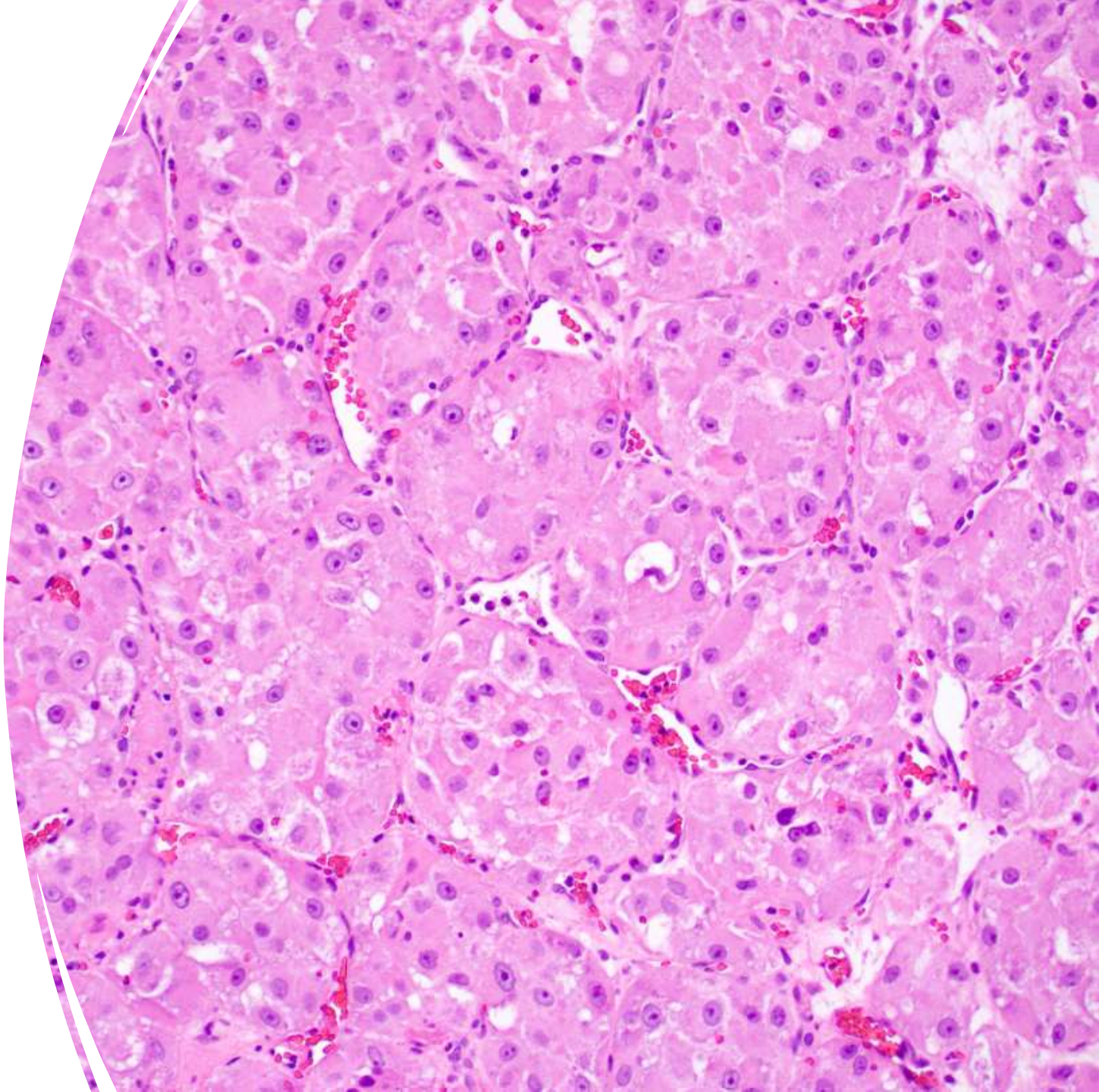


- **PROXIMAL LARGE CELL TYPE**
  - Infiltrative growth pattern
  - Large polygonal cells with abundant eosinophilic cytoplasm
  - Rhabdoid morphology common
  - Vesicular nuclei with prominent macronucleoli
  - Mitoses, necrosis and hemorrhage common



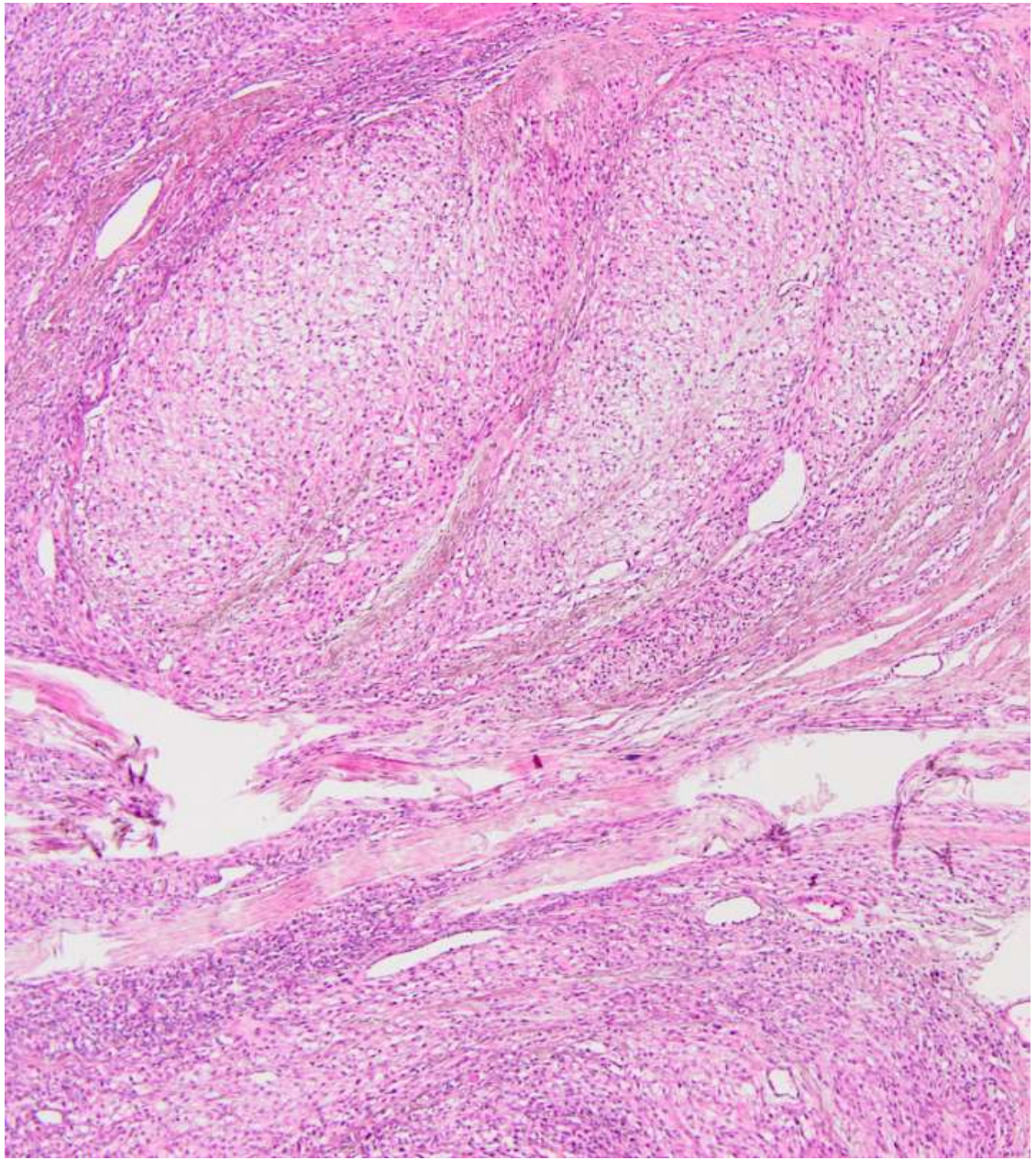
ALVEOLAR SOFT PART SARCOMA

- Large, round to polygonal cells with well defined cell borders
- Abundant eosinophilic granular cytoplasm
- Round, vesicular nucleus with a prominent nucleolus
- Organoid and nest-like growth pattern
- Central discohesion results in characteristic pseudoalveolar-like structures
- Lobules of tumor are divided by thick fibrous septa and rich capillary vascular network
- IHC: TEF3, Cathepsin K and PAS



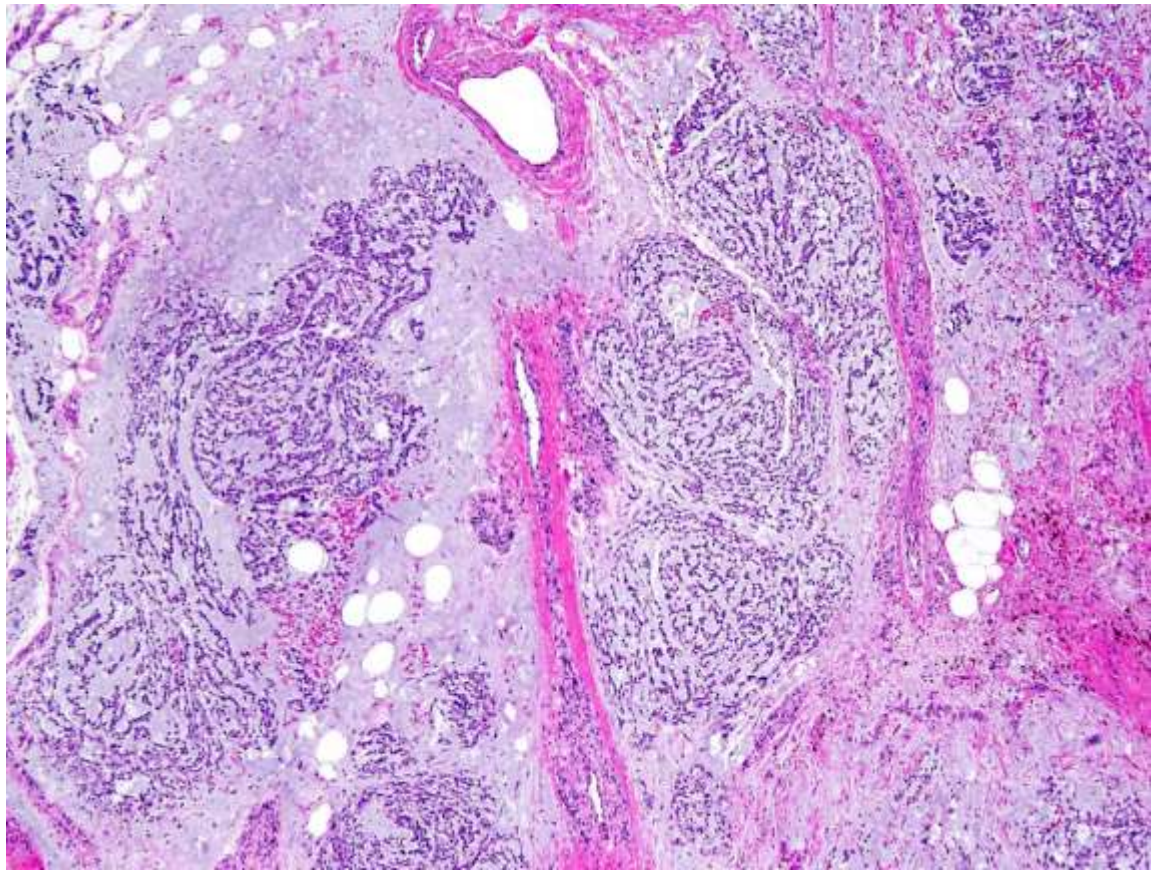
CLEAR CELL SARCOMA

- Nests of epithelioid spindle cells with clear eosinophilic cytoplasm and prominent nucleoli plus melanocytic differentiation
- Vaguely organoid (neuroendocrine-like) pattern: nests and short fascicles of epithelioid or spindle cells, surrounded by a delicate framework of fibrocollagenous tissue contiguous with the adjacent tendons and aponeurosis
- Diffuse pattern: solid sheets of epithelioid to spindle cells
- Pseudoalveolar pattern: reminiscent of alveolar soft part sarcoma
- Myxoid / microcystic pattern
- Inflammatory pattern: reminiscent of seminoma
- Cells: Epithelioid to spindled with Monotonous round to oval nuclei with prominent nucleoli
- Clear cells typically comprise only a subset of the tumor
- Melanin pigment in scattered cells in half of the cases
- IHC: S100, SOX10, HMB45 and BCL2



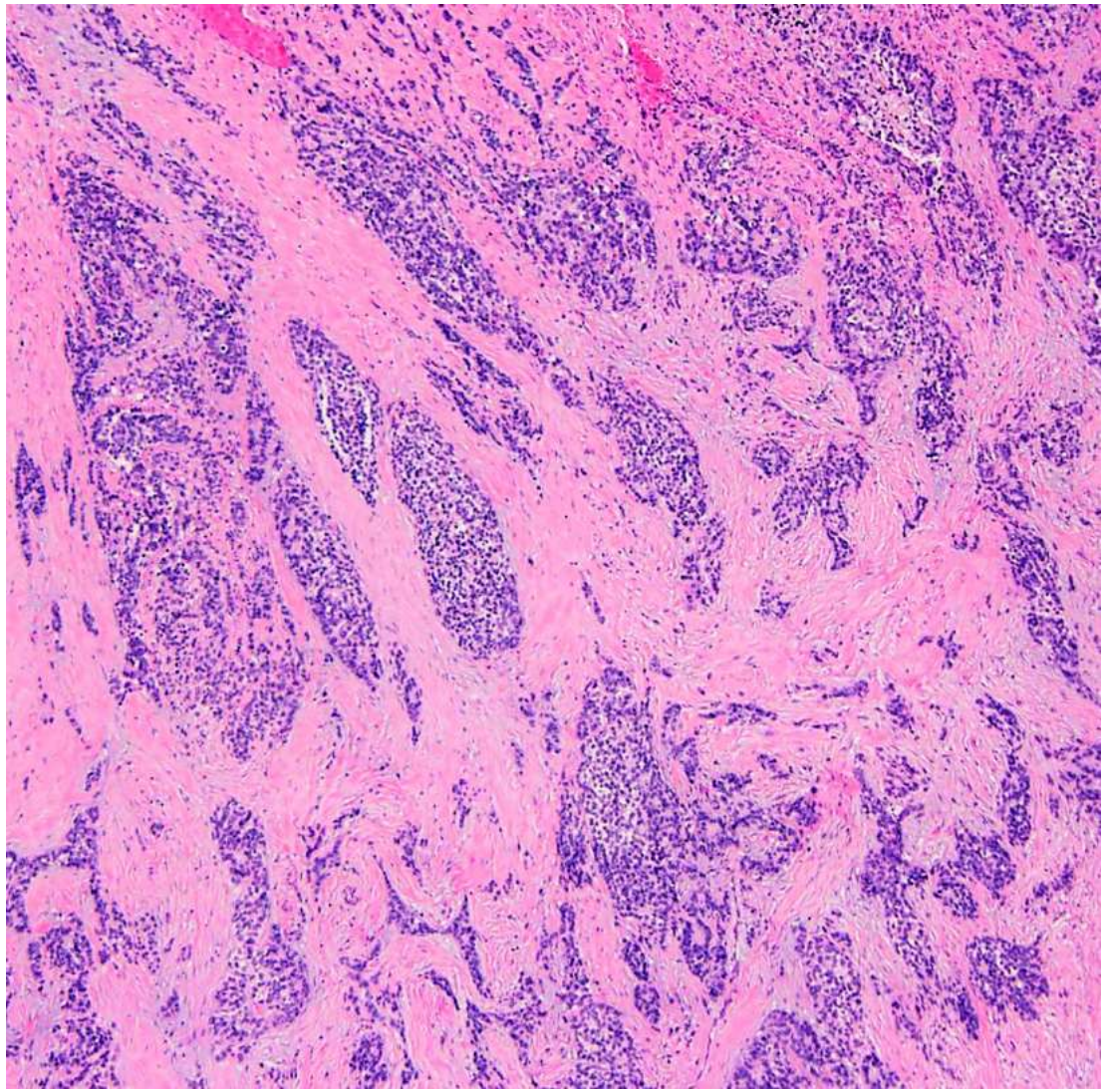
Extraskeletal myxoid chondrosarcoma

- Multinodular architecture
- Fibrous septa divide the tumor in pools of abundant myxoid or chondromyxoid matrix containing tumor cells
- Uniform cells with eosinophilic to vacuolated cytoplasm, often with long delicate cytoplasmic processes and round to oval nuclei
- Tumor cells are characteristically interconnected with one another to form cords, small clusters and complex trabecular or cribriform arrays
- IHC: INSM1, NSE, Synaptophysin and S100

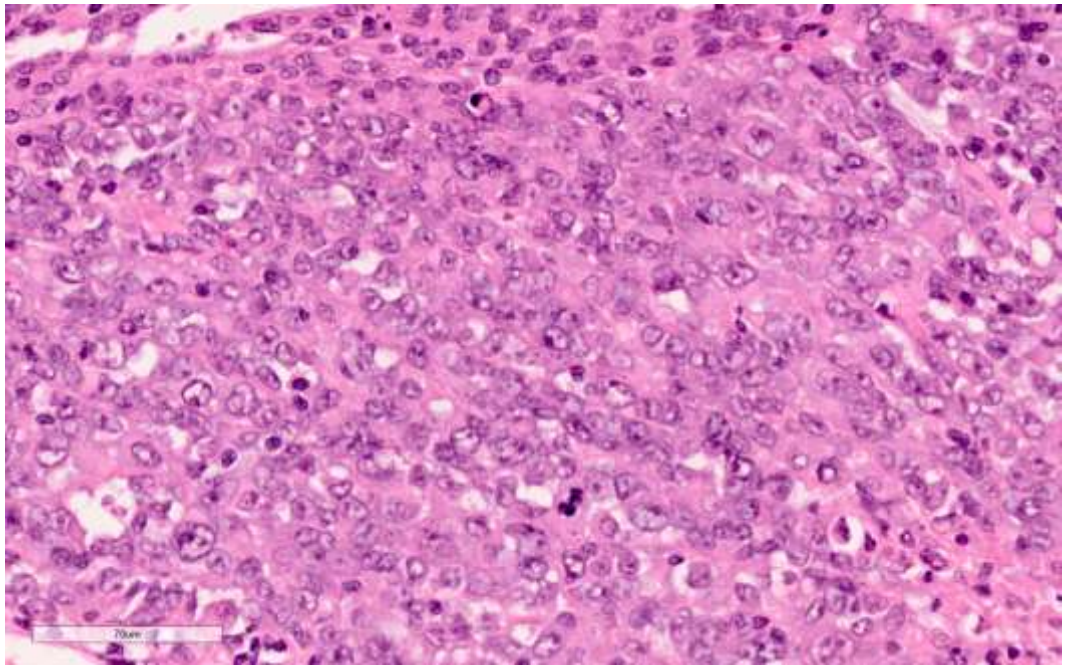


Desmoplastic small round cell tumor

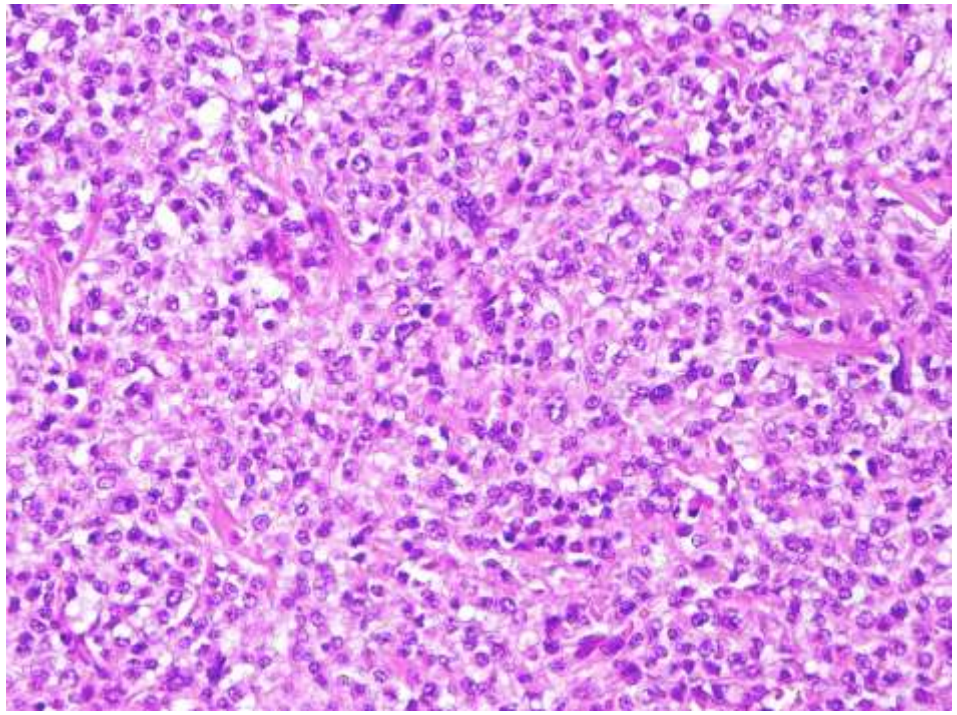
- Nests of epithelioid spindle cells with clear eosinophilic Well defined nests of small round cells separated by desmoplastic stroma
- Uniform cells with small hyperchromatic nuclei, inconspicuous nucleoli, scant cytoplasm and indistinct cytoplasmic borders
- Peripheral palisading is common
- Rosette-like structures and pseudopapillae may be observed
- IHC: WT1, S100, Myogenin, SMA and chromogranin



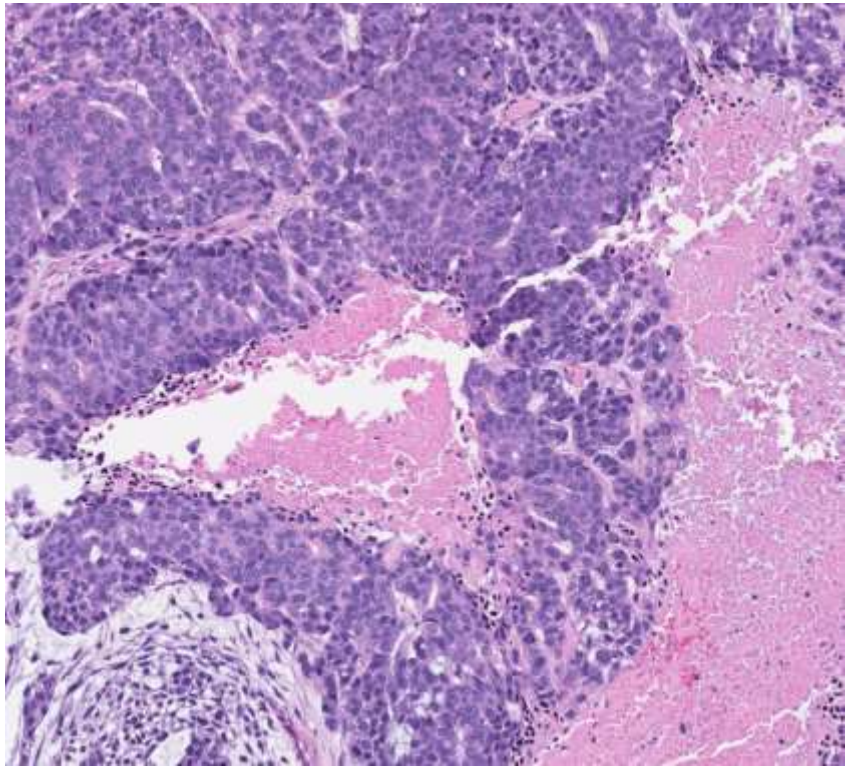
- **Rabdoid tumor**
- Sheets of noncohesive, monotonous looking tumor cells with abundant eosinophilic cytoplasm
- Nuclei are large, vesicular and contain 1 - 2 prominent nucleoli
- High mitotic activity; mild to moderate cellular pleomorphism
- IHC: Vimentin, CD99, CK, EMA, Desmin



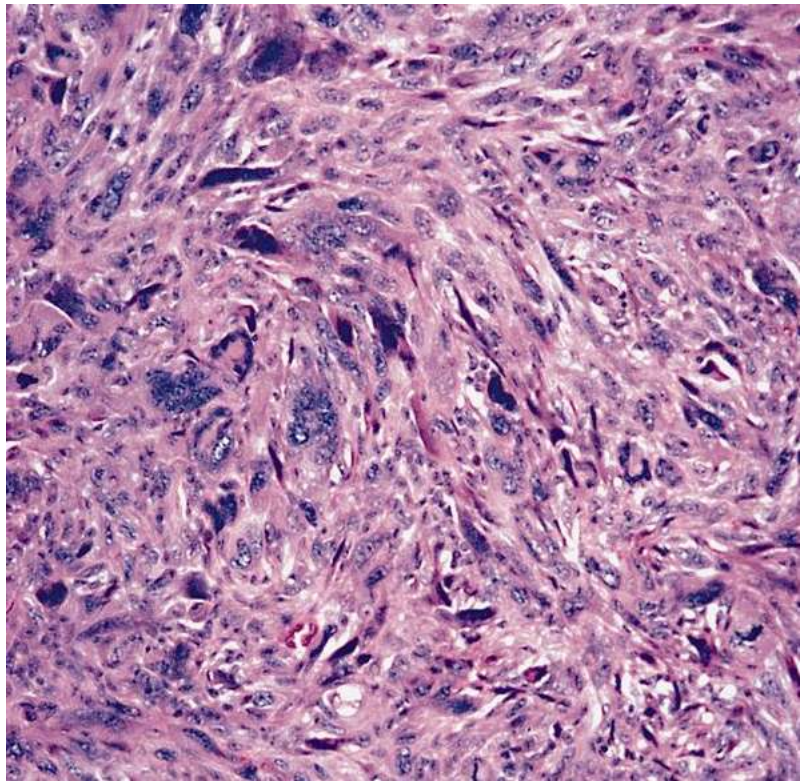
- **Perivascular epithelioid tumor, malignant**
- Noncohesive epithelioid cells with clear to eosinophilic granular cytoplasm
- Variable cytologic atypia and mitotic index
- Melanoma-like nucleoli, intranuclear pseudoinclusions, multinucleated cells
- IHC: HMB45, SMA, Desmin



- **Myoepithelial carcinoma**
- Expansile invasive multinodular growth
- Myoepithelial cells showing various cytologic features, including clear cell, epithelioid, plasmacytoid or spindle cell morphology
- IHC: S100, Calponin, SMA, CK



- **Pleomorphic sarcoma**
- Storiform pattern or irregular fascicles of pleomorphic and bizarre cells with marked atypia
- Multinucleated giant cells may be seen
- Numerous mitotic figures, including atypical forms
- IHC: Vimentin, Alpha1 AT, CD68



CONCLUSION

- SARCOMA PATHOLOGY – A CHALLENGE FOR THE HISTOPATHOLOGIST
- EXTREMELY DIVERESE NATURE OF ENTITIES AND OERLAPPING MOPHOLOGICAL FEATURES AND COMPLEX GRADING SYSTEMS
- IHC AND MOLECULAR DIAGNOSTICS ARE USUALLY NOT READILY AVAILABLE
- NEED EXPERTISE AND CONSTANT ACADEMIC UPDATION
- REQUIRES AN INTEGRATED APPROACH FOR PROPER DIAGNOSIS AND BETTER PATIENT OUTCOMES

IDENTIFY THE PLACE AND THE CEREMONY

ATTARI BODER – WAGAH BORDER

RETREAT CEREMONY


THANK YOU