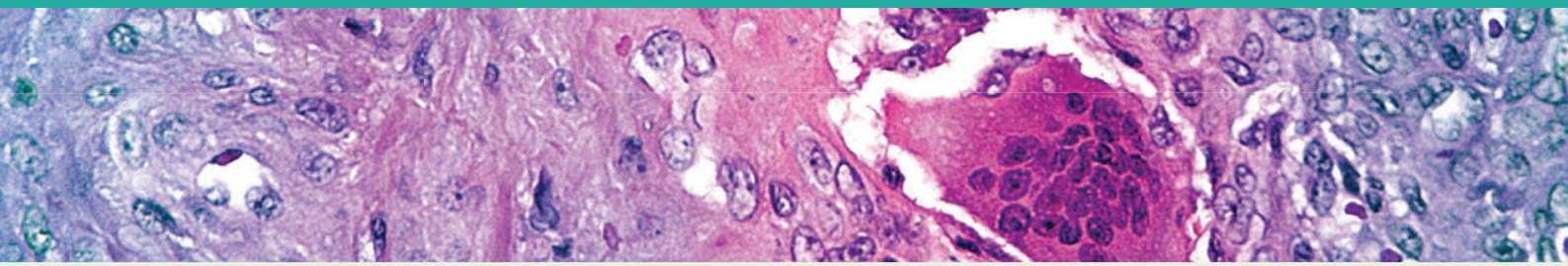
SECTION 2

Diagnostic Approach to Soft Tissue Tumors



Overview

Biopsy and Resection of Soft Tissue Tumors 20

Clinical Approach

Age- and Location-Based Approach to Diagnosis 24

Histologic Approach

Pattern-Based Approach to Diagnosis 26
Feature-Based Approach to Diagnosis 34

OVERVIEW

General Points

- A variety of diagnostic procedures are currently available to surgeons and clinicians to evaluate soft tissue tumors
  - Initial tumor tissue sampling may or may not be sought, depending on overall impression of tumor biologic potential derived from synthesis of clinical features and imaging characteristics
    - Tumors that appear likely benign are often surgically excised without sampling, or followed clinically
    - Tumors that appear likely malignant or potentially malignant are usually sampled preoperatively
      - With increasing frequency, soft tissue tumors are sampled initially by core needle biopsy, fine-needle aspiration (FNA), or limited biopsy due to minimal morbidity to the patient
      - Nondiagnostic results may reflex into larger open surgical biopsy with intraoperative frozen section evaluation or even outright resection, depending on clinical impression of tumor biology
      - Successful diagnosis usually leads to local excision, wide resection with margins, or preoperative adjuvant chemotherapy &/or radiation
- Smaller specimens are generally more challenging to evaluate due to sampling problems and issues related to immunohistochemistry
  - Underdiagnosis often poses greater risk than overdiagnosis
  - Misclassification is possible if several different tumors share morphologic overlap

Types of Specimens

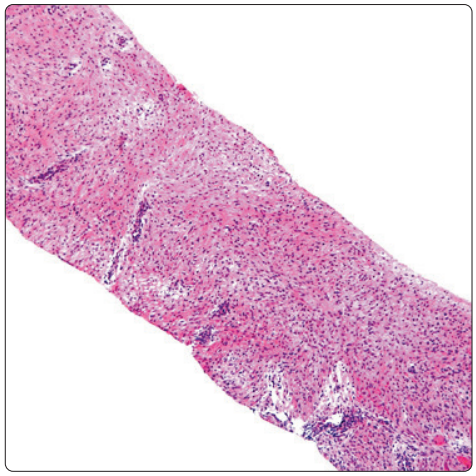
- Core needle biopsy
  - Very small sample of a tumor/lesion
  - Popular due to minimal risk of morbidity to patient
  - May be done in outpatient setting for superficial lesions or under CT guidance for deep or visceral lesions
- FNA
  - Very small sample of a tumor/lesion
  - Aspiration allows for immediate evaluation of sampling adequacy (success or failure of attaining diagnostic tissue) with added benefit of cell block for histologic and immunohistochemical evaluation
  - Popular due to minimal risk of morbidity to patient
- Open surgical biopsy
  - Small sample of tumor/lesion, but generally contains more intact tissue than core needle biopsy or FNA
  - Tissue may be sent for intraoperative frozen section consultation or just permanent sectioning
  - Smaller risk of underdiagnosis or misdiagnosis compared to needle biopsy and FNA
- Local excision
  - Entire tumor available for histologic evaluation
  - Surgical focus is on removal of tumor and not achieving rim of uninvolved soft tissue
  - Standard approach for benign, superficial tumors that are not believed to be locally aggressive
- Resection with margins
  - Includes wide resection and radical resection
    - Radical resection often contains extensive normal tissue or, in cases of intraabdominal, intrathoracic, or retroperitoneal tumors, may contain organs involved by tumor
  - Entire tumor available for histologic evaluation
  - Standard approach for locally aggressive benign tumors (e.g., fibromatosis), deep (subfascial) tumors, and sarcomas
  - May be performed following chemotherapy &/or radiation to improve resectability and decrease potential morbidity

BIOPSY SPECIMENS

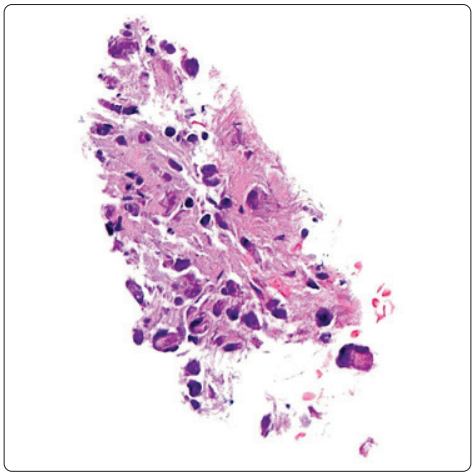
General Histologic Approach

- Ensure that lesional tissue is present
- Evaluate histologic growth pattern and architecture in conjunction with cytologic features of tumor cells
  - Looks for histologic clues that suggest specific differentiation (e.g., lipoblasts)
- Assess mitotic activity and presence or absence of necrosis

Core Needle Biopsy



Fine-Needle Aspiration



(Left) *Collecting tissue by core needle biopsy has become popular due to both the ease of performance and minimal morbidity to the patient as compared with open surgical biopsy. Despite the limited tissue sample, a diagnosis is often possible with careful histologic evaluation and judicious use of ancillary techniques.* **(Right)** *Cell block collected from a fine-needle aspiration (FNA) can also be used for diagnosis. However, tissue is often heavily fragmented and scant, as depicted.*

- Utilize ancillary studies (e.g., immunohistochemistry, molecular analysis) as needed
- If constellation of features is classic for particular tumor, diagnosis can be made
- If clear diagnosis cannot be made, determine whether tumor appears benign, low-grade malignant, or high-grade malignant
  - Even in absence of clear diagnosis, this information is helpful to guide surgical/clinical planning

Caveats

- Always exclude carcinoma, melanoma, lymphoma, and mesothelioma before committing to a mesenchymal diagnosis
- At times, actual tumor does not get sampled
  - Some tumors may incite prominent peripheral host fibroblastic or inflammatory reaction that is inadvertently sampled
  - Normal subcutaneous fat adjacent to tumor may be sampled and mistaken for lipomatous tumor
- Be wary of sampling issues related to biopsy evaluation
  - Tumors that appear low grade on biopsy may contain higher grade areas upon resection
    - Particularly important in tumors of adipocytic and neural origin
  - Tumors that appear as nonspecific high-grade pleomorphic sarcomas on biopsy often can be more specifically classified on resection
    - e.g., dedifferentiated liposarcoma, pleomorphic liposarcoma, extraskeletal osteosarcoma
    - Diagnosis "undifferentiated pleomorphic sarcoma" should not be made on biopsy, as it is a diagnosis of exclusion
- Awareness of particular idiosyncrasies of soft tissue pathology is very important
  - Sarcomas may appear paradoxically bland and therefore benign
    - e.g., low-grade fibromyxoid sarcoma, myxoid liposarcoma, myxoid synovial sarcoma
  - Benign tumors may show histologic features that suggest malignancy
    - e.g., nodular fasciitis, proliferative fasciitis/myositis, cellular schwannoma
- Only commit to clear diagnosis on biopsy if it is well supported
  - In general, a conservative diagnosis on biopsy better serves the patient

Reporting

- Every effort should be taken to establish a clear diagnosis (and histologic grade, if applicable) on biopsy
  - Modern ancillary techniques are making this much easier for pathologists
  - Margin status cannot be evaluated
- If clear diagnosis cannot be established, descriptive diagnosis can help guide surgical/clinical planning
  - e.g., benign fibroblastic lesion
  - e.g., low-grade myxoid neoplasm, favor benign
  - e.g., high-grade pleomorphic sarcoma, not further classified
- A descriptive comment is highly recommended in many cases to discuss differential diagnosis options
  - e.g., "Although these findings are suggestive of a low-grade neoplasm such as an intramuscular myxoma, a low-grade sarcoma such as low-grade fibromyxoid sarcoma or low-grade myxofibrosarcoma cannot be excluded in this limited sample."
  - e.g., "Although the histologic features are consistent with a neurofibroma, given the large size of the lesion clinically, the possibility of an unsampled malignant component cannot be excluded in this limited sample."

RESECTION SPECIMENS

General Histologic Approach

- Surgical removal without neoadjuvant therapy
  - If tumor has been sampled previously, review original biopsy (if available) and confirm diagnosis and adequacy of sampling
    - If diagnosis is established or confirmed, assure accuracy of histologic grade (if applicable)
      - Tumors diagnosed as "low grade" on biopsy may contain higher grade areas in resection specimen
    - Ancillary techniques (e.g., immunohistochemistry, molecular analysis) may be utilized as needed
  - If tumor has not been sampled previously, evaluate all histologic sections of tumor to establish diagnosis
    - Ancillary techniques may be utilized as needed
  - Evaluate margin status (mainly sarcomas and locally aggressive benign tumors)
- Surgical removal following neoadjuvant therapy
  - If tumor has been sampled previously, review original biopsy (if available) and confirm diagnosis
  - Determine whether diagnosis can be established or confirmed on resection (may not be possible due to treatment effect)
    - Overall histologic picture depends heavily upon biologic response of tumor to therapy
      - Tumors may be extensively necrotic, inflamed, &/or fibrotic/hyalinized
      - Tumor cells may become markedly pleomorphic and atypical, including bizarre cytomorphologies
  - Document approximate percentage of residual tumor viability
  - Evaluate margin status

Caveats

- Despite all efforts, a small percentage of soft tissue tumors defy classification after resection
  - Distinction between benign, low-grade malignant, and high-grade malignant should be the goal in these cases
  - Always ensure carcinoma, melanoma, lymphoma, and mesothelioma have been excluded before committing to a soft tissue diagnosis
- Care is warranted when attempting to classify a soft tissue tumor treated preoperatively with chemotherapy/radiation
  - Tumors that are usually cytologically monomorphic may appear pleomorphic following therapy
  - Cytoplasmic vacuolizations may be prominent, mimicking lipoblastic differentiation
  - Ancillary techniques are unreliable following chemotherapy/radiation and should not be utilized

Reporting

- Surgical pathology reports for soft tissue resections should contain tumor diagnosis, histologic grade (if applicable), and margin status (if appropriate)
  - Additional staging information (e.g., size) can be included as a checklist
- For tumors that cannot be definitively classified after all options are exhausted, a descriptive diagnosis can be utilized
  - e.g., low-grade myxoid sarcoma, not otherwise specified (NOS)
  - e.g., epithelioid malignant mesenchymal neoplasm, favor high-grade sarcoma
- For tumors treated with neoadjuvant therapy prior to resection
  - High grade sarcoma with extensive therapy effect (20% tumor viability)

SPECIAL TOPICS

Intraoperative Frozen Section Consultation for Diagnosis

- May be requested by surgeon in certain scenarios
  - Tumor has not been sampled previously
  - To confirm previous biopsy diagnosis
  - Tumor was sampled previously by biopsy but no specific diagnosis was attained
  - Tumor with previous benign or low-grade biopsy diagnosis, and there is clinical concern for unsampled, higher grade component
- Intraoperative diagnosis or confirmation of diagnosis can be sought to confirm surgical/clinical treatment plan
  - Variability exists between individual surgeons
    - May continue with resection plans for benign or low-grade malignancies
    - May halt further surgery and administer neoadjuvant therapy if high-grade malignancy
- In many instances, specific soft tissue diagnosis cannot be made by frozen section evaluation
  - Most helpful information the pathologist can provide: Whether tumor appears benign, low-grade malignant, or high-grade malignant
    - Exercise caution when calling soft tissue tumor "benign" on frozen section
      - Use of term "low grade" recommended over "benign," unless benignity is absolutely certain
      - Some low-grade sarcomas can be easily mistaken for benign tumors on frozen section, which can lead to inappropriately conservative treatment
  - If diagnosis cannot be made on frozen section, and alternative descriptive interpretation cannot be comfortably provided by the pathologist, it is appropriate to document the presence of satisfactory lesional tissue and defer to evaluation of permanent sections
  - Examples of appropriate frozen section interpretations
    - Low-grade spindle cell proliferation
    - High-grade sarcoma
    - Spindle cell sarcoma, favor low grade
    - Tumor present, defer to permanents
    - Malignant neoplasm, defer to permanents

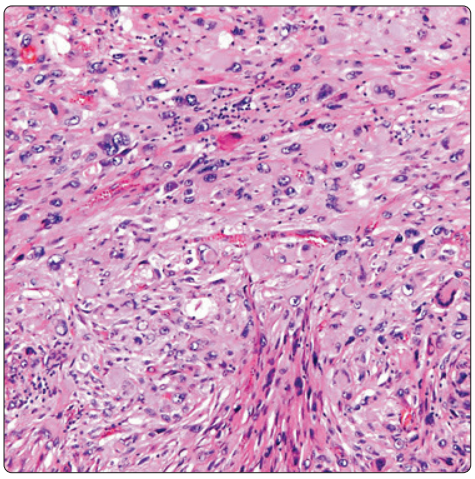
Evaluation by Ancillary Testing

- Immunohistochemistry (IHC)
  - Wide array of antibodies available today has made it easier for pathologists to make confident soft tissue diagnoses on limited tissue samples
  - It is recommended that every attempt be made to establish the diagnosis or a limited differential by routine histology
  - When needed, limited screening panel of immunohistochemical stains is helpful for supporting (or excluding) diagnoses
    - Specific screening panels vary depending on pathologist's comfort level with soft tissue pathology
  - Common 5-stain screening panel: Keratin, S100 protein, SMA, desmin, CD34
    - Provides reasonably broad coverage
    - Can be modified with additional stains as necessary depending upon histologic/clinical context
  - Recommendations and caveats
    - Always confirm that external and internal controls are functioning properly
    - Examine entire slide and all tissue fragments
    - Know what constitutes positive staining for each antibody (e.g., nuclear, cytoplasmic, membranous expression)
    - If stain appears positive, confirm that actual cells of interest are staining
    - Important: On very limited tissue sample, negative staining for a particularly antibody may not reflect status of entire tumor
      - e.g., myogenin expression in embryonal rhabdomyosarcoma can be patchy and focal
- Molecular analysis
  - Representative paraffin tissue block can be used for variety of sophisticated testing (e.g., FISH, RT-PCR)

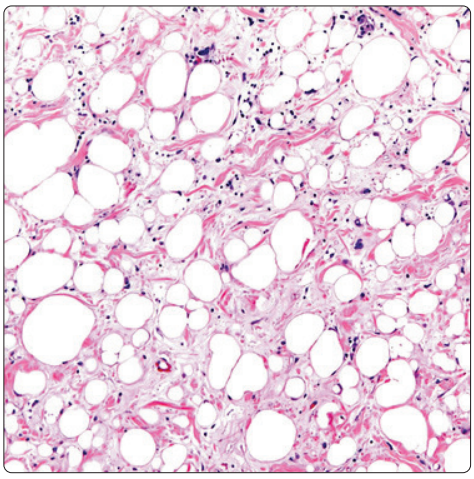
Expert Consultation

- Pathologists who are experienced in evaluation of soft tissue tumors may be consulted to review a case
- Common reasons
  - Primary pathologist is uncomfortable with &/or has limited experience in soft tissue pathology
  - Surgeon, primary care provider, or patient may request second opinion
    - Histologic diagnosis is at odds with clinical impression
    - Diagnosis of very rare or unusual tumor is rendered
  - Newer immunohistochemical antibodies or molecular tests are not readily available to primary pathologist
- Sending 1 or more paraffin tissue blocks along with slides for ancillary testing can be helpful
  - Ideal blocks contain well-processed tissue and minimal to no necrosis
    - Blocks containing areas of lower grade histology are more like to show diagnostically useful antigen expression than blocks containing predominantly high-grade pleomorphic morphology
- Inclusion of recent clinical history, imaging reports, and surgical notes can also provide useful information

High-Grade Pleomorphic Sarcoma

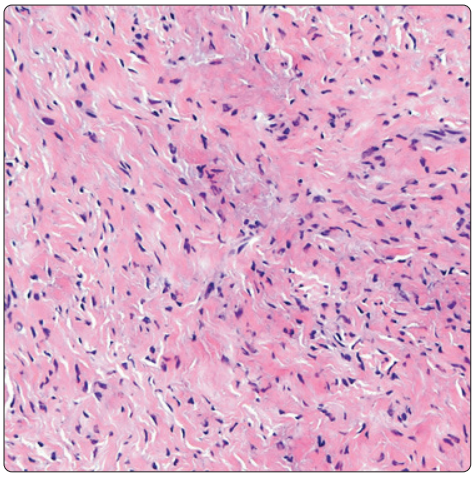


Well-Differentiated Adipocytic Neoplasms

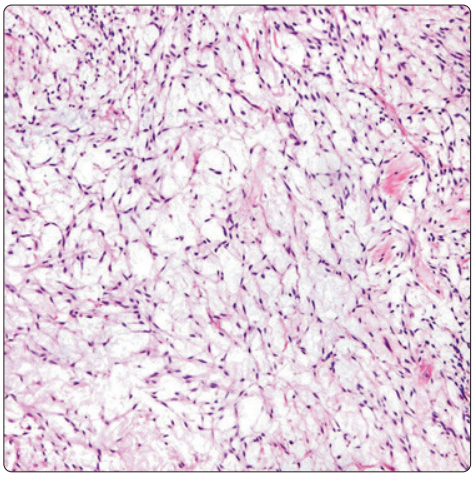


(Left) *On core needle biopsy, it may be difficult to distinguish 1 high grade pleomorphic sarcoma from another, particularly if discriminatory immunohistochemical stains or molecular tests are not available to the pathologist. Fortunately, in many cases, designation of "high-grade sarcoma" is often sufficient.* **(Right)** *Care should be taken in classifying well-differentiated adipocytic neoplasms on limited biopsy, as atypical lipomatous tumor/well-differentiated liposarcoma can contain large areas resembling conventional lipoma.*

Low-Grade Spindle Cell Neoplasm

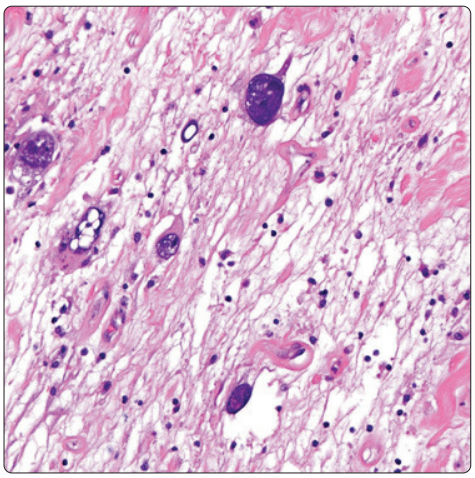


Deceptively Bland Sarcoma

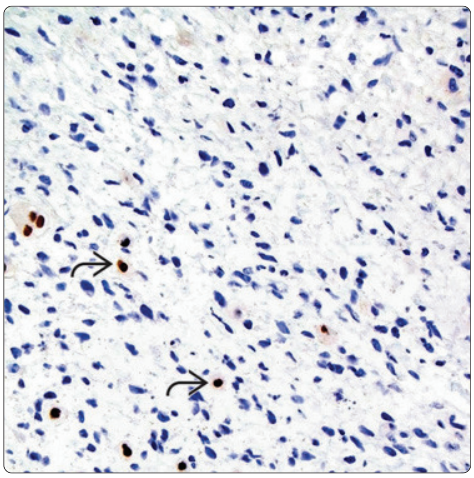


(Left) *Classification of low-grade spindle cell neoplasms on limited biopsy can be challenging without ancillary tests, mainly because some low-grade sarcomas can closely resemble benign entities morphologically. This image shows a core biopsy specimen of a low-grade fibromyxoid sarcoma mimicking a benign neural or fibroblastic neoplasm.* **(Right)** *This image depicts a largely myxoid synovial sarcoma. On a limited biopsy specimen, this tumor could easily be mistaken for a benign or low-grade process.*

Post-Therapy Changes



Immunohistochemistry



(Left) *If a specific diagnosis is not established prior to neoadjuvant therapy, definitive classification of a soft tissue sarcoma may not be possible due to therapy-related histologic changes, including bizarre nuclear atypia, stromal fibrosis, and edema. Immunohistochemistry and molecular analysis are also largely unhelpful in this setting.* **(Right)** *Care must always be taken with IHC performed on limited tissue. One pitfall is focal tumor antigen expression (e.g., myogenin, shown) that is not present on biopsy.*

DIRECTIONS

How to Use These Guides

- The following guides are neither comprehensive nor perfect and are meant to serve only as a starting point for working up a suspected mesenchymal neoplasm
- Includes entities that are most commonly or classically associated with particular clinical and histologic findings

Specific Directions for This Guide

- For each site and associated age range listed below, a selection of most commonly or characteristically associated diagnoses are provided
- Compile an assortment of potential diagnoses from the guide using age of patient and provided tumor site from your particular case
- Compare this selection to those created from the other 2 approach chapters
- Overlapping diagnoses derived from these 3 distinct approaches are highest yield and should be your focus
- Once high-yield diagnoses have been identified, specific entity chapters should be directly consulted for detailed information and image galleries
  - In particular, the Differential Diagnosis sections should be fully utilized to broaden search and increase chances of securing the correct diagnosis

Important Caveat

- Always exclude carcinoma, melanoma, lymphoma, and mesothelioma before committing to a mesenchymal diagnosis

AGE-BASED APPROACH

Infancy (< 3 Years Old)

- Fibrous hamartoma of infancy
- Inclusion body fibromatosis
- Infantile fibrosarcoma
- Lipoblastoma
- Lipofibromatosis
- Myofibroma

Infants, Children, or Adolescents (< 20 Years Old)

- Angiomatosis
- Calcifying aponeurotic fibroma
- Dabska tumor (infants and children)
- Embryonal rhabdomyosarcoma
- Extrarenal rhabdoid tumor (infants and children)
- Gardner fibroma
- Giant cell fibroblastoma
- Kaposiform hemangioendothelioma (infants and children)

Adolescents to Young Adults (~ 10 to 35 Years Old)

- Alveolar rhabdomyosarcoma
- Alveolar soft parts sarcoma
- Angiomatoid fibrous histiocytoma
- Desmoplastic small round cell tumor (also children)
- Epithelioid sarcoma (classic type)
- Inflammatory myofibroblastic tumor
- Low-grade fibromyxoid sarcoma
- Myxoid liposarcoma
- Plexiform fibrohistiocytic tumor
- Synovial sarcoma

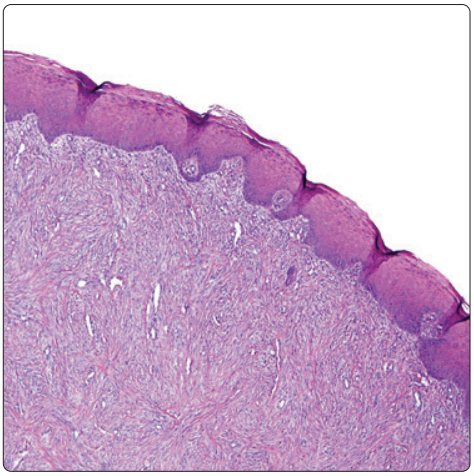
Young to Middle-Aged Adults (~ 20 to 50 Years Old)

- Clear cell sarcoma
- Dermatofibrosarcoma protuberans
- Epithelioid hemangioendothelioma
- Epithelioid sarcoma (proximal-type)
- Fibroma of tendon sheath
- Granular cell tumor
- Hibernoma
- Leiomyosarcoma
- Localized-type tenosynovial giant cell tumor
- Myositis ossificans
- Nodular fasciitis
- Ossifying fibromyxoid tumor
- Pseudomyogenic hemangioendothelioma

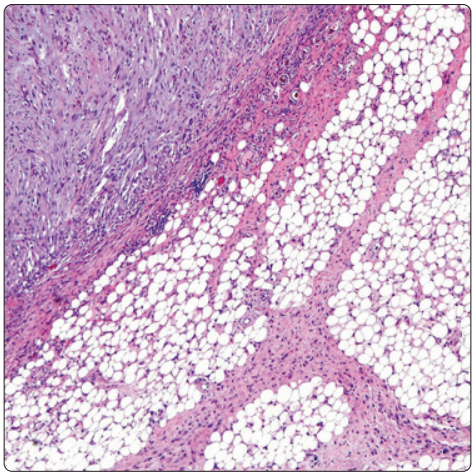
Middle-Aged to Older Adults (~ 45 to 60 Years Old)

- Atypical lipomatous tumor/well-differentiated liposarcoma
- Dedifferentiated liposarcoma

Inclusion Body Fibromatosis



Dedifferentiated Liposarcoma



(Left) *Some mesenchymal neoplasms show a striking predilection for very specific age groups and very specific anatomic locations. For example, inclusion body fibromatosis (a.k.a. infantile digital fibromatosis) most frequently arises in the digits of infants.* **(Right)** *Dedifferentiated liposarcoma is the most common pleomorphic sarcoma of the retroperitoneum and should always be at the top of the differential diagnosis for retroperitoneal tumors in older adults.*

- Desmoplastic fibroblastoma
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal osteosarcoma
- Hemosiderotic fibrolipomatous tumor
- Intramuscular myxoma
- Proliferative fasciitis/myositis
- Sclerosing epithelioid fibrosarcoma
- Spindle cell/pleomorphic lipoma

Older and Elderly Adults (> 50 Years Old)

- Atypical fibroxanthoma
- Elastofibroma
- Ischemic fasciitis
- Myxofibrosarcoma
- Pleomorphic liposarcoma
- Pleomorphic rhabdomyosarcoma
- Undifferentiated pleomorphic sarcoma

LOCATION-BASED APPROACH

Distal (Acral) Extremities

- Calcifying aponeurotic fibroma
- Clear cell sarcoma
- Composite hemangioendothelioma
- Epithelioid sarcoma (classic type)
- Hemosiderotic fibrolipomatous tumor
- Lipofibromatosis
- Palmar/plantar fibromatosis
- Pleomorphic hyalinizing angiectatic tumor

Fingers and Toes

- Acral fibromyxoma
- Dermal nerve sheath myxoma
- Epithelioid hemangioma
- Fibroma of tendon sheath
- Glomus tumor
- Inclusion body fibromatosis
- Localized-type tenosynovial giant cell tumor
- Myxoinflammatory fibroblastic sarcoma
- Soft tissue chondroma

Genital Region and Groin

- Angiomyofibroblastoma
- Cellular angiofibroma
- Deep (aggressive) angiomyxoma
- Genital rhabdomyoma
- Intranodal palisaded myofibroblastoma
- Mammary-type myofibroblastoma
- Spindle cell rhabdomyosarcoma (paratesticular)

Mesentery/Omentum/Peritoneum

- Desmoid fibromatosis
- Desmoplastic small round cell tumor
- Gastrointestinal stromal tumor
- Inflammatory myofibroblastic tumor

Head and Neck

- Alveolar soft part sarcoma (infants and children)
- Atypical fibromyxoma
- Cellular neurothekeoma
- Granular cell tumor
- Ectopic meningioma
- Embryonal rhabdomyosarcoma
- Epithelioid hemangioma
- Rhabdomyoma (adult and fetal types)
- Solitary circumscribed neuroma
- Spindle cell rhabdomyosarcoma

Retroperitoneum

- Dedifferentiated liposarcoma
- Deep leiomyoma
- Desmoid fibromatosis
- Extrarenal rhabdoid tumor
- Ganglioneuroma
- Inflammatory myofibroblastic tumor
- Leiomyosarcoma
- PEComa
- Schwannoma (cellular variant)
- Well-differentiated liposarcoma

Trunk, Shoulders, and Back

- Dermatofibrosarcoma protuberans
- Desmoid fibromatosis
- Elastofibroma
- Epithelioid sarcoma (proximal type)
- Giant cell fibroblastoma
- Spindle cell/pleomorphic lipoma

GASTROINTESTINAL MESENCHYMAL TUMORS (MOST COMMON BY LOCATION)

Esophagus

- Leiomyoma (mural)
- Granular cell tumor

Stomach

- Gastrointestinal stromal tumor
- Inflammatory fibroid polyp
- Schwannoma

Small Bowel

- Gastrointestinal stromal tumor
- Inflammatory fibroid polyp

Colorectum

- Leiomyoma (polyp; nonmural)
- Gastrointestinal stromal tumor

MESENCHYMAL TUMORS INVOLVING LYMPH NODES (MOST COMMON)

Metastasis

- Epithelioid sarcoma
- Clear cell sarcoma
- Rhabdomyosarcomas

Nodal Primary

- Kaposi sarcoma
- Intranodal palisaded myofibroblastoma

DIRECTIONS

How to Use These Guides

- The following guides are neither comprehensive nor perfect and are meant to serve only as a starting point for working up a suspected mesenchymal neoplasm
- They include entities that are most commonly or classically associated with particular histologic patterns in soft tissue

Specific Directions for This Guide

- The following list of histologic patterns has been generated using a combination of cell types (spindle or epithelioid), cytologic features (monomorphism vs. pleomorphism), and various stromal characteristics (e.g., myxoid, prominent vasculature)
- For each histologic pattern listed below, a selection of more commonly or characteristically associated diagnoses are provided
- Compile an assortment of potential diagnoses from each guide using main histologic pattern(s) from your particular case
- Compare this selection to those created from the other 2 Approach chapters
- Overlapping diagnoses derived from these 3 distinct approaches are highest yield and should be your focus
- Once high-yield diagnoses have been identified, specific entity chapters should be directly consulted for detailed information and image galleries
  - In particular, the Differential Diagnosis sections should be fully utilized to broaden the search and increase the chances of securing the correct diagnosis

Important Caveats

- Always exclude carcinoma, melanoma, lymphoma, and mesothelioma before committing to a mesenchymal diagnosis
- Always exclude gastrointestinal stromal tumor (GIST) when tumor arises within abdominal cavity or pelvis
  - Can demonstrate almost any morphologic pattern

MONOMORPHIC SPINDLE CELL PATTERNS

Monomorphic Spindle Cells Arranged in Sheets

- Angiomatoid fibrous histiocytoma
- Pseudomyogenic hemangioendothelioma
- Solitary fibrous tumor
- Synovial sarcoma

Monomorphic Spindle Cells Featuring Hyper- and Hypocellular Areas

- Low-grade fibromyxoid sarcoma
- Malignant peripheral nerve sheath tumor
- Schwannoma
- Solitary fibrous tumor
- Synovial sarcoma

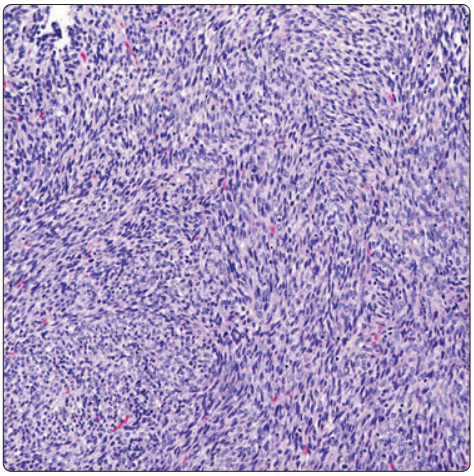
Monomorphic Spindle Cells Arranged in Bundles or Fascicles

- Angioleiomyoma
- Deep leiomyoma
- Fibromatosis
- Fibrous hamartoma of infancy
- Inclusion body fibromatosis
- Kaposi sarcoma
- Leiomyosarcoma
- Lipofibromatosis
- Low-grade myofibroblastic sarcoma
- Mammary-type myofibroblastoma
- Plexiform fibrohistiocytic tumor
- Schwannoma
- Solitary circumscribed neuroma

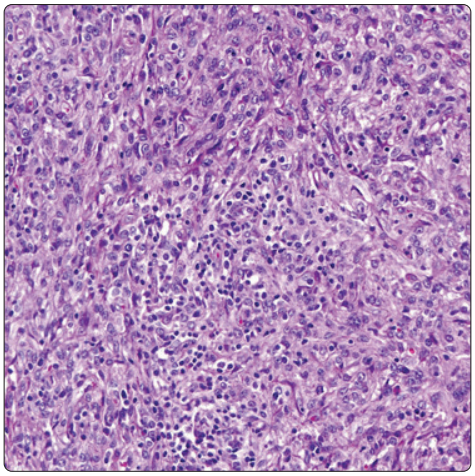
Monomorphic Spindle Cells Arranged in Cellular "Herringbone" Fascicles

- Adult-type fibrosarcoma
- Fibrosarcomatous dermatofibrosarcoma protuberans
- Infantile fibrosarcoma
- Malignant peripheral nerve sheath tumor
- Spindle cell rhabdomyosarcoma
- Synovial sarcoma

Monomorphic Spindle Cells: Sheets



Monomorphic Spindle Cells: Sheets (Syncytia)



(Left) *A sheet-like pattern tends to feature diffuse growth of spindle cells without obvious directional orientation; however, areas of bundled or fascicular growth are not uncommon. This pattern is common in synovial sarcoma (shown) and solitary fibrous tumor.* **(Right)** *Sheets of spindled cells can also have a syncytial appearance in which cytoplasmic borders are inconspicuous and independent cell nuclei appear to share the same cytoplasm. This appearance is common in angiomatoid fibrous histiocytoma.*

Monomorphic Spindle Cells Arranged in Storiform or Whorled Architecture

- Deep benign fibrous histiocytoma
- Dermatofibroma (fibrous histiocytoma)
- Dermatofibrosarcoma protuberans
- Follicular dendritic cell sarcoma
- Hybrid nerve sheath tumor
- Inclusion body fibromatosis
- Low-grade fibromyxoid sarcoma
- Low-grade myofibroblastic sarcoma
- Nodular fasciitis
- Perineurioma

Monomorphic Spindle Cells Arranged in Multinodular or Plexiform Architecture

- Granular cell tumor
- Plexiform fibrohistiocytic tumor
- Plexiform neurofibroma
- Plexiform schwannoma
- Solitary circumscribed neuroma

Monomorphic Spindle Cells Arranged in Reticular or Microcystic Pattern

- Extraskeletal myxoid chondrosarcoma
- Myoepithelioma
- Perineurioma (variant)
- Schwannoma (variant)

Monomorphic Spindle Cells Within Myxoid Stroma

- Acral fibromyxoma
- Deep ("aggressive") angiomyxoma
- Dermal nerve sheath myxoma
- Dermatofibrosarcoma protuberans (myxoid type)
- Desmoid fibromatosis
- Embryonal rhabdomyosarcoma
- Hybrid nerve sheath tumor
- Inflammatory myofibroblastic tumor
- Intramuscular myxoma
- Leiomyosarcoma (variant)
- Low-grade fibromyxoid sarcoma
- Myxoid liposarcoma
- Neurofibroma
- Nodular fasciitis
- Perineurioma
- Proliferative fasciitis/myositis
- Synovial sarcoma
- Spindle cell lipoma

Monomorphic Spindle Cells Within Collagenous, Hyalinized, or Sclerotic Stroma

- Acral fibromyxoma
- Calcifying fibrous tumor
- Cellular angiofibroma
- Desmoplastic fibroblastoma
- Elastofibroma
- Fibroma of tendon sheath
- Fibromatosis
- Inflammatory myofibroblastic tumor
- Low-grade fibromyxoid sarcoma
- Low-grade myofibroblastic sarcoma
- Neurofibroma
- Nodular fasciitis
- Perineurioma
- Sclerosing rhabdomyosarcoma
- Solitary fibrous tumor

Monomorphic Spindle Cells Amidst Prominent Stromal Vasculature

- Angiofibroma of soft tissue
- Angioleiomyoma
- Deep "aggressive" angiomyxoma
- Dermatofibrosarcoma protuberans (myxoid type)
- Low-grade fibromyxoid sarcoma
- Myopericytoma
- Myxoid liposarcoma
- Schwannoma
- Solitary fibrous tumor

Monomorphic Spindle Cells Associated With Mature Adipose Tissue

- Angiomyofibroblastoma
- Cellular angiofibroma
- Elastofibroma
- Fibrous hamartoma of infancy
- Hemosiderotic fibrolipomatous tumor
- Lipoblastoma
- Lipofibromatosis
- Mammary-type myofibroblastoma
- Myolipoma
- Solitary fibrous tumor (variant)
- Spindle cell lipoma

PLEOMORPHIC SPINDLE CELL PATTERNS

Pleomorphic Spindle Cells Arranged in Sheets

- Angiosarcoma
- Atypical fibromyxoma
- Dedifferentiated liposarcoma
- Extraskeletal osteosarcoma
- Malignant PEComa
- Pleomorphic liposarcoma
- Pleomorphic rhabdomyosarcoma
- Undifferentiated pleomorphic sarcoma

Pleomorphic Spindle Cells Arranged in Fascicles

- Dedifferentiated liposarcoma
- Leiomyosarcoma
- Malignant peripheral nerve sheath tumor
- Pleomorphic rhabdomyosarcoma
- Undifferentiated pleomorphic sarcoma

Pleomorphic Spindle Cells Within Myxoid Stroma

- Ancient schwannoma
- Atypical neurofibroma
- Embryonal rhabdomyosarcoma (anaplastic)
- Giant cell fibroblastoma
- Malignant peripheral nerve sheath tumor
- Myxofibrosarcoma
- Myxoinflammatory fibroblastic sarcoma
- Well-differentiated liposarcoma (variant)

Pleomorphic Spindle Cells Within Collagenous, Hyalinized, or Sclerotic Stroma

- Atypical lipomatous tumor/well-differentiated liposarcoma
- Giant cell fibroblastoma
- Myxoinflammatory fibroblastic sarcoma
- Undifferentiated pleomorphic sarcoma

Pleomorphic Spindle Cells Arranged in Storiform Architecture

- Dedifferentiated liposarcoma
- Myxofibrosarcoma (high grade)
- Pleomorphic liposarcoma
- Undifferentiated pleomorphic sarcoma

Pleomorphic Spindle Cell Amidst Prominent Stromal Vasculature

- Myxofibrosarcoma
- Pleomorphic hyalinizing angiectatic tumor
- Undifferentiated pleomorphic sarcoma

EPITHELIOID CELL PATTERNS

Epithelioid Cells Arranged in Nests or Lobules

- Alveolar rhabdomyosarcoma
- Alveolar soft part sarcoma
- Cellular neurothekeoma
- Clear cell sarcoma
- Desmoplastic small round cell tumor
- Epithelioid malignant peripheral nerve sheath tumor (MPNST)
- Epithelioid sarcoma (classic type)
- Glomus tumor
- Granular cell tumor
- Myoepithelioma of soft tissue
- Paraganglioma
- Perivascular epithelioid cell tumor (PEComa)

Epithelioid Cells Arranged in Cords or Trabeculae

- Ossifying fibromyxoid tumor
- Mammary-type myofibroblastoma (epithelioid variant)
- Myoepithelioma of soft tissue
- Sclerosing epithelioid fibrosarcoma

Epithelioid Cells Arranged in Sheets (Abundant Cytoplasm)

- Adult rhabdomyoma
- Alveolar soft part sarcoma
- Epithelioid angiosarcoma
- Epithelioid sarcoma (proximal type)
- Extrarenal rhabdoid tumor
- Tenosynovial giant cell tumor, diffuse-type

Epithelioid Cells Arranged in Sheets (Minimal/Scant Cytoplasm)

- Alveolar rhabdomyosarcoma
- Ewing sarcoma
- Extrarenal rhabdoid tumor
- Extraskeletal mesenchymal chondrosarcoma
- Infantile fibrosarcoma
- Neuroblastoma
- Synovial sarcoma (poorly differentiated)

Epithelioid Cells Within Myxoid Stroma

- Epithelioid hemangioendothelioma
- Epithelioid MPNST
- Extraskeletal myxoid chondrosarcoma
- Glomus tumor
- Myoepithelioma of soft tissue
- Myxofibrosarcoma (variant)
- Soft tissue chondroma

Epithelioid Cells Within Collagenous, Hyalinized, or Sclerotic Stroma

- Desmoplastic small round cell tumor
- Epithelioid sarcoma
- Myoepithelioma of soft tissue
- Perineurioma (variant)
- Sclerosing epithelioid fibrosarcoma
- Tenosynovial giant cell tumor, localized-type

Epithelioid Cells Associated With Prominent Stromal Vasculature

- Alveolar soft part sarcoma
- Angiomyofibroblastoma
- Glomus tumor
- Paraganglioma
- PEComa
- Cellular solitary fibrous tumor (formerly hemangiopericytoma)

Epithelioid Cells Associated With Adipose Tissue

- Angiomyofibroblastoma
- Chondroid lipoma
- Hibernoma

OTHER PATTERNS

Mixed Epithelioid and Spindle Cells

- Angiomyofibroblastoma
- Epithelioid sarcoma
- Leiomyoma
- Malignant mesothelioma (biphasic)
- Myoepithelioma of soft tissue
- PEComa
- Plexiform fibrohistiocytic tumor
- Schwannoma
- Synovial sarcoma (biphasic)

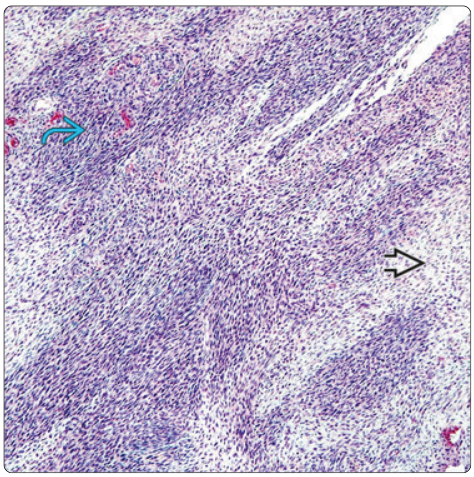
"Checkerboard" Skeletal Muscle Pattern

- Intramuscular hemangioma
- Intramuscular lipoma
- Intramuscular myxoma
- Low-grade myofibroblastic sarcoma
- Proliferative myositis

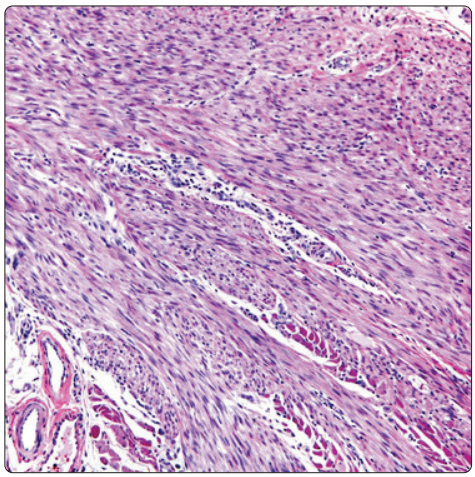
Nuclear Palisading

- Dermatofibroma (fibrous histiocytoma)
- Leiomyoma
- Leiomyosarcoma
- Malignant peripheral nerve sheath tumor
- Schwannoma
- Synovial sarcoma

Monomorphic Spindle Cells: Hypocellular and Hypercellular Areas

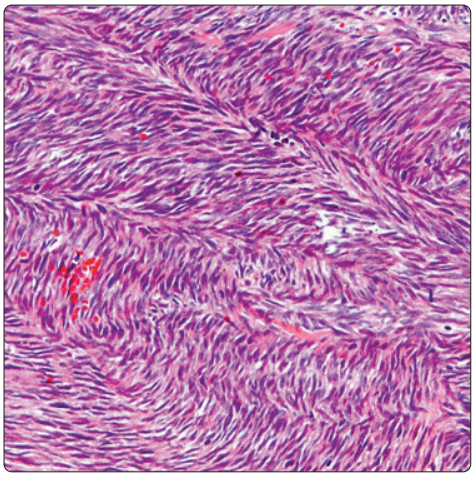


Monomorphic Spindle Cells: Bundles or Fascicles

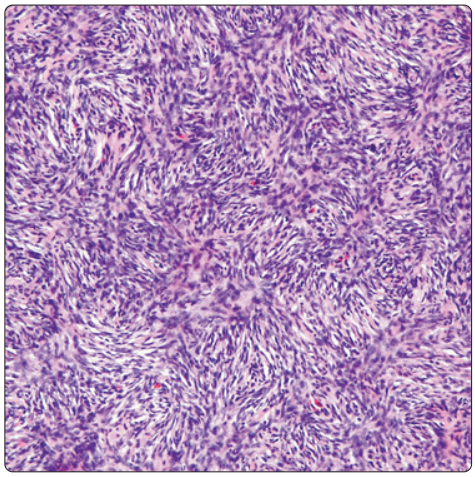


(Left) *A mixed light and dark pattern due to alternating areas of low ⇨ and high ⇨ cellularity is often best appreciated at low magnification. This pattern is commonly seen in schwannoma and MPNST.* **(Right)** *Classic bundled or fascicular growth features cells oriented in parallel groups. Directionality is more conspicuous than is usually seen in the sheet-like pattern, and bundles/fascicles may intersect or be organized in different directions. This image shows fibrous hamartoma of infancy.*

Monomorphic Spindle Cells: Cellular Herringbone Fascicles

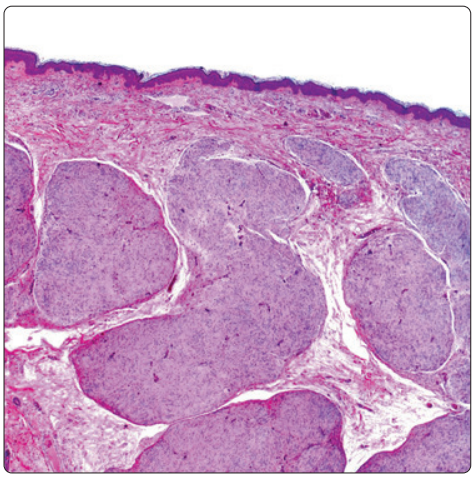


Monomorphic Spindle Cells: Storiform or Whorled Architecture

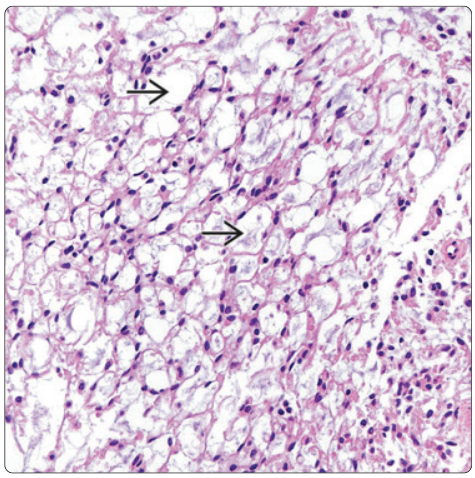


(Left) *A herringbone pattern is created when spindle cells within adjacent fascicles are oriented in roughly the same direction yet appear to slope away from each other. This orientation results in a wide V-shaped or chevron morphology.* **(Right)** *A storiform pattern is manifested by spindled cells that appear to radiate outward from a central point, often with a vague swirling or whorling, similar to a pinwheel. This pattern is most closely associated with DFSP but may be seen in a variety of other tumors.*

Monomorphic Spindle Cells: Multinodular or Plexiform Architecture



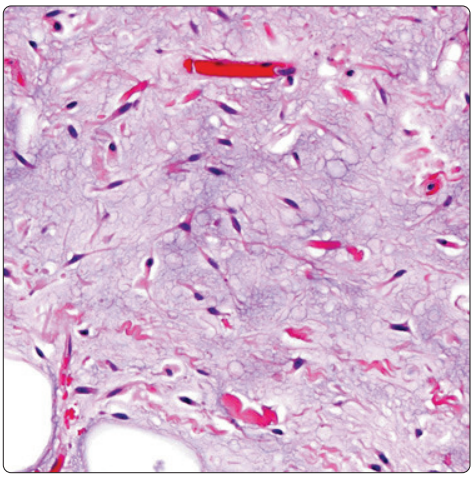
Monomorphic Spindle Cells: Reticular or Microcystic Pattern



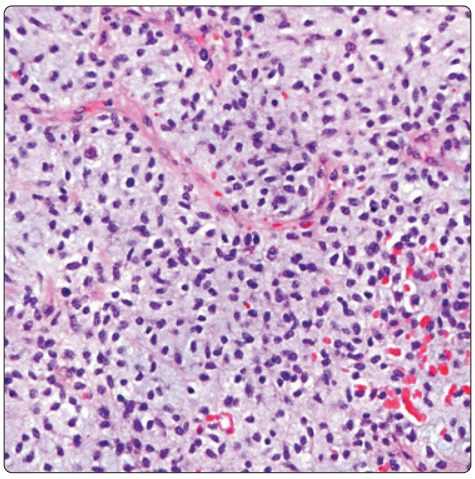
(Left) *Plexiform growth is characterized by discrete globular &/or serpiginous nodules of tumor cells. It tends to be most common in neural tumors, including plexiform neurofibroma and plexiform schwannoma (shown).* **(Right)** *A reticular pattern is created by thin spindled or stellate cells arranged such that cytoplasmic extensions appear to interconnect in a net-like or sieve-like fashion. Acellular microcystic ⇨ spaces in between cells are also seen.*

(Left) *Myxoid stroma is very common in soft tissue tumors, particularly spindled lesions that are cytologically monomorphic. This pattern is inherent to some tumors (e.g., intramuscular myxoma) but is often seen in variants of other tumors (e.g., spindle cell lipoma, DFSP).* **(Right)** *Some tumors, such as myxoid liposarcoma (shown) or low-grade fibromyxoid sarcoma, may feature areas of increased cellularity. However, significant nuclear pleomorphism is absent.*

Monomorphic Spindle Cells: Myxoid Stroma

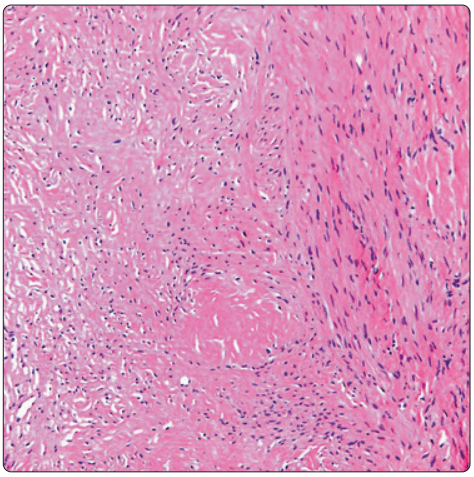


Monomorphic Spindle Cells: Myxoid Stroma (Cellular)

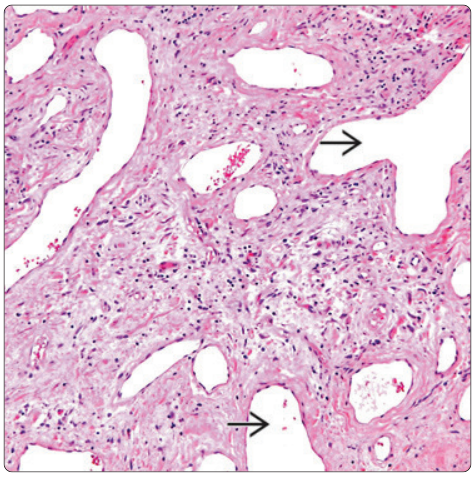


(Left) *Some monomorphic spindle cell tumors characteristically feature a conspicuous collagenous stroma that may or may not show prominent hyalinization or dense sclerosis. Tumor cells may show fascicular, storiform, or haphazard arrangements.* **(Right)** *Large, dilated or ectatic blood vessels ⇨ are relatively common as a focal finding in soft tissue tumors. Although these vessels are not usually prominent, some tumors (particularly solitary fibrous tumor) are notable exceptions.*

Monomorphic Spindle Cells: Collagenous, Hyalinized, Sclerotic Stroma

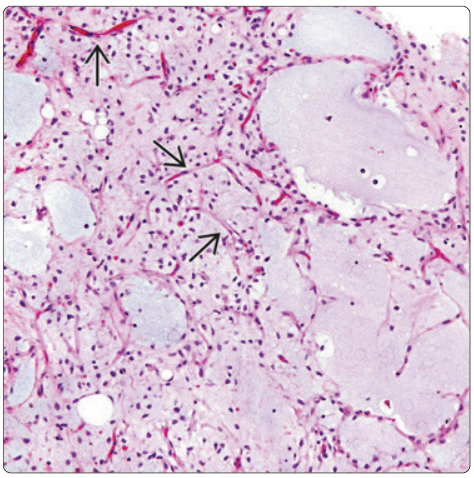


Monomorphic Spindle Cells: Prominent Stromal Vasculature (Large)

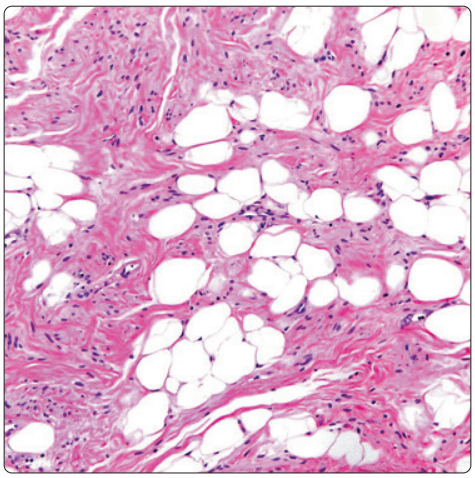


(Left) *Smaller capillary vascular channels ⇨ are conspicuous in some lesions, perhaps most notably myxoid liposarcoma.* **(Right)** *Although mature adipose tissue may be present in a tumor as a result of infiltration, some lesions feature fat as a true component of the tumor. Examples include spindle cell lipoma and mammary-type myofibroblastoma.*

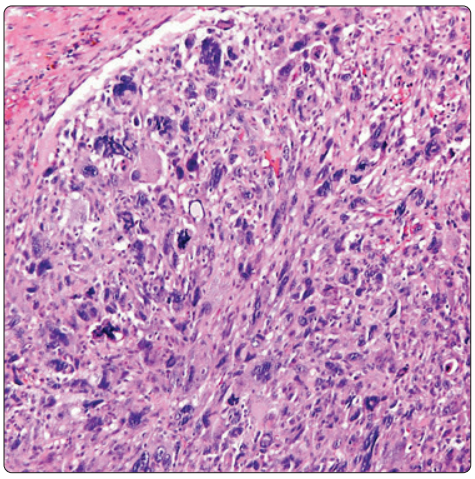
Monomorphic Spindle Cells: Prominent Stromal Vasculature (Small)



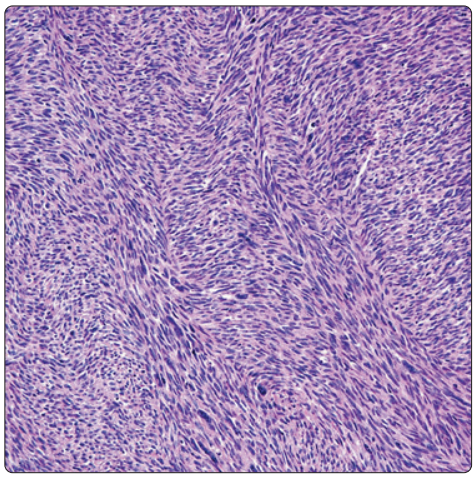
Monomorphic Spindle Cells: Adipose Tissue Component



Pleomorphic Spindle Cells: Sheets

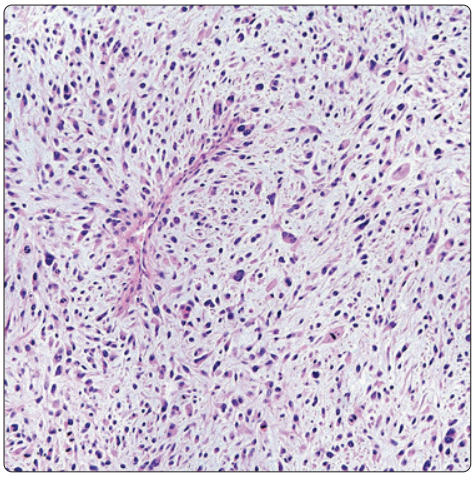


Pleomorphic Spindle Cells: Bundles and Fascicles

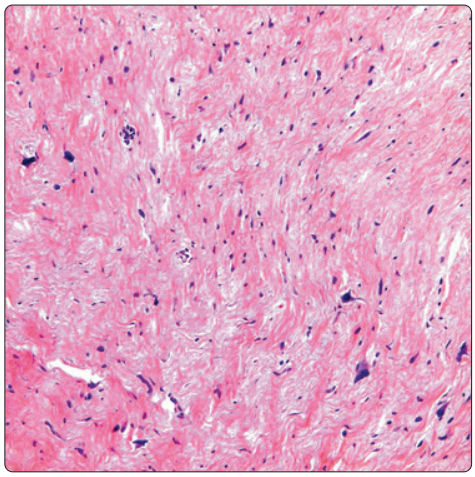


(Left) *Diffuse, cellular sheets of highly pleomorphic cells are typical of many high-grade sarcomas, including undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, and high-grade myxofibrosarcoma.* **(Right)** *Fascicular and bundled growth patterns can also be present in pleomorphic spindle cell neoplasms, particularly leiomyosarcoma and MPNST. Pleomorphic cells within a herringbone growth pattern is often MPNST.*

Pleomorphic Spindle Cells: Myxoid Stroma

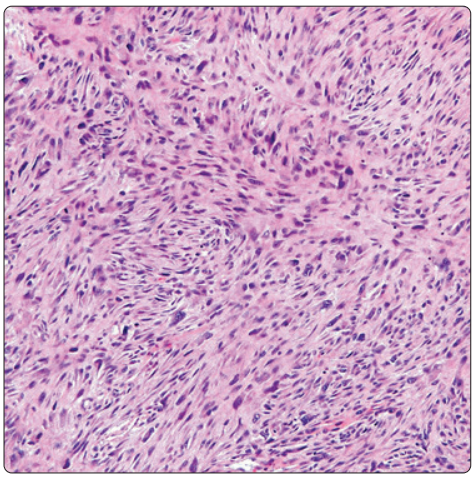


Pleomorphic Spindle Cells: Collagenous, Hyalinized, or Sclerotic Matrix

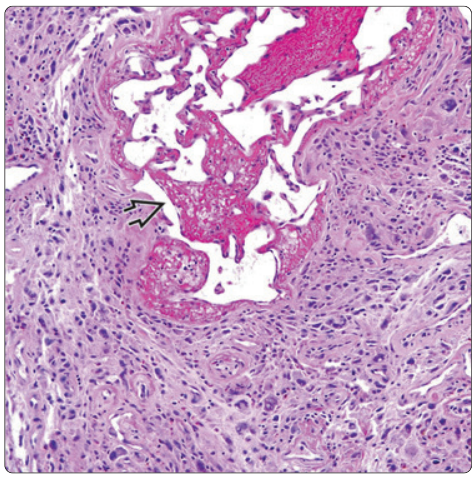


(Left) *Significant pleomorphism within a prominent myxoid stroma is most frequently associated with myxofibrosarcoma; however, it can also be seen in dedifferentiated and pleomorphic types of liposarcoma.* **(Right)** *Pleomorphism within a prominent collagenous matrix is often associated with various high-grade sarcomas; however, it can also be the pattern of sclerosing well-differentiated liposarcoma (shown).*

Pleomorphic Spindle Cells: Storiform or Whorled Architecture



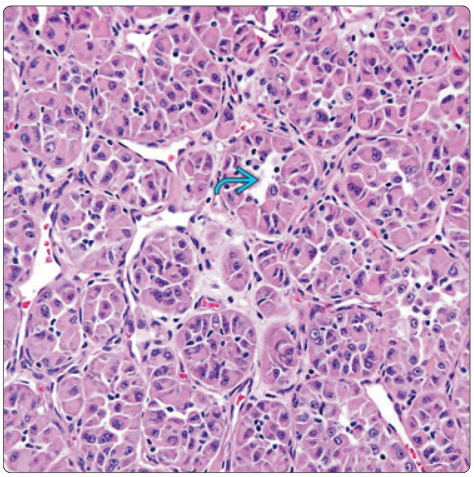
Pleomorphic Spindle Cells: Prominent Stromal Vessels



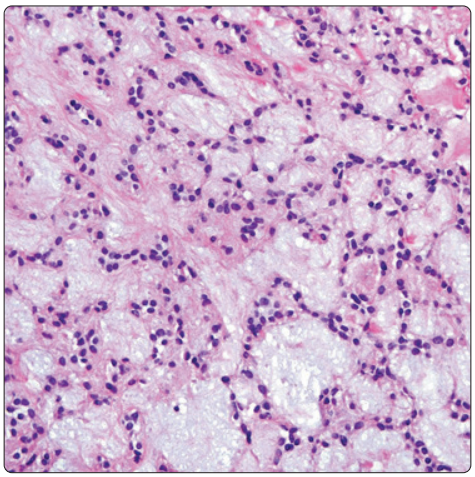
(Left) *The pattern of pleomorphic spindle cells arranged in whorls or storiform arrays is rather nonspecific and can be seen in a variety of often morphologically similar high-grade sarcomas.* **(Right)** *A prominent nonneoplastic stromal vasculature ⇨ is a feature of some pleomorphic spindle cell neoplasms, including both low-grade (e.g., pleomorphic hyalinizing angiectatic tumor, shown) and higher grade (e.g., myxofibrosarcoma) tumors.*

(Left) *Nested or lobular patterns are common in epithelioid neoplasms. Some tumors, such as alveolar soft part sarcoma (shown), may also show a central loss of cellular cohesion imparting a pseudoalveolar appearance.* **(Right)** *Distinct, linear arrangements of epithelioid cells may be seen within a myxoid, fibromyxoid, or fibrous stroma. Myoepithelioma and ossifying fibromyxoid tumor (shown) are examples.*

Epithelioid Cells: Nests or Lobules

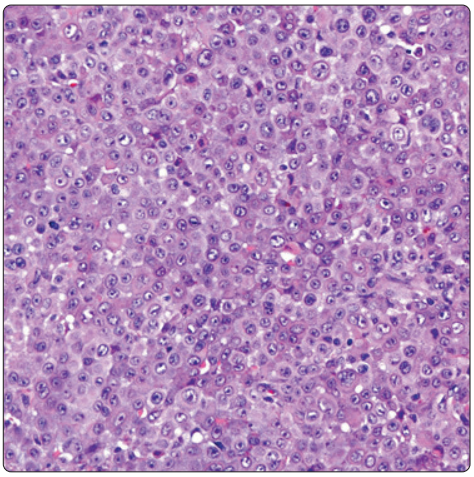


Epithelioid Cells: Cords or Trabeculae

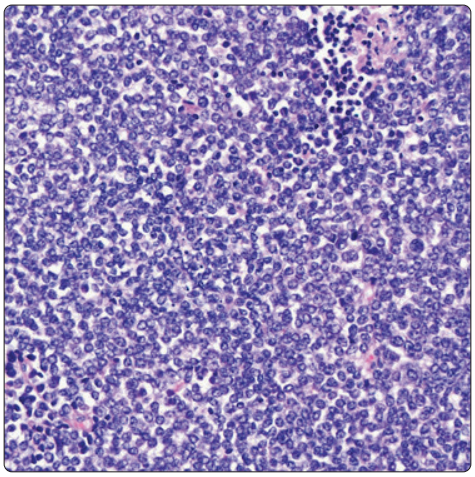


(Left) *Tumors that show a diffuse sheet-like arrangement of epithelioid cells are often high grade and feature marked cytologic atypia and mitotic activity. This morphology can closely mimic carcinoma or melanoma.* **(Right)** *Tumors with sheets of smaller epithelioid cells with minimal cytoplasm appear very blue or basophilic due to increased cell density. These neoplasms are often referred to as small, round, blue cell tumors. Immunohistochemistry is often necessary for diagnosis.*

Epithelioid Cells: Sheets (Abundant Cytoplasm)

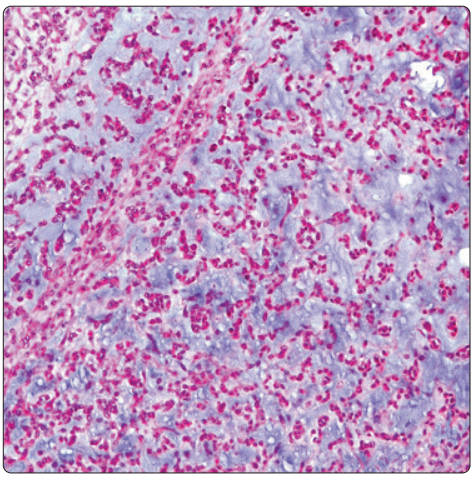


Epithelioid Cells: Sheets (Minimal/Scant Cytoplasm)

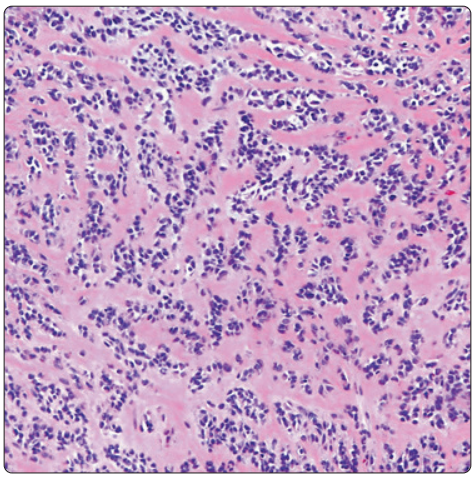


(Left) *The pattern of epithelioid cells within a myxoid stroma is distinctive but not generally common. Examples of tumors include myoepithelioma, extraskeletal myxoid chondrosarcoma, and epithelioid MPNST.* **(Right)** *Epithelioid cells within a collagenous stroma should always lead to consideration of sclerosing epithelioid fibrosarcoma (shown); however, this pattern can also be seen in myoepithelioma, epithelioid sarcoma, and others.*

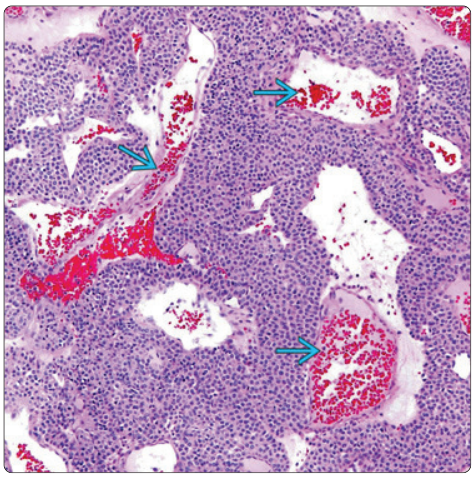
Epithelioid Cells: Myxoid Stroma



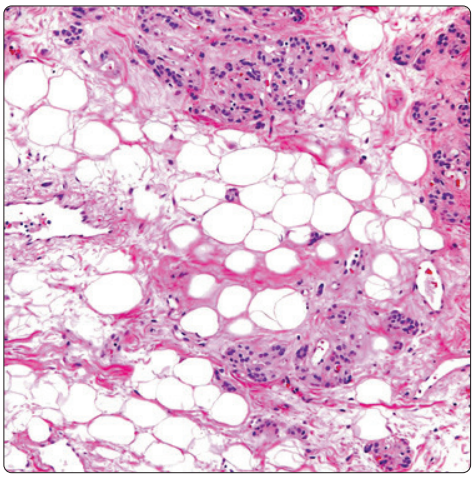
Epithelioid Cells: Collagenous, Hyalinized, or Sclerotic Stroma



Epithelioid Cells: Prominent Stromal Vasculature

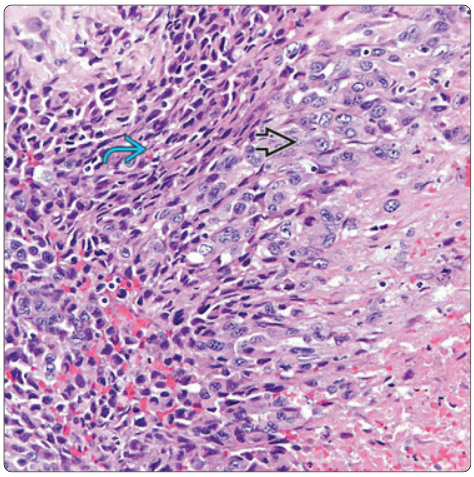


Epithelioid Cells: Adipose Tissue Component

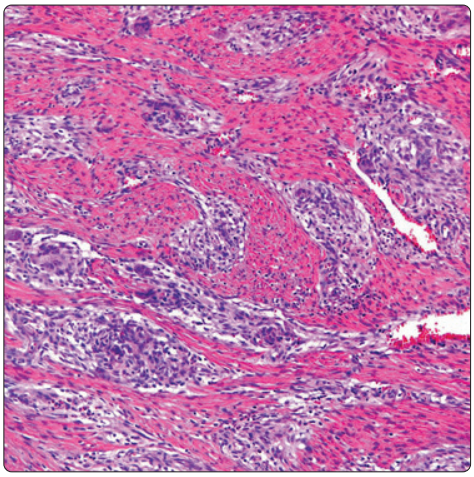


(Left) *Sheets or nests of epithelioid cells arranged around a prominent vasculature (either small or larger vessels) is classically associated with glomus tumor but can also be seen in cellular solitary fibrous tumor (previously hemangiopericytoma) and others.* **(Right)** *Adipose tissue can be an integral part of some epithelioid soft tissue tumors but is generally uncommon. Examples include angiomyofibroblastoma (shown) and chondroid lipoma.*

Mixed Spindle and Epithelioid Cells

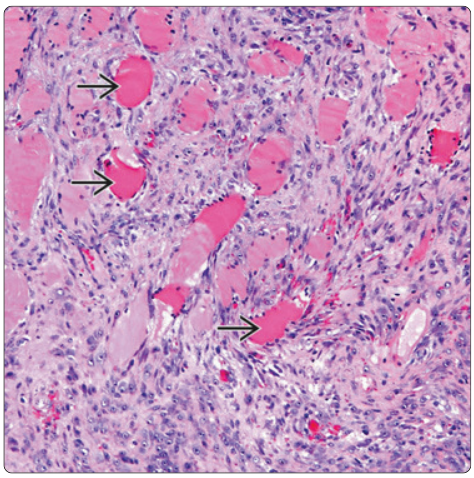


Spindle and Epithelioid Cells

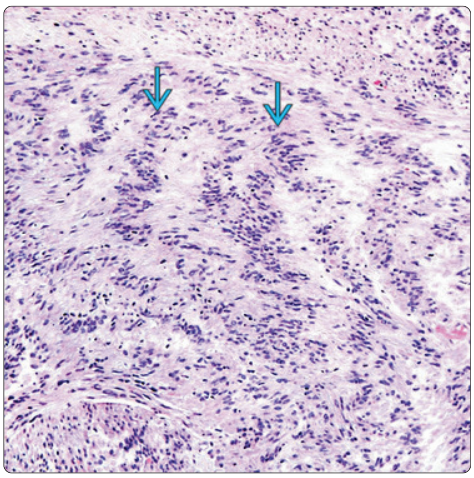


(Left) *Some soft tissue tumors feature a mixture of spindled and epithelioid tumor cells, either as discrete components or closely admixed. Examples include synovial sarcoma and epithelioid sarcoma (shown).* **(Right)** *Plexiform fibrohistiocytic tumor is a neoplasm that may feature predominantly spindled cells in bundles/fascicles, predominantly epithelioid cells in nests, or a mixture of the 2 patterns (shown).*

Checkerboard Skeletal Muscle Pattern



Nuclear Palisading



(Left) *Although any intramuscular neoplasm can show infiltration of normal skeletal muscle, some tumors characteristically feature cells growing in between fibers, imparting a checkerboard pattern. Examples include proliferative myositis and low-grade myofibroblastic sarcoma.* **(Right)** *Linear rows of nuclei (or cells) typify a palisading pattern, as shown. Although classically associated with neural tumors, this pattern can also be seen in nonneural tumors including leiomyoma, GIST, and synovial sarcoma.*

DIRECTIONS

How to Use These Guides

- The following guides are neither comprehensive nor perfect and are meant to serve only as starting point for working up a suspected mesenchymal neoplasm
- They include entities that are most commonly or classically associated with particular clinical and histologic findings

Specific Directions for This Guide

- The following list contains a variety of distinctive histologic features ranging from unique nuclear and cellular morphologies to specific stromal components
  - Each listed feature is more commonly or characteristically associated with some soft tissue tumors and not others
- For each histologic feature listed below, a selection of most commonly or characteristically associated diagnoses are provided
- Compile an assortment of potential diagnoses from the guide using the particular feature(s) from your particular case
  - Compare this selection to those created from other 2 Approach chapters
  - Overlapping diagnoses derived from these 3 distinct approaches are highest yield and should be your primary focus
- Once high-yield diagnoses have been identified, chapters on specific entities should be directly consulted for detailed information and image galleries
  - In particular, the Differential Diagnosis sections should be fully utilized to broaden search and increase chances of securing the correct diagnosis

Important Caveat

- Always exclude carcinoma, melanoma, lymphoma, and mesothelioma before committing to mesenchymal diagnosis

CYTOLOGIC FEATURES

Clear Cells

- Alveolar soft part sarcoma
- Clear cell sarcoma
- Desmoplastic small round cell tumor
- Ewing sarcoma
- Myoepithelioma
- Myoepithelial carcinoma
- PEComa
- Sclerosing epithelioid fibrosarcoma

Granular Cells

- Adult rhabdomyoma
- Alveolar soft part sarcoma
- Chondroid lipoma
- Congenital granular cell epulis
- Extranodal Rosai-Dorfman disease
- Granular cell tumor
- Hibernoma
- Leiomyoma
- PEComa

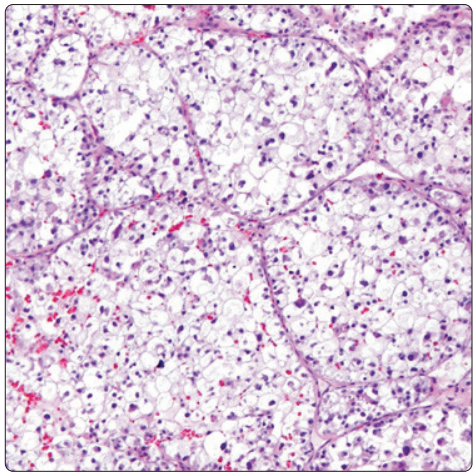
Hobnail Cells

- Epithelioid hemangioma
- Hobnail hemangioma
- Papillary intralymphatic angioendothelioma (Dabska)
- Retiform hemangioendothelioma

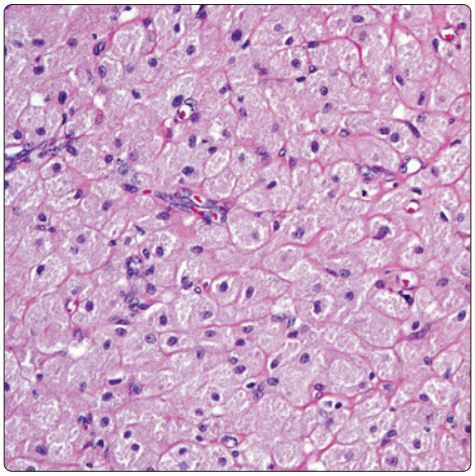
Rhabdoid Cells

- Angiomatoid fibrous histiocytoma
- Desmoplastic small round cell tumor
- Epithelioid MPNST
- Epithelioid sarcoma
- Extrarenal rhabdoid tumor
- Extraskeletal myxoid chondrosarcoma
- Myoepithelial carcinoma
- Pseudomyogenic hemangioendothelioma
- Synovial sarcoma (poorly differentiated)

Clear Cells



Granular Cells



(Left) *Soft tissue tumors featuring cells with clear cytoplasm include myoepithelioma, PEComa, and alveolar soft part sarcoma (shown), among others. Unlike epithelial neoplasms, clear cell change in mesenchymal tumors is usually focal or patchy and rarely diffuse.* **(Right)** *Cells with prominent granular, eosinophilic cytoplasm are most commonly associated with granular cell tumor but can also be seen in congenital granular cell epulis (shown), PEComa, hibernoma, and adult rhabdomyoma.*