Pathology for Clinicians

Kyle Perry

Soft Tissue Pathology for Clinicians

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This book is dedicated to my wife, Anamarija, and my daughter, Anabelle, for the support they have given me during my career. I would also like to thank my mother and father in-law, Vojimira Morovic and Ante Surac, for their support.

Preface

Similar to other areas of oncology, the diagnosis and treatment of sarcomas are increasingly accomplished as a collaboration of a diverse team of subspecialists. This allows modern medicine to maintain a holistic and pragmatic approach when caring for cancer patients. However, the ability of physicians to effectively administer care in this manner largely depends on clear communication across specialty boundaries.

Soft tissue pathology encompasses a vast amount of neoplasms that are typically not unique to a particular anatomic location, and pathologists are increasingly incorporating an expanding catalogue of immunohistochemical and genetic tests when making a diagnosis. With this in mind, this book was written to give perspective in the diagnosis of soft tissue tumors to those practicing outside of pathology. In particular, this book will focus on the key characteristics of common soft tissue neoplasms and the approach taken to render a diagnosis. It will also cover critical aspects of soft tissue pathology that are encountered by a treating physician, such as tumor staging, intraoperative consultation, and considerations in processing soft tissue surgical specimens.

Many excellent reference books have been written to discuss soft tissue pathology in a comprehensive manner. By focusing on the interdisciplinary interactions involving soft tissue pathology, it is hoped that this concise booklet will be of value to oncologists, surgeons, medical oncology trainees, and mid-level providers by further facilitating meaningful communication in a team practice environment.

Winnipeg, Manitoba, Canada — Kyle Perry

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Critical Concepts in Soft Tissue Pathology

1

1.1 General Principles of Classification

Soft tissue pathology is a subspecialty that involves the diagnosis of lesions that are neither epithelial nor skeletal and do not originate from the central nervous system. This includes neoplasms of muscle, connective fascia, vasculature, and the peripheral nervous system [1]. With such an ambitious definition, the scope of this subspecialty is broad and encompasses a formidable number of entities with specific histologic, genetic, and clinical features.

When encountering such an abundance of terms and neoplasms, one can be tempted to view soft tissue tumors simply by histologic grade. Although this approach simplifies several hundred neoplasms into low-, intermediate-, or high-grade sarcoma, it overgeneralizes and is incompatible with increasingly individualized treatment regimens. By classifying soft tissue neoplasms to a particular histologic entity, pathologists have been able to attribute unique clinical behaviors to specific tumors and establish a conceptual framework for future advances in soft tissue oncology [2]. Consequently, clinicians who frequently treat sarcoma patients can benefit from understanding the diagnostic terms and approach of soft tissue pathologists.

In order to maintain consistency, the diagnostic nomenclature of soft tissue pathology is determined by a consensus of international experts. Every few years, this terminology is edited to reflect the addition of newly discovered neoplasms or reassignment of entities to different categories. These efforts are published as a volume in the World Health Organization Classification of Tumours book series, titled *Pathology and Genetics of Tumours of Soft Tissue and Bone* [3].

Unlike carcinomas that are often classified by site of occurrence (e.g. colorectal adenocarcinoma, gastric adenocarcinoma), a soft tissue tumor can arise in multiple areas and is not amenable to description by anatomic location. Instead, these neoplasms are described according to the connective tissue that they most closely

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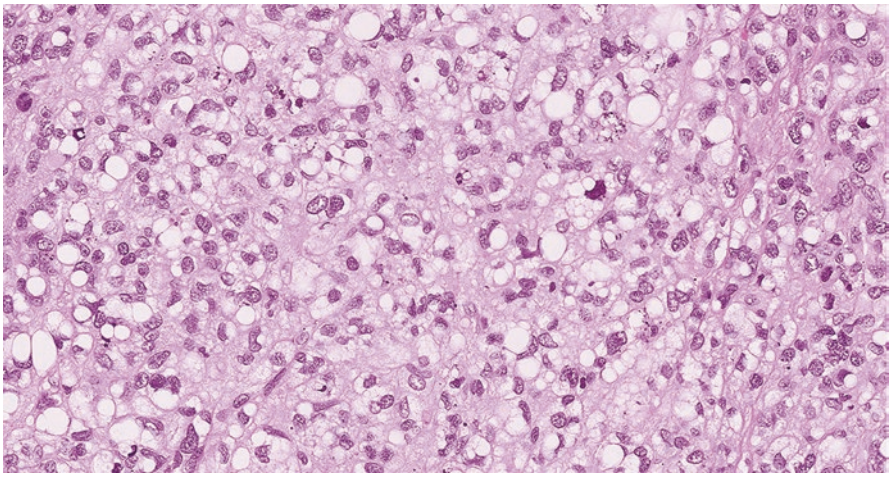

Fig. 1.1 Pleomorphic liposarcoma with lipoblasts

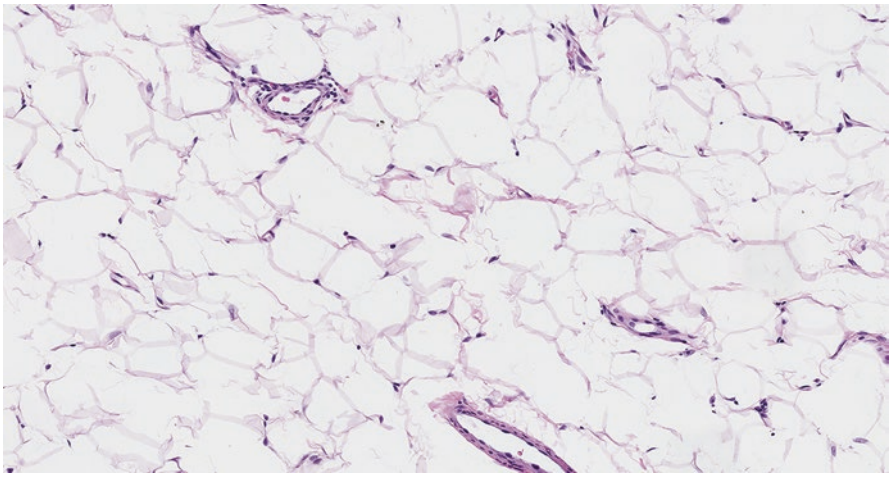

Fig. 1.2 Normal adipose tissue

resemble. Such entities include pleomorphic liposarcoma (Fig. 1.1) that resembles fat (Fig. 1.2) or leiomyosarcoma (Fig. 1.3) that resembles smooth muscle (Fig. 1.4). Many soft tissue tumors do not resemble any specific mesenchymal tissue and are simply designated as "tumors of uncertain differentiation" [3].

Following primary histologic classification, soft tissue tumors are further subdivided into clinical categories of benign, intermediate (locally aggressive), intermediate (rarely metastasizing), and malignant. Most benign lesions do not recur, and rare instances of recurrence are easily cured by complete local excision. Intermediate

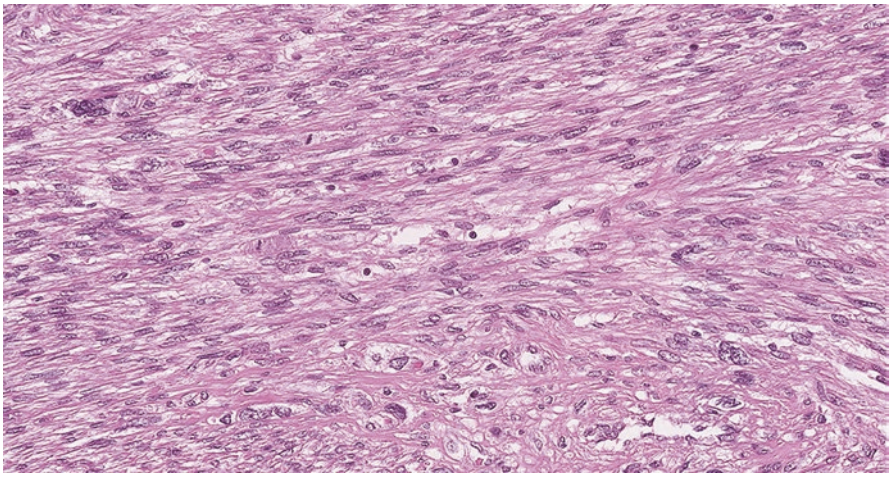

Fig. 1.3 Leiomyosarcoma with neoplastic muscle cells showing mitoses and nuclear atypia

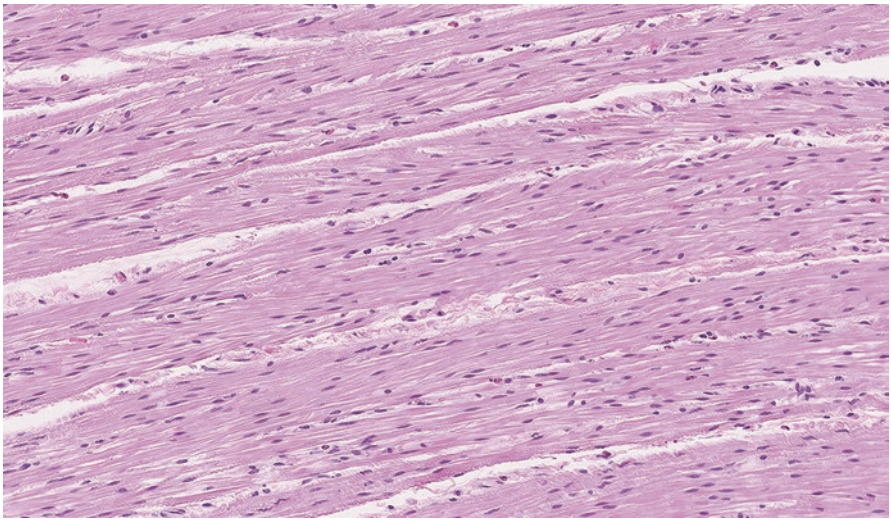

Fig. 1.4 Normal smooth muscle

(locally aggressive) tumors will not metastasize but are prone to recurrence and require wide excision given their infiltrative growth pattern. Intermediate (rarely metastasizing) soft tissue tumors are typically locally aggressive, but demonstrate the capability to occasionally metastasize (less than 2% risk). Malignant tumors are locally destructive and often metastasize. Generally, high-grade tumors tend to metastasize more frequently than low-grade tumors [3].

1.2 Acquisition, Handling, and Processing of Soft Tissue Specimens

Ultrasound or computed tomography (CT)-guided needle core biopsies have become the preferred procedure for diagnosing soft tissue neoplasms, as they are minimally invasive and less prone to surgical complications. Histologic interpretation of these biopsies is both sensitive (99.4%) and specific (98.7%) when distinguishing benign from malignant tumors [5]. The accuracy of needle core biopsies for a specific histologic diagnosis is also impressive (approximately 95% correct) [6]. Assessment of tumor grade in biopsies (low vs. intermediate vs. high) is helpful but slightly less accurate (approximately 85% correct) [7]. The interpretation of a needle core biopsy often represents a critical juncture in the care of a patient with a soft tissue neoplasm. A benign lesion might be monitored or undergo simple excision. A low-grade sarcoma is resected without neoadjuvant therapy, and an intermediate- or high-grade sarcoma often receives presurgical adjuvant treatment.

Following a biopsy or resection, the tissue is submitted to the pathology laboratory for evaluation. In order to prevent tissue degradation, many hospitals or clinics will place the biopsies directly into formalin in the operating suite. However, if a clinician or pathologist has an interest in culturing or freezing a representative part of the biopsy for possible cytogenetic or molecular studies, then at least some of the tissue must be maintained in a fresh, viable state and transported in cell culture media. Close communication with the pathologist is helpful in assuring the tissue is appropriately handled.

Upon arrival to the laboratory, the specimen must pass through a standardized process prior to visualization as a glass slide under the microscope. The tissue initially arrives in a labeled container with an accompanying requisition form that is reviewed by lab personnel (Fig. 1.5a). Including critical information on this form about the history of the patient or nature of the lesion facilitates a timely and accurate diagnosis. Awareness of the site and size of the mass helps the pathologist formulate a differential diagnosis based on anatomic location. Knowledge of previous malignancies (including prior diagnosis of carcinoma, melanoma, or hematolymphoid neoplasm) alerts the pathologist to recurrent or metastatic tumors that might mimic a sarcoma. Communication of familial syndromes, such as neurofibromatosis, helps raise a suspicion of certain malignant neoplasms like malignant peripheral nerve sheath tumor [4].

After reviewing the requisition and confirming the specimen is appropriately labeled, the pathologist or pathology assistant will typically describe the appearance of the tissue received (i.e. gross examination). For needle core biopsies, the number and size of the biopsies are documented. With resection specimens, the pathologist describes the location and size of the mass, as well as the distance from the surgical resection margin. The surgeon will often designate multiple anatomically specific margins by orienting the specimen with sutures (e.g., long suture, superior margin; short suture, medial margin). To preserve this orientation, the pathologist will typically paint the corresponding margins with an ink that can be seen under the microscope after processing. If there is a particular area of concern for margin involvement,

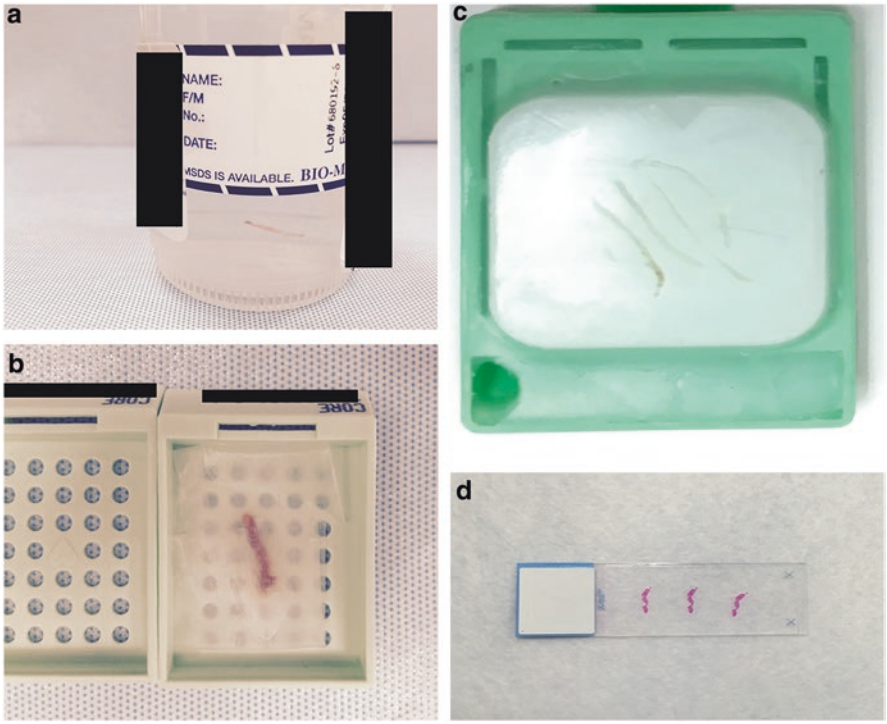

Fig. 1.5 (**a**) Specimen container with a needle core biopsy, (**b**) needle core biopsy wrapped in tissue paper for processing, (**c**) needle core biopsy embedded in paraffin wax after tissue processing, (**d**) needle core biopsy after being processed, cut and stained with hematoxylin and eosin

specific designation by the surgeon can assure this focus is appropriately examined and referenced in the report. Moreover, if the margin has become artificially ruptured, proactively notifying the pathologist can help avoid an erroneous report.

Once gross examination is complete, the tissue is submitted for processing. For needle core biopsies, the objective is to have sufficient tissue for diagnosis and grading. Consequently, many pathology laboratories will submit all of the received biopsies in a formalin fixative solution that suspends enzymatic processes and halts tissue degradation (Fig. 1.5b). Following formalin fixation, the biopsy is processed and ultimately immersed in paraffin wax, termed a "paraffin block" (Fig. 1.5c). A thin slice of this biopsy is then cut, placed on a glass slide and stained for microscopic examination (Fig. 1.5d).

For resection specimens, the pathologist must select which tissue fragments to submit for microscopic examination. Generally, multiple sections of tumor (often one per centimeter) are submitted to confirm the diagnosis or assess for treatment effect. Other sections are typically submitted to evaluate the relation of the tumor with various surgical margins. Following submission, the tissue is processed for microscopic examination similar to a needle core biopsy.

Facts to Remember

1. Soft tissue tumors are described according to the connective tissue they most resemble and are further categorized as benign, malignant, or intermediate in clinical behavior.
2. The needle core biopsy has become the primary specimen for diagnosis of soft tissue neoplasms. Appropriate and timely handling of the tissue is critical for successful classification.
3. Documentation of key clinical features on the requisition form, such as the anatomic site and size of the mass, previous malignancies, familial syndromes, and previous therapy can be immensely helpful for accurate and efficient diagnosis.
4. Communication of specimen orientation or areas that are suspicious for tumor involvement can facilitate clear pathologic reporting.

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Histologic Examination and Ancillary Studies in Soft Tissue Pathology

2

2.1 Pathologist Approach to Diagnosis

Soft tissue biopsies are often challenging specimens to diagnose. There is an almost overwhelming amount of entities to consider, many of which are very rare. Moreover, numerous ancillary studies, such as immunohistochemical or molecular tests, are often necessary for appropriate investigation [1].

Visualization of a tumor on an hematoxylin and eosin (H&E) slide remains central to the diagnosis of soft tissue neoplasms. This H&E staining technique, which is over 100 years old, allows the pathologist to examine tumor cells by highlighting nuclei in blue (by hematoxylin) and cytoplasm in red (by eosin).

When viewing an H&E slide, a pathologist assesses the overall architecture at a low power magnification and then analyzes the cytological features of the tumor cells at higher power. Groups of soft tissue tumors manifest characteristic patterns that can be utilized by pathologists in considering diagnostic possibilities. Familiarity with these patterns and associated terminology can lend insight into the diagnostic process [2]. Frequent histologic patterns include spindle cell, epithelioid, round cell, pleomorphic, myxoid, cartilaginous, osseous, and vascular.

Spindle Cell Tumors

One of the most frequent morphologies encountered in soft tissue tumors is a spindled cell pattern, in which the tumor cells exhibit slender and elongated nuclei and cytoplasmic borders. These spindle cells can be arranged in haphazard manner (Figs. 2.1 and 2.2) as seen in nodular fasciitis or placed in organized bundles (often termed a "fascicular" or "herringbone pattern") as seen in malignant peripheral nerve sheath tumor (Fig. 2.3). Finally, the spindle cells can be arranged in a whirling or storiform architecture, as seen in dermatofibrosarcoma protuberans (Fig. 2.4).

Epithelioid Tumors

Although mesenchymal in nature, soft tissue tumor cells can have an epithelioid appearance. Morphologically, these cells have cytoplasmic and nuclear borders that

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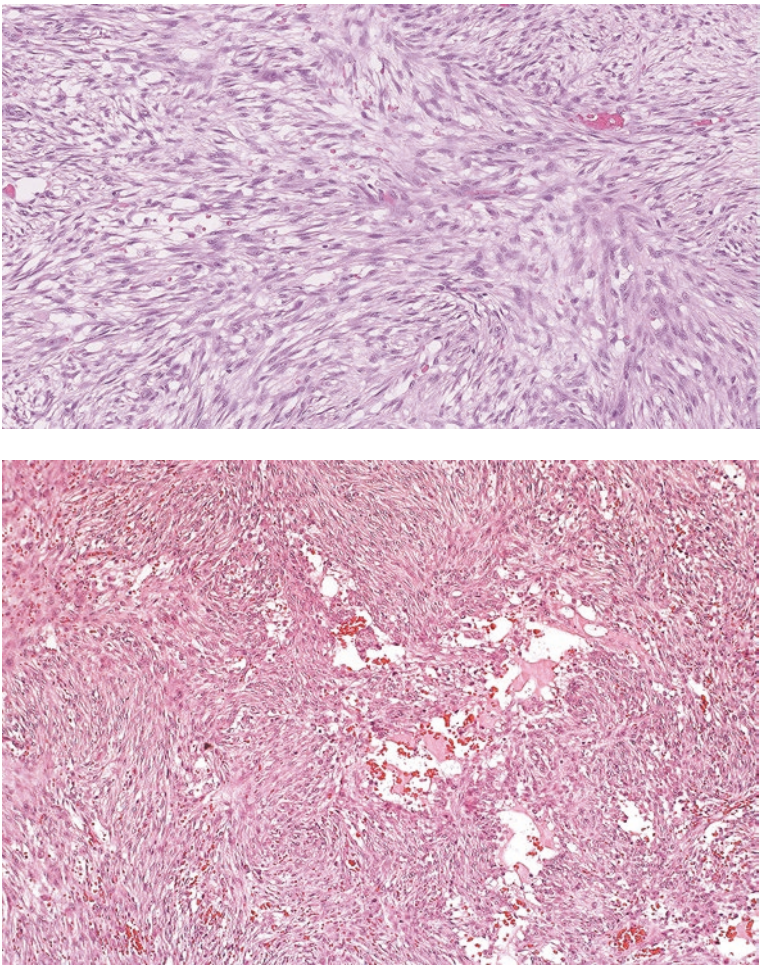

Figs. 2.1 and 2.2 Nodular fasciitis with haphazard arrangement of spindle cells

are round or oval (Fig. 2.5). Examples of epithelioid type soft tissue neoplasms include epithelioid sarcoma, epithelioid hemangioendothelioma, and epithelioid gastrointestinal stromal tumor. Epithelioid-type sarcomas can be mistaken for poorly differentiated carcinomas, particularly if the pathologist is unaware of the anatomic location or clinical history of the lesion.

Round Cell Tumors

Round cell tumors encompass a broad range of soft tissue neoplasms that are made up of cells that have a high nuclear to cytoplasmic ratio, similar to the appearance of a lymphocyte. As hematoxylin will stain the nucleus of a cell violet or blue, round cell neoplasms generally appear blue at low magnification. Examples of round cell

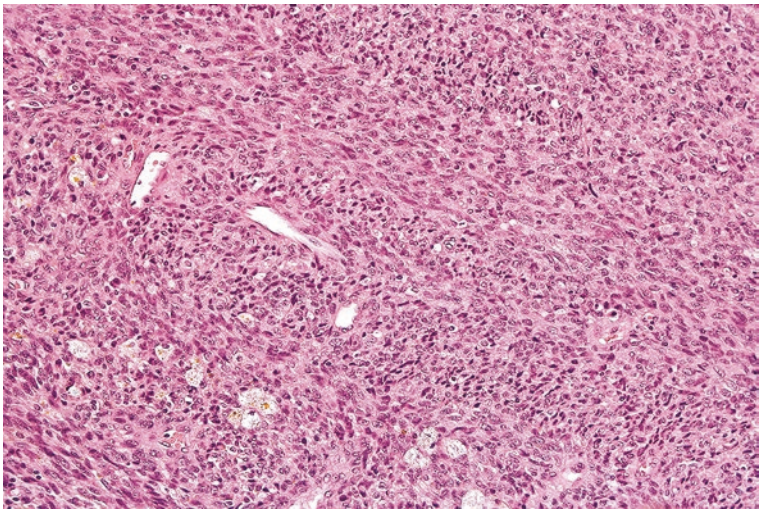

Fig. 2.3 Malignant peripheral nerve sheath tumor with spindle cells that are organized in bundles, often called a fascicular pattern

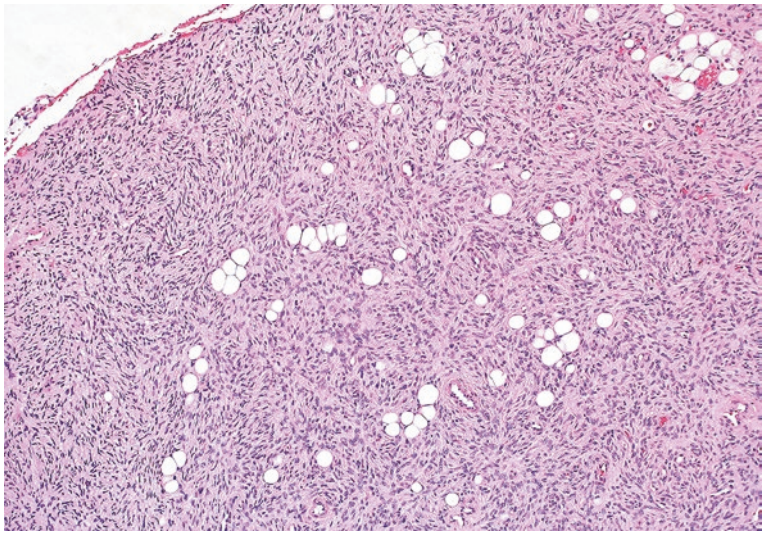

Fig. 2.4 Dermatofibrosarcoma protuberans with spindle cells arranged in a vague whirling or storiform pattern

soft tissue neoplasms include embryonal rhabdomyosarcoma or Ewing sarcoma (Fig. 2.6). Although these neoplasms have substantially overlapping morphologic appearances, many exhibit unique genetic features that facilitate diagnosis. Round cell tumors can also be confused for neuroendocrine carcinomas or lymphomas.

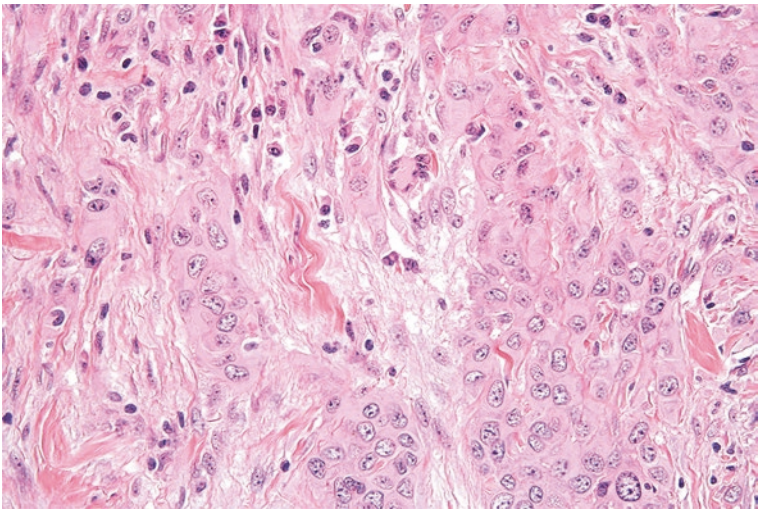

Fig. 2.5 This epithelioid sarcoma contains epithelioid-appearing tumor cells with round to ovoid nuclei

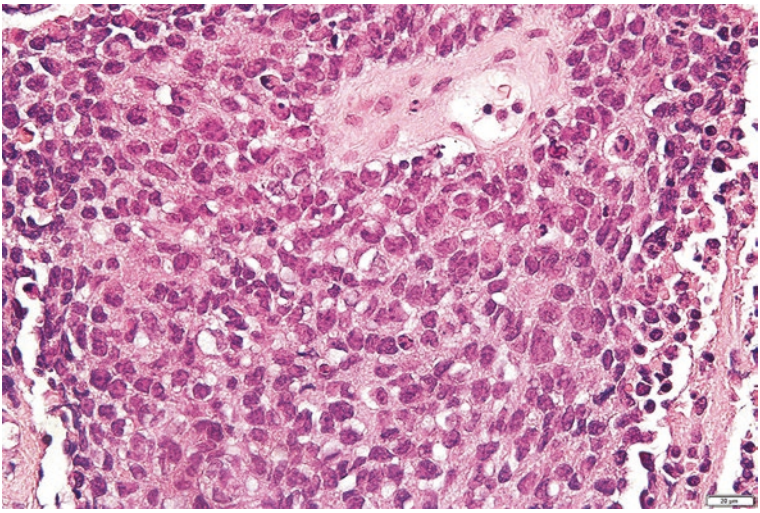

Fig. 2.6 Ewing sarcoma containing round tumor cells with a high nuclear to cytoplasmic ratio

Pleomorphic Tumors

Many high-grade sarcomas can exhibit pleomorphic or bizarre-appearing cells. The tumor cells of this pattern demonstrate substantial variation in the size and shape of the nuclei (Fig. 2.7). Highly atypical mitoses can often be identified. One of the most frequently occurring pleomorphic soft tissue neoplasms is an undifferentiated high-grade pleomorphic sarcoma, previously designated as "high-grade malignant fibrous histiocytoma (MFH)." Pleomorphic sarcomas must be distinguished from pleomorphic carcinoma, hematolymphoid neoplasms, or melanomas that can have a similar appearance.

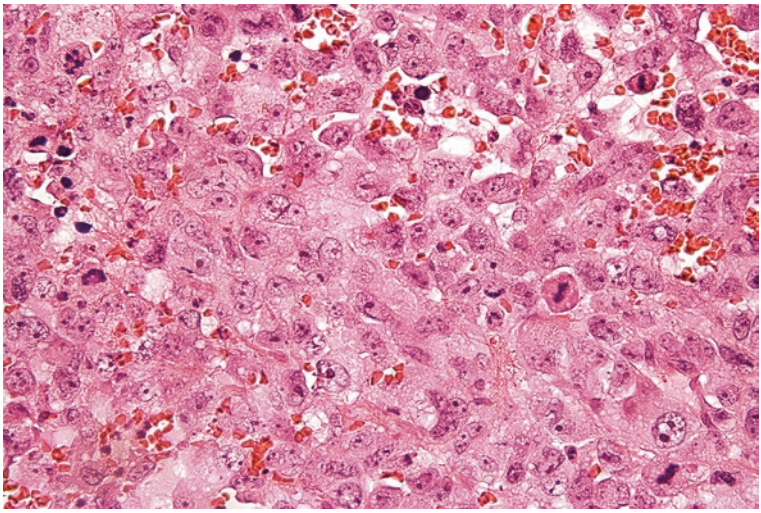

Fig. 2.7 Undifferentiated pleomorphic sarcoma with tumor cells that contain large and irregular nuclei with increased mitoses

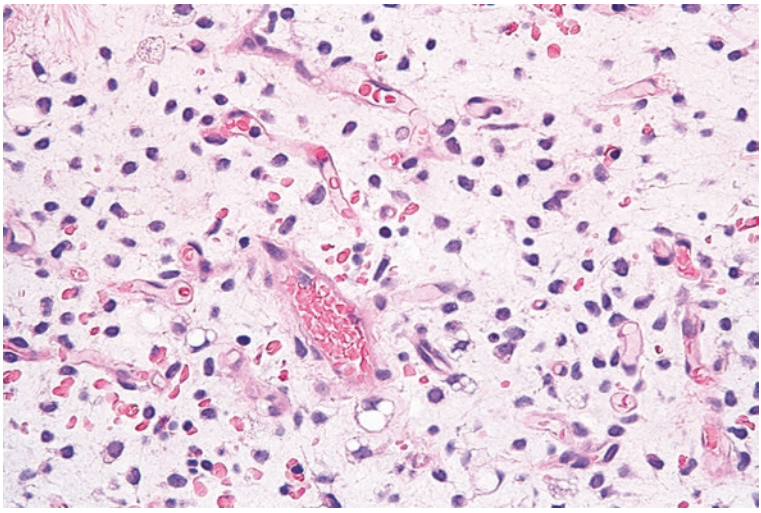

Fig. 2.8 Myxoid liposarcoma with substantial amount of background myxoid material and delicate capillaries

Myxoid Tumors

Myxoid soft tissue tumors exhibit varying amounts of a background bluish mucoid-like substance (Fig. 2.8). The neoplasms in this pattern can be difficult to differentiate based on architecture, as the tumor cells often freely float in this myxoid material. Examples of these tumors include myxoid liposarcoma, myxofibrosarcoma, and aggressive angiomyxoma.

Cartilaginous, Osseous, Adipocytic, and Vascular Tumors

The endothelial nature of vascular tumors is frequently apparent by the formation of infiltrative vascular channels (Fig. 2.9). Adipocytic tumors can often be identified by obvious fat cells or lipoblasts that contain large clear vacuoles in the cytoplasm (Fig. 2.10). Cartilaginous tumors will exhibit deposition of a blue or pink background chondroid-like matrix (Fig. 2.11). Osseous tumors show at least focal dense and eosinophilic extracellular osteoid material (Fig. 2.12).

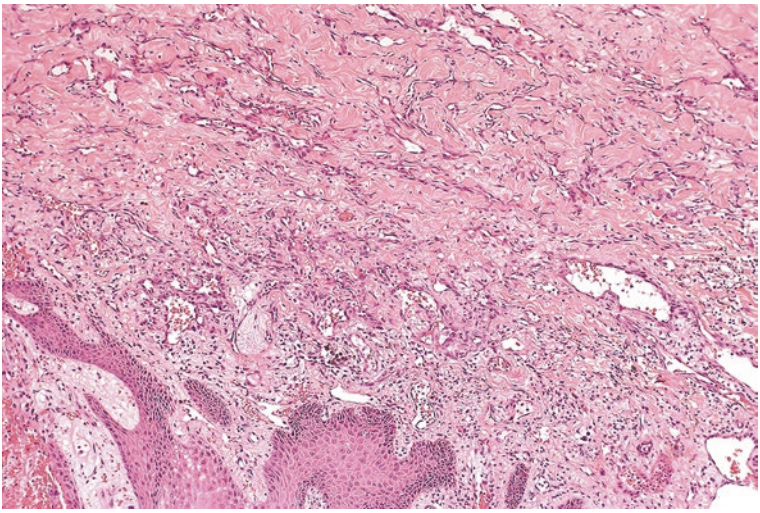

Fig. 2.9 Well-differentiated angiosarcoma with vascular channels that dissect through tissue

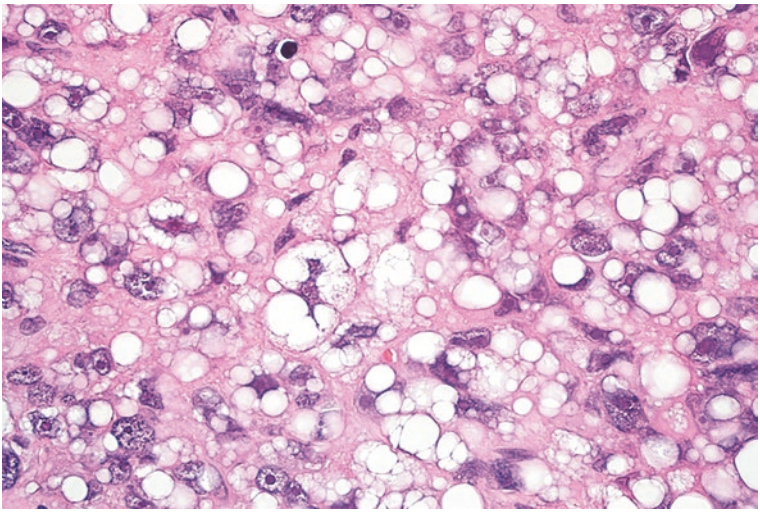

Fig. 2.10 Lipoblasts seen in a pleomorphic liposarcoma

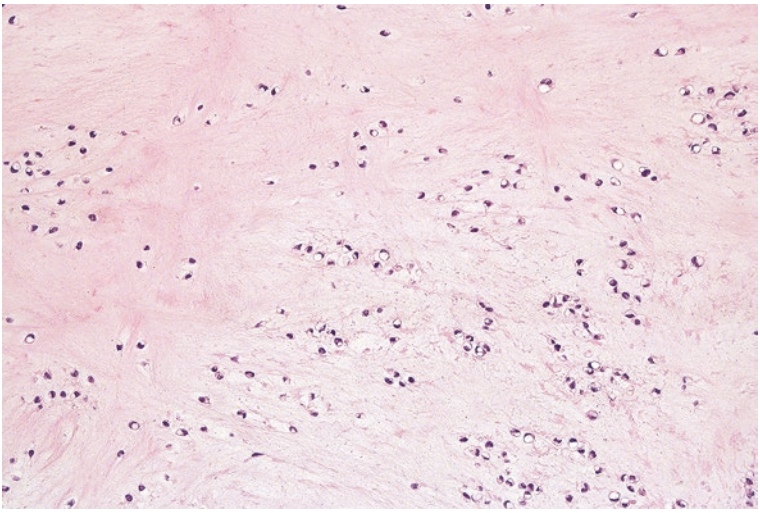

Fig. 2.11 Variably blue and pink background chondroid matrix in a soft tissue chondroma

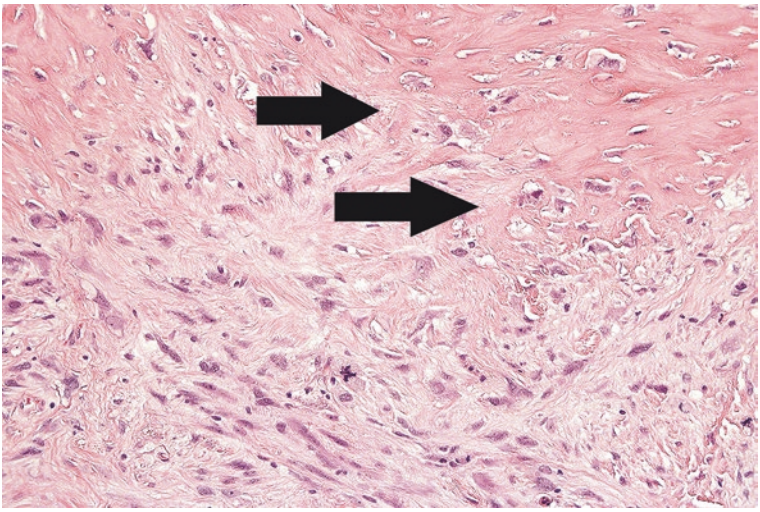

Fig. 2.12 Extraskeletal osteosarcoma with deposition of pink osteoid material (*arrows*)

It is important to understand that these patterns serve as a starting point in investigating the ultimate differentiation and diagnosis of a particular soft tissue tumor. At the microscope, an individual tumor may manifest multiple patterns, such as a synovial sarcoma, which can contain spindle cells, epithelioid cells, and round cells in the same tumor (Fig. 2.13a–c.) After assessing for these patterns and features, the pathologist can then progress to a more detailed examination and incorporate various ancillary tests to evaluate specific diagnostic considerations.