Pathological Diagnosis of Retroperitoneal Tumors

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1 Approach to the Pathological Diagnosis of Retroperitoneal Tumors

1.1 Clinical Information

To achieve the correct diagnosis, the pathologist should be apprised of clinical information, including the age of the patient, as well as the location and growth features of the tumor (Tambo et al. 2007). The imaging data, particularly magnetic resonance imaging (MRI), can help demonstrate the extent and texture of the lesion and its relationship to peripheral structures.

1.2 Biopsy Diagnosis

Biopsy for soft tissue tumors was decided by the size and location of the lesion. For example, incision biopsy could be considered for a large and deeply situated mass. Its principal disadvantages are spillage of tumor cells into adjacent compartments attributed to poor hemostasis or faulty biopsy placement, wound infection, and the requirement for hospitalization. Excision biopsy is more expedient and can obtain an entire lesion; however, it could only be performed on small and superficial lesions amenable to complete resection. Fine needle aspiration biopsy may be considered when complete surgical resection is impossible and especially suitable for lesions suspected to be sensitive to chemotherapy by clinical data, e.g., malignant lymphoma.

The biopsy paradigm has evolved in the direction of core needle biopsy, a minimally invasive technique to obtain tissue sample, which is convenient for subsequent procedures, including immunohistochemical staining and molecular test, to reach a correct diagnosis. It is essential to understand the limitations and pitfalls of core needle biopsy. Following basic principles should be kept in mind. First, the pathologist should be aware of the clinician's expectation. The goal of a core needle biopsy may be as simple as to discern primary mesenchymal neoplasm as opposed to lymphoma or metastatic lesion; a distinction usually can be easily made in majority of such cases with the help of adjuvant immunohistochemistry. If definitive surgery will be arranged based on the biopsy, the priority is to determine whether or not the lesion is a sarcoma. If the intention is to provide preoperative

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(neoadjuvant) radio- or chemotherapy, the diagnosis of sarcoma is a requisite. Moreover, the lesion should be subclassified and graded as far as possible. Occasionally, it may be impossible to reliably grade a sarcoma on the basis of limited samples obtained by core needle biopsy. If a serial of biopsies has indicated a high grade, the lesion is often diagnosed as a high-grade sarcoma. Meanwhile, if the lesion is insufficiently sampled or imaging examination suggests characteristics of high-grade sarcoma (i.e., necrosis), this lesion to be hastily diagnosed as low grade should be with more cautions.

Anatomical constraints restrict wide surgical resection of retroperitoneal sarcomas (RPS). Preoperative radiotherapy for RPS is resource intensive, requiring joint effort from diagnostic and treatment teams (Alford et al. 2013). An accurate preoperative diagnosis is required before formulating the therapeutic strategy. Correct diagnosis heavily depends on imaging which determines the acquirement of specimens for pathological assessment with limited amounts of sample.

1.3 Frozen Section Diagnosis

Frozen section diagnosis was commonly performed in the past, with the expectation that definitive surgery would be accomplished using the same intraoperative procedure. However, frozen sections are now procured primarily to assure the surgeon that representative tissue has been obtained that is adequate for the diagnosis or to evaluate resection margin. The former may be accomplished by freezing a portion of the sample or performing a touch preparation (as in the case of a needle biopsy). On a touch preparation, the presence of malignant cells in a nonnecrotic background ensures that the specimen is adequate. A background of reactive or necrotic cells suggests either a pseudocapsule or largely necrotic specimen, requiring additional material depending on the clinical impression.

1.4 Evaluation of Resection Specimens

If malignancy is suspected when a tumor is grossly checked, careful assessment of its relationship with surrounding structures is mandatory. This includes its location, size, relation to vital structure, and the status of necrosis (if it can be judged grossly). For a sarcoma, size provides information about T description for the surgeon. Lesions less than 5 cm are classified as T1, whereas those larger than 5 cm are classified as T2 (Tsujimoto et al. 1988; Trojani et al. 1984). Assessment of the degree of necrosis is important for untreated sarcomas, as this parameter is used in grading systems. The extent of necrosis in lesions treated with preoperative irradiation or chemotherapy is also vital, as it helps to assess the efficacy of the treatment, although it does not carry the same implication as it is in an untreated lesion. The gross appearance of the tumor may be deceptive. Sarcomas may appear to be well circumscribed, whereas some benign tumors present infiltrative and invasive growth patterns. Encapsulation is often misleading, leading to inadequate excision by shelling out or enucleation of the tumor.

To some extent, sampling is tailored according to the specific case. For a benign lesion, a few representative blocks are sufficient, and the entire lesion can be handled if it is small. For a sarcoma, different approaches should be taken. It may be less important to submit numerous sections for a high-grade sarcoma than for a low-grade lesion in which the sampling is being driven by the need to rule out the presence of a high-grade lesion. Generally, one section is obtained for each centimeter of tumor diameter, with no more than ten sections if the lesion appears uniform. Representative sections of the margins or sections designed to display impingement on vital structures are required. Blocks are selected for margins judiciously, depending on the gross appearance of the lesion. Lesions several centimeters away from a margin seldom have positive margins microscopically. Therefore, extensive margin sampling in these situations is less critical

than with excisions containing grossly close margins. One exception is epithelioid sarcoma, a lesion that is deceptive in its gross extent. Digital images can provide visual clues as to the orientation of the specimen and sampling sites.

Most specimens would be handled adequately as described above. However, when diagnostic difficulty is anticipated, archiving some frozen tissue for the possible future ancillary molecular studies is important.

1.5 Microscopic Examination

The first and most important step in reaching a correct diagnosis is careful scrutiny of H&E-stained sections with light microscopy under low-power magnification. Specifically, microscopic features include the size and depth of the lesion, its relation to overlying skin and underlying fascia, and the nature of the borders (e.g., pushing, infiltrative, clear, and ill-defined). The key question is whether the lesion is a reactive process or a neoplasm. Once a reactive lesion can be excluded, the pathologist is justified in proceeding with analysis of the neoplasm. At low power, the architectural pattern, the appearance of the cells, and the characteristics of the stroma can contribute to various differential diagnostic categories categories (Weiss and Goldblum 2001).

1.5.1 Fasciculated Spindle Cell Tumors

These lesions comprise a large group of tumors characterized by long fascicles. Most spindle cell tumors arising from retroperitoneal location are malignant, e.g., malignant peripheral nerve sheath tumor (MPNST) and synovial sarcoma. Cellular schwannoma and fibromatosis must be distinguished from the others, because of their non-metastatic behavior. Fibromatosis is typically a lesion with low cellularity and low-grade nucleus. Cellular schwannoma is characterized by diffuse and intense S100 protein immunoreactivity.

1.5.2 Myxoid Lesion

Soft tissue tumors may appear myxoid from time to time; many lesions display myxoid features consistently. In adults, the differential diagnosis of myxoid tumors includes myxoma, myxoid malignant fibrous histiocytoma (myxofibrosarcoma), myxoid liposarcoma, and myxoid chondrosarcoma. The vascular pattern, the degree of nuclear atypia, and occasionally the staining characteristics of the matrix indicate this distinction. An intricate vasculature suggests myxoid liposarcoma and myxoid malignant fibrous histiocytoma, instead of myxoid chondrosarcoma or myxoma.

1.5.3 Epithelioid Tumors

For the differential diagnosis of epithelioid soft tissue tumors, it is essential to rule out metastatic carcinoma, melanoma, and large-cell lymphomas in the first place. Immunohistochemistry plays a decidedly pivotal role in this regard.

1.5.4 Round Cell Tumors

Round cell tumor is not equivalent to round cell sarcoma, as some benign lesions (e.g., glomus tumor, tenosynovial giant cell tumor poor of giant cell) also enter the differential diagnosis. Some non-soft tissue malignancies that mimic round cell sarcomas (e.g., lymphoma, poorly differentiated carcinoma) should be excluded as well. In general, the age of the patient helps to reach the correct diagnosis of round cell sarcomas. In children, the most common sarcomas are neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma/primitive neuroectodermal tumor (Ewing/PNET), and the rare desmoplastic small round cell tumor. Most of these tumors would not be considered first in adults.

1.5.5 Pleomorphic Tumors

The differential diagnosis of pleomorphic sarcomas relies heavily on sufficient tumor sampling, in conjunction with immunohistochemistry, to identify regions of specific differentiation. Most

pleomorphic sarcomas are actually the extreme manifestation of other tumors, most common with carcinoma, melanoma, and lymphoma, which must be excluded. With the advances of immunohistochemistry and molecular approach, pleomorphic undifferentiated sarcoma (malignant fibrous histiocytoma) has been very rarely encountered.

1.5.6 Hemorrhagic and Vascular Lesions

Although sarcomas are generally highly vascularized, soft tissue lesions presenting as a hemorrhagic mass are limited, including nonvascular (non-endothelial) tumors. Conversely, many vascular tumors (e.g., intramuscular hemangiomas) do not appear hemorrhagic. When evaluating vascular lesions, it is necessary to ascertain whether the lesion is predominantly intravascular or extravascular. Intravascular lesions are always benign, including primarily organizing thrombus/hematoma followed by the occasional angiocentric vascular tumors. Extravascular lesions can be either benign or malignant; features that favor benignancy include sharp circumscription, lobular arrangement of vessels, and the presence of both large (thick-walled) and small vessels. On the other hand, angiosarcomas have irregular margins, lack a lobular arrangement of vessels, and are composed of naked endothelial cells that dissect randomly through tissue planes.

H&E-stained sections provide critical information on growth patterns, degree of cellularity, as well as amount and type of matrix. Growth patterns vary considerably among tumors, ranging from fascicular, herringbone, or storiform patterns in fibroblastic, myofibroblastic, and fibrohistiocytic tumors to plexiform or endocrine patterns, palisading, as well as Homer-Wright and Flexner-Wintersteiner rosettes in various benign and malignant neural tumors. Biphasic cellular patterns with epithelial and spindle cell areas are characteristic of synovial sarcoma and mesothelioma. Although growth patterns could not provide a definitive diagnosis, they help to narrow the various differential diagnostic possibilities.

In addition, the amount and type of extracellular matrix can aid in the differential diagnosis. Abundant myxoid material is produced by a variety of benign and malignant soft tissue tumors, for example, myxoma, myxoid neurofibroma, myxoid liposarcoma, and myxoid chondrosarcoma. Abundant myxoid is usually an indication of a relatively slow-growing tumor. The degree of myxoid change in some malignant tumors is inversely related to the metastatic potential (e.g., myxoid malignant fibrous histiocytoma, myxoid liposarcoma). Abundant collagen formation is more frequently observed in slowly growing tumors than in rapidly growing ones. However, this finding is not always significant and may be a prominent feature of some highly malignant fibrous histiocytomas and postirradiation sarcomas. Examination may provide information as to the presence of calcification and metaplastic changes, especially metaplastic cartilage and bone formation.

The degree and type of cellular differentiation can be determined under high-power examination. Lipoblasts are characterized by sharply defined intracellular droplets of lipid and centrally or peripherally placed round or scalloped nuclei. Round- and spindle-shaped rhabdomyoblasts can be identified in conventionally H&E-stained sections, characterized by deeply eosinophilic cytoplasm with whorls of eosinophilic fibrillary near the nucleus and cytoplasmic cross-striations. Caution is indicated because occasionally entrapped normal or atrophic fat or muscle tissue may closely resemble lipoblasts or rhabdomyoblasts, respectively. Differentiated smooth muscle cells are characterized by elongated shape, eosinophilic longitudinal fibrils, as well as long, slender (cigar-shaped) nuclei, with juxtanuclear vacuoles. Other spindle cells are even more difficult to identify. Distinguishing fibroblasts, myofibroblasts, Schwann cells, and the spindle cells of synovial sarcoma and mesothelioma usually relies on the location and growth pattern rather than on cytologic features. Correct identification of these cells usually relies on immunohistochemical staining. Intracellular inclusions are rare in soft tissue pathology; alveolar soft part sarcoma can be identified by intracellular periodic acid-Schiff (PAS)-positive crystalline material; and digital fibromatosis can

be identified by eosinophilic inclusions consisting of actin-like microfilaments.

Examination under high-power field [HPF] is essential for mitotic counts. Atypical mitotic figures are rare in benign soft tissue tumors, almost always indicating malignancy. Mitotic counts are pivotal for differentiating benign from malignant nerve sheath tumor or smooth muscle tumors; however, they are of little use for diagnosing nodular fasciitis, localized and diffuse giant cell tumors, or malignant fibrous histiocytoma. Although nuclear atypia is associated with malignancy, it may occur as a degenerative feature in benign lesions, such as in ancient schwannoma.

1.5.7 Immature Teratoma

Immature teratoma is usually seen in children and adolescents. It is composed of a mixture of embryonal and adult tissues derived from all three germ layers. Its major components are neuroepithelial and mesodermal elements. Some tumors are predominantly composed of endodermal derivatives, including the esophagus, liver, and intestinal structures. The grading systems of teratomas arising from ovary are as follows:

Grade I: Tumors with rare foci of immature neuroepithelial tissue that occupy <1 low-power field in any slide (low grade)

Grade II: Tumors with similar elements, occupying one to three low-power fields in any slide (high grade)

Grade III: Tumors with a large amount of immature neuroepithelial tissue occupying >3 low-power fields in any slide (high grade)

Obviously, thorough tumor sampling is necessary for this grading scheme; the amount of immature neuroepithelial tissue may be expressed as an estimated percentage of all the tissue examined microscopically. It is important to separate from this group the teratomas with yolk sac or embryonal carcinoma patterns.

1.5.8 Mature Solid Teratoma

Mature solid teratoma has a predominantly solid gross appearance, but multiple small cystic areas also are present. Clearly, extensive sampling is required to exclude the grade I immature teratoma.

1.5.9 Mature Cystic Teratoma

The cystic cavities are lined by mature epidermis. Skin appendages and neural (particularly glial) tissue are extremely common, followed by the cartilage, respiratory tissue, and gastrointestinal tract tissue. Other tissues include the thyroid, various types of melanin-containing tissue, anterior pituitary, various types of neuroendocrine cells, prostate, pancreas, and cavernous blood vessels. By definition, all of the components present in mature cystic teratomas should appear histologically mature. However, on occasions, microscopic foci of immature tissue can be visible, but less than one low-power field in any slide. The behavior of these tumors is usually benign.

1.5.10 Yolk Sac Tumor

Yolk sac tumor is generally a neoplasm of children and young adults. Microscopically, the appearance of yolk sac tumors is very variable. There are reticular or microcystic areas formed by a loose meshwork lined by flat or cuboidal cells, rounded or festooning pseudopapillary processes with central vessels (Schiller-Duval bodies), and solid undifferentiated areas. The mesenchyme-like component has pluripotent properties.

1.5.11 Embryonal Carcinoma

Embryonal carcinoma occurs in children and adolescents (with a median age of 15 years). Microscopically, it looks similar to the embryonal carcinoma of the testis, composed of solid sheets and nests of large primitive cells, occasionally forming papillae and abortive glandular structure. Syncytiotrophoblast-like tumor cells are frequently seen scattered among the smaller cells, immunoreactive for HCG.

1.6 Immunohistochemistry

H&E-stained sections represent the main approach of diagnosis, but usually require the support of ancillary techniques. Immunohistochemistry is the ancillary modality of choice for most diagnostic situations. To use immunostains in the most effective way, it is useful to have an algorithmic approach and to apply the markers in

panels. For example, a panel of antibodies to differentiate carcinomas, melanomas, sarcomas, and lymphomas from one another would be selected before a series of B- and T-cell markers.

1.7 Molecular Pathology

1.7.1 Genetic Profiling

Genetic profiling has been applied into the study of retroperitoneal tumors, including comparative genomic hybridization (CGH) and gene expression arrays. Antoine Italiano's study found that among soft tissue leiomyosarcomas, retroperitoneal leiomyosarcomas represent a specific clinical and molecular entity (Italiano et al. 2013). Indeed, in comparison with leiomyosarcomas of the extremities, retroperitoneal leiomyosarcomas are characterized by a higher risk of metastasis and a distinct genomic and expression profile. Most of the genes overexpressed in retroperitoneal leiomyosarcomas encode proteins involved in muscle differentiation. On the contrary, non-retroperitoneal leiomyosarcomas are characterized by overexpression of genes encoding proteins mainly involved in extracellular matrix, wounding, and adhesion pathways.

1.7.2 Fluorescence In Situ Hybridization (FISH)

Fluorescent in situ hybridization (FISH) is a powerful technique using fluorescent labeled DNA probes to target the given sequences within a nucleus, resulting in colored signals that are detected with a fluorescence microscope. It circumvents the needs for tumor cell culture (fresh or paraffin-embedded interphase nuclei can be analyzed directly) and provides a quick and precise screening approach over large quantities of cells.

It should be emphasized that for certain tumors, FISH studies are essential to make the diagnosis or help to predict its clinical behavior. For example, FISH is highly recommended for childhood neuroblastoma to measure N-myc amplification and for alveolar rhabdomyosarcoma to measure FOXO1 gene rearrangement (Bhargava et al. 2005).

1.7.3 DNA Sequencing

DNA sequencing is essential for some soft tissue tumors, for example, to check c-kit and PDGFRA gene mutation status in the gastrointestinal stromal tumors (GIST) especially when target therapy is applied.

1.7.4 Next-Generation Sequencing

As a revolutionary change to the traditional method, next-generation sequencing is a high-throughput sequencing technology, in which hundreds of thousands to millions of DNA molecules can be sequenced at the same time. High-throughput sequencing obtains a detailed picture of a species transcriptome, also known as deep sequencing. Next-generation sequencing offers a cost-efficient tool for analyzing hundreds of exons. Jenny Welander revealed that a germline mutation (c.223C_T, p.Arg75X) in *SDHA* gene in paraganglioma was validated by Sanger sequencing (Welander et al. 2013).

2 Techniques in Pathological Diagnosis of Various Retroperitoneal Tumors

Retroperitoneal tumors mostly originate from kidneys, adrenal gland, retroperitoneal lymph nodes, and soft tissues. They have a wide range of histological manifestations. Various subtypes often display overlapping morphological features; therefore, pathological techniques such as special staining, immunohistochemistry, and molecular testing are required to further confirm the diagnosis (Frans Graadt Van Roggen and Hogendoorn 2000).

2.1 Special Staining

Specific elements such as mucus, glycogen, collagen fibers, reticular fibers, and secretory granules can be revealed by special staining, which plays an important role in the differential diagnosis of retroperitoneal tumors. For example, characteristic periodic acid-Schiff (PAS)-positive needlelike crystals are visible in the alveolar soft tissue sar-

comas. Reticular fiber is stained to differentiate cancer and sarcomas; PTAH staining is used to label tumors with striated muscle differentiation.

2.2 Immunohistochemical Staining

Retroperitoneal tumors include a wide range of pathologic types and exhibit a variety of histological features. Immunohistochemistry plays a pivotal role in diagnosis and differential diagnosis, especially for poorly differentiated soft tissue tumors with atypical morphology. However, due to inherent limitations of immunohistochemistry, a comprehensive diagnosis should be made based on a combination of histological classification, special staining, and molecular genetic testing:

1. Epithelial markers, including epithelial membrane antigen (EMA) and cytokeratin (CK), are expressed in a number of biphasic tumors (such as synovial sarcoma, mesothelioma, and epithelioid sarcoma) and poorly differentiated tumors (such as malignant peripheral nerve sheath tumors, high-grade sarcoma-like renal carcinoma, and nephroblastoma) (Miettinen et al. 2000).
2. Mesothelial markers mainly include calretinin, D2-40, CK5/6, WT1, and mesothelin. D2-40 is used to label mesothelial and lymphatic endothelial cells assisting in the diagnosis of lymphangioma, Kaposiform hemangioendothelioma, Kaposi's sarcoma, and mesothelioma (Chu et al. 2005; Ordonez 2005).
3. Endothelial cell markers include CD31, CD34, D2-40, factor VIII-related antigen, and Fli-1. CD31 is mainly used to identify vascular neoplasms, whereas it is also expressed in macrophages, megakaryocytes, and small lymphocytic lymphoma. CD34 is often used to label blood vessels and lymphatic vessels for diagnosis of vascular tumors; it also aids in the diagnosis of lipoma, solitary fibrous tumor/hemangiopericytoma, dermatofibrosarcoma protuberans (DSFP), epithelioid sarcoma, and gastrointestinal stromal tumors (GIST) (Hasegawa et al. 1996). CD34 is also expressed in multiple soft tissue tumors, such as neurofibromatosis, dendritic fibromyxoid lipomas and spindle cell lipoma (Alawi and Freedman 2004; McNiff et al. 2005).
4. Nerve cell markers include S100, MBP, CD57, NSE, NF, GFAP, CgA, Syn, and calretinin (Gray et al. 1989). S100 is used to label neurogliocytes, Schwann cells, melanocytes, fat cells, myoepithelial cells, cartilage cells, Langerhans cells, and dendritic cells. S100-positive staining is localized in the nucleus and cytoplasm.
5. Muscle cell markers include desmin, MyoD1, myogenin, muscle-specific actin (MSA), smooth muscle actin (SMA), caldesmon, calponin, and myoglobin. Desmin is widely used in the diagnosis of tumors arising from striated and smooth muscles. It is also use to label tumors containing rhabdomyoblastic differentiation and myoblast component, such as malignant triton tumor, carcinosarcoma, fibroepithelial polyp, inflammatory myofibroblastic tumor, aggressive angiomyxoma, and malignant fibrous histiocytoma/undifferentiated sarcoma. Desmin can be used in the differential diagnosis of gastrointestinal smooth muscle tumors and stromal tumors. In desmoplastic small round cell tumor, typical desmin-positive punctate staining adjacent to the nucleus has diagnostic value. Myogenin and MyoD1 are used to label most of rhabdomyosarcomas and tumors containing striated muscle component. MSA mainly labels smooth muscle cells, vascular pericytes, striated muscle cells, and epithelial cells, and therefore, it is usually used for the diagnosis of leiomyoma, leiomyosarcoma, glomus tumor (angioneuromyoma), myoepithelioma, and rhabdomyosarcoma.
6. Histiocytic and dendritic cell markers include CD68, lysozyme, α1-antitrypsin, α1-antichymotrypsin, S100 protein, CD163, CD1a, CD21, CD23, and CD35.
7. Melanocyte and perivascular epithelioid cell markers include HMB45, melan-A, tyrosinase, S100 protein, and CD63.

8. Other markers: CD117 is a marker for gastrointestinal stromal tumor (GIST) cells, mast cells, and malignant melanoma. DOG1 and PDGFRA are used for the diagnosis of GIST. CD99 is mainly used to label synovial sarcoma, as well as bone Ewing's sarcoma/peripheral primitive ectoderm tumors. BCL-2 is mainly used to label solitary fibrous tumors, synovial sarcoma, Kaposi's sarcoma, and GIST (Hasegawa et al. 1996). ALK is used for inflammatory myofibroblastic tumor. Overexpression of EGFR correlates with a poor prognosis of sarcomas.

2.3 Electron Microscope

Since it can be used to observe the ultrastructure of cells, electron microscope plays an important role in the diagnosis of tumors. For example, a lipid droplet is visible near the squeezed nucleus in liposarcoma; pinocytosis vesicles in Langerhans cell histiocytosis and Birbeck granules in the cytoplasm are characteristic in Langerhans cell sarcoma; and numerous intertwined columnar protrusions on the cell surface are features of interdigital dendritic cell sarcoma.

2.4 Oncogenes and Tumor Suppressor Genes

Oncogenes and tumor suppressor genes play key roles in the formation, growth, and differentiation of tumors. Overgrowth of malignant cells results from activation of oncogenes and inhibition of tumor suppressor genes (negative regulators). Oncogenes and tumor suppressor genes are essential to the diagnosis and prognosis of soft tissue tumors. Those genes include *EWS* and related genes, *SYT*, *SSX*, *PAX*, *FKHR*, *protein tyrosine kinase*, *ASPL*, *TFE3*, *ALK*, and *NTRK3* (Argani et al. 2010). *EWS-FLI1* fusion gene arising from Ewing's sarcoma enables antiapoptosis of tumor cells. *SYT-SSX* fusion genes can be detected in synovial sarcomas, of which *SYT-SSX1* indicates high proliferation and a poor prognosis, whereas *SYT-SSX2* is suggestive of a relatively better prognosis.

2.5 Fluorescence In Situ Hybridization (FISH)

FISH can be used to detect specific DNA or RNA in tumor tissue on sections or smears using fluorescent-labeled complementary probes, so that the corresponding chromosomal segments or a whole chromosome can be displayed under a fluorescence microscope. FISH can detect cells in metaphase and interphase, to effectively quantify chromosomal translocations, deletions, and gene amplifications.

In soft tissue tumors, chromosomal translocation can be detected by both break-apart and dual fusion probes. It is used for diagnosis and differential diagnosis of various soft tissue tumors. For example, fusion between the *SYT* gene located on chromosome 18 and the *SSX* gene located on the X chromosome occurs in more than 90% of synovial sarcoma; thus, *SYT-SSX* fusion gene is of great diagnostic value.

3 Pathological Classification of Retroperitoneal Tumor

A variety of benign and malignant lesions, either primary or metastatic, can be found in the retroperitoneum, while malignant tumors occur four times more frequently than benign lesions. Primary retroperitoneal tumors can be of many types. Soft tissue sarcomas are rare tumors, with retroperitoneal sarcoma representing the second most common sites of origin of malignant mesenchymal tumors after the lower extremities. Sarcomas account for 90% of primary retroperitoneal malignancies, with liposarcoma and leiomyosarcoma making up more than 80% of these tumors. As a group, retroperitoneal soft tissue sarcomas are associated with a poor long-term survival rate. The main reason is the extreme difficulty encountered in performing a complete surgical removal with a rim of normal tissue around the tumor. Complete surgical excision at the time of the initial presentation offers the best chance of long-term survival.

The large majority of the retroperitoneal malignant lymphomas are of non-Hodgkin type

and B-cell derivation. Most are follicular center cell lymphomas. These tumors can be diagnosed by fine needle aspiration, supplemented if necessary by immunostaining.

3.1 Adipose Tissue Tumors

Adipose tissue tumors are the most frequent primary retroperitoneal soft tissue neoplasms. They are particularly prone to arise and grow in the perirenal region. At the time of excision, they are usually extremely large. Some cases present as multiple independent tumor nodules. Liposarcomas in this location present a worse prognosis than those located in the extremities. Total or near-total excision followed by radiation therapy offers the best chance of cure. Histologically, liposarcoma is classified into four subtypes with an increase in malignant nature: well-differentiated, dedifferentiated, myxoid/round cell, and pleomorphic.

The large majority of retroperitoneal liposarcomas are of well-differentiated type (also called atypical lipomatous tumors) or of dedifferentiated type. Myxoid liposarcomas are practically nonexistent at this site; before making this diagnosis, the alternative possibility of a well-differentiated tumor with secondary myxoid changes should be considered. A certain proportion of well-differentiated liposarcoma of the retroperitoneum (higher than at other sites) undergo dedifferentiation, sometimes associated with divergent differentiation in the form of rhabdomyosarcoma (Fig. 5.1). In the presence of a pleomorphic and not easily classifiable retroperitoneal sarcomas, this possibility should be considered, and sampling of the adjacent areas searching for well-differentiated liposarcoma elements (which may look grossly like normal fat) should be carried out. Indeed, the majority of retroperitoneal tumors diagnosed as malignant fibrous histiocytomas represent dedifferentiated liposarcomas. When theses tumors metastasize, the clinical course is rapidly fatal.

Truly benign lipomas of the retroperitoneum are very rare. They are usually very large at the time of diagnosis and can be multiple. Any adipose tissue tumor of the retroperitoneum with atypical features should be designated as well-differentiated liposarcoma, no matter how focal these features are, in view of its marked tendency for recurrence and poor long-term prognosis.

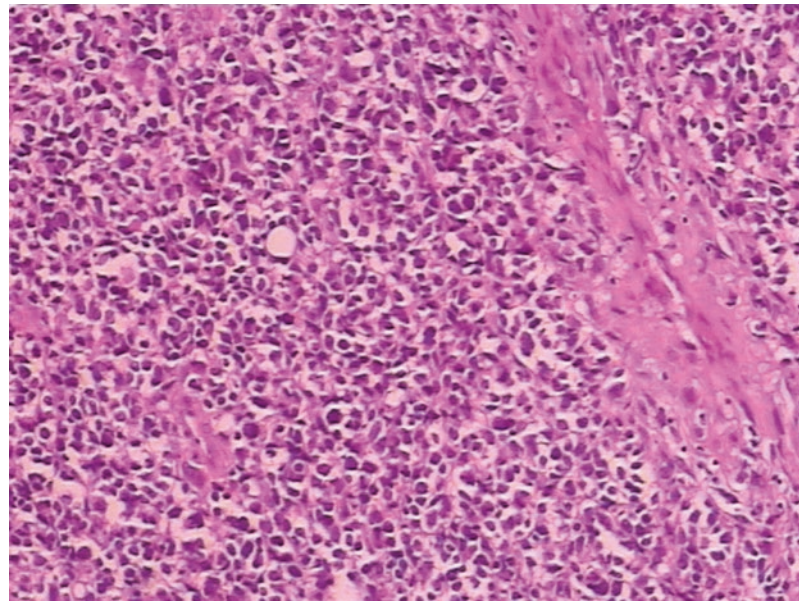

Fig. 5.1 Dedifferentiated liposarcoma, with the component of rhabdomyosarcoma

3.2 Pleomorphic Sarcoma

Pleomorphic sarcoma is the second most common retroperitoneal sarcoma. Three histological subtypes have been identified: undifferentiated high-grade, giant cell, and inflammatory pleomorphic sarcoma. The latter two are usually considered low-grade sarcomas. It is inadvisable to classify these deep-seated lesions as benign no matter how bland their microscopic appearance may be, in view of the fact that some of them will result in repeated recurrences and even metastases.

3.3 Leiomyosarcoma and Leiomyoma

Leiomyosarcoma is the third most common sarcomas, with a particular tendency to undergo massive cystic degeneration when occurring in the retroperitoneal region (Bharti et al. 2014). Retroperitoneal smooth muscle tumors containing ≥5 mitoses per 50 high-power fields should be classified as leiomyosarcomas. Tumor cell necrosis or a tumor size >10 cm is strongly suggestive of malignancy, even in the presence of a low mitotic count. When these criteria are applied to retroperitoneal tumors, nearly all of them qualify as leiomyosarcomas (Fig. 5.2). The local control is obtained with wide surgical excision and neoadjuvant or adjuvant radiation therapy. Chemotherapy is employed for the treatment of systemic disease. Peculiar morphologic variations in retroperitoneal leiomyosarcoma are granular cell changes and focal skeletal muscle differentiation.

Previous series focusing on retroperitoneal sarcomas have shown the higher metastatic risk of leiomyosarcomas in comparison with other retroperitoneal histologic subtypes including liposarcomas.

Leiomyoma is very rare as a primary retroperitoneal neoplasm. When encountering a tumor in this region with a leiomyomatous appearance, one should consider the alternative possibilities of uterine leiomyoma extending posteriorly, well-differentiated leiomyosarcoma, benign or malignant GIST, lymphangiomyoma, and angiomyolipoma. The majority of truly benign smooth muscle tumors presenting as retroperitoneal masses are anatomically and/or functionally related to the female genital tract.

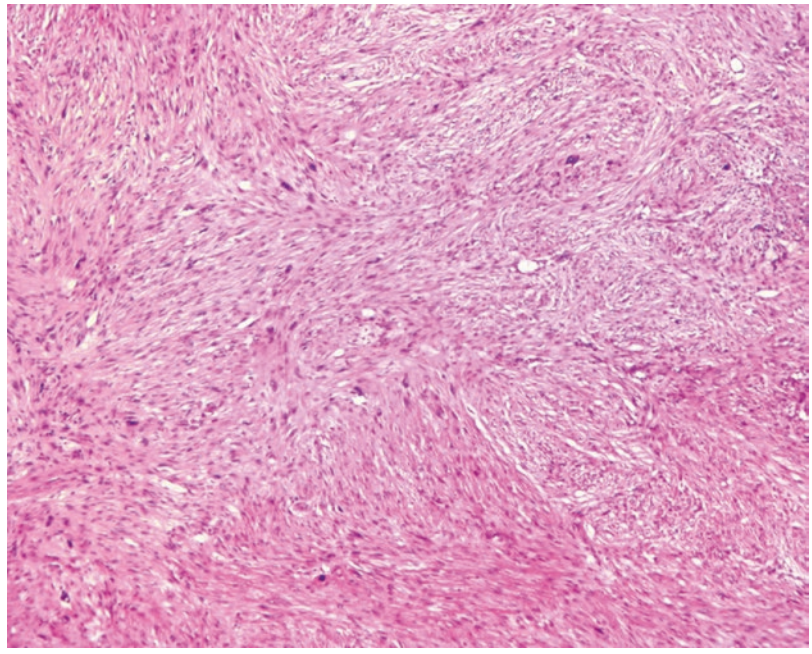

Fig. 5.2 Leiomyosarcoma

3.4 Renal Angiomyolipoma

Renal angiomyolipoma is a generally benign retroperitoneal tumor that can be easily confused with leiomyosarcoma in a biopsy specimen due to the atypia commonly seen in the smooth muscle elements (Fig. 5.3). The primarily intrarenal location, the admixture with mature fat and thick-walled blood vessels, and the immunoreactivity for HMB-45 should allow the recognition of this entity. Primary extrarenal examples of this tumor do exist; some of them are epithelioid and malignant.

3.5 Rhabdomyosarcoma

Rhabdomyosarcoma of the retroperitoneum is usually of the embryonal type (including its botryoid variety) and rarely of the alveolar type and mostly affects infants, children, and young adults. The differential diagnosis of retroperitoneal rhabdomyosarcoma includes malignant lymphoma, Ewing's sarcoma/PNET, and (intra-abdominal) desmoplastic small cell tumor. Adults are uncommonly afflicted with rhabdomyosarcoma (Simon et al. 2003). Local control is important in the curative treatment of adult RMS. Adult RMS carries a much worse prognosis compared to childhood RMS.

3.6 Rhabdomyoma

Rhabdomyoma is practically nonexistent in the retroperitoneum; however, a convincing case combining features of the fetal and adult types of this tumor has been reported in neonate (Whitten and Benjamin 1987).

3.7 Fibromatosis

Fibromatosis may occur in association with mediastinal involvement (Casillas et al. 1991). It is characterized by fibroblastic proliferation that disrupts soft tissue planes. This process occurs without any inflammation or signs of definite neoplasia.

In contrast to idiopathic retroperitoneal fibrosis (a disorder with which it is often confused), it lacks a prominent inflammatory component, except for perivascular lymphocytic cuffing at the growing edge.

3.8 Solitary Fibrous Tumor

Solitary fibrous tumor (SFT) can present as a primary retroperitoneal mass, accompanied by hypoglycemia (Demicco et al. 2012). The solitary fibrous tumor is a distinct spectrum of

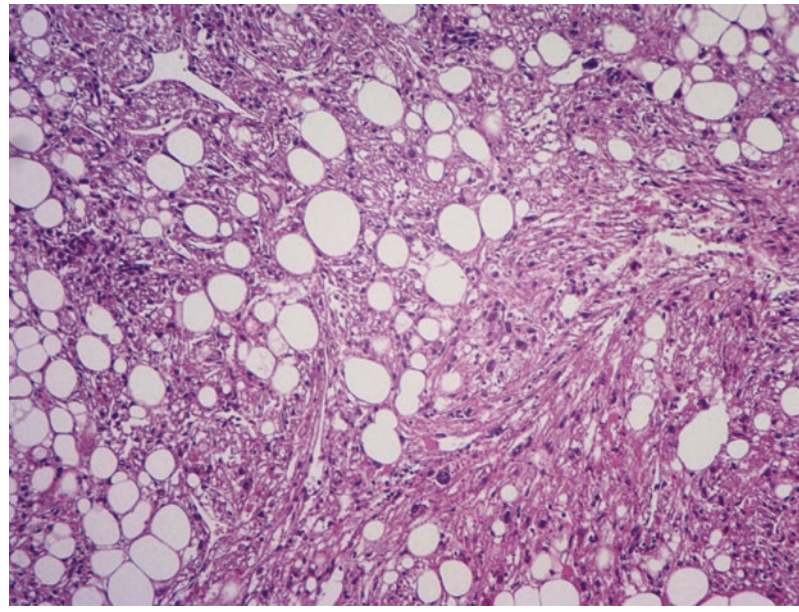

Fig. 5.3 Angioleiomyolipoma

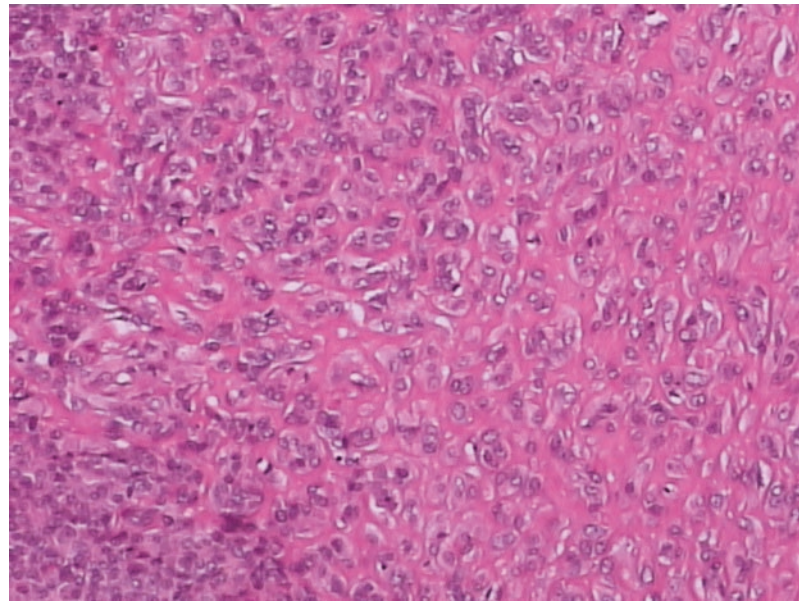

Fig. 5.4 Malignant solitary fibrous tumor

mesenchymal tumors, of which hemangiopericytoma is considered as a phenotypic variant. This tumor is composed of variably pleomorphic spindle cells admixed with collagen. The tumor is CD34 positive, with a dilated "staghorn"-like vascular network (Hasegawa et al. 1996). The solitary fibrous tumor is categorized as intermediate biological potential with low risk of metastasis and a relatively indolent course. The diagnostic criteria of malignant solitary fibrous tumors (MSFTs) (Fig. 5.4) include high cellularity, high mitotic activity (>4/10 HPF), pleomorphism, hemorrhage, and necrosis (England et al. 1989; Ito et al. 2008). Metastasis may occur even in benign SFTs. Even if the histological diagnosis of SFT is malignant, complete excision of the tumor is thought to have a favorable prognosis.

3.9 Vascular Tumors

Vascular tumors include hemangioma, lymphangioma, lymphangiomyoma, and angiosarcoma. Some of the angiosarcomas are of the epithelioid pattern (Fig. 5.5); prominent eosinophilic globules may be present in the cytoplasm of the tumor cells. A peculiar variant of infantile hemangioendothelioma mimicking Kaposi's sarcoma, accompanied by thrombocytopenia and hemorrhage (Kasabach-Merritt syndrome), has a special tendency for a retroperitoneal location.

3.10 Peripheral Nerve Tumors

Peripheral nerve tumors (PNSTs) of both benign and malignant types occur; as a matter of fact, the retroperitoneum is a relatively common site for their development. The benign tumors include schwannomas, neurofibromas, and (rarely but diagnosed with increasing frequency) perineuriomas. Malignant peripheral nerve tumors (MPNSTs) usually present as paraspinal masses and tend to behave in an aggressive fashion. They may directly invade the bone and metastasize distantly.

Synovial sarcoma, alveolar soft part sarcoma, extraskeletal osteosarcoma, and endometrial stromal sarcoma can present as primary retroperitoneal neoplasms.

3.11 Germ Cell Tumors

Primary extragonadal germ cell tumors are rare, accounting for approximately 5% of all primary retroperitoneal tumors (Su et al. 2012).

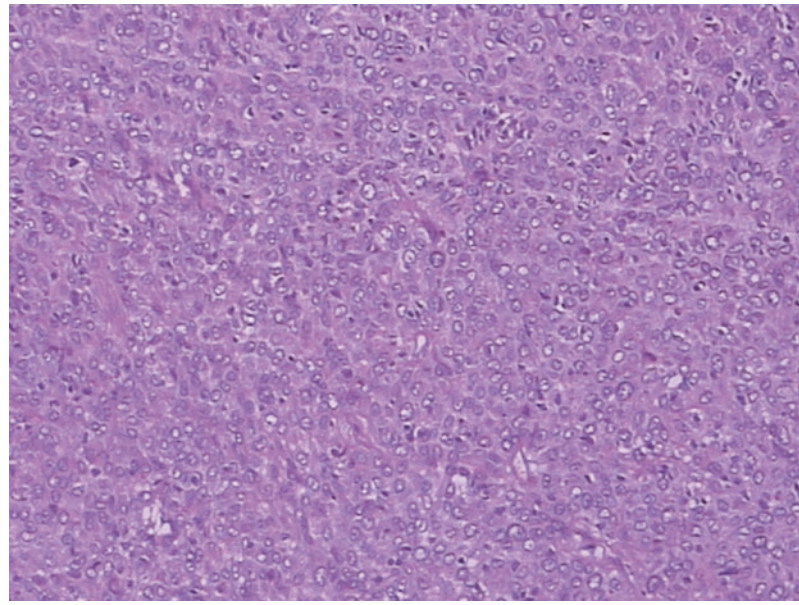

Fig. 5.5 Epithelioid hemangioendothelioma

The retroperitoneum is the second most common extragonadal sites for germ cell tumors, after mediastinum. Primary extragonadal germ cell tumors are predominantly non-seminomatous in histology.

Retroperitoneal germ cell tumors in children are represented by mature and immature teratoma, embryonal carcinoma, and yolk sac tumor. These tumors may occur in combination. Their features merge with those of sacrococcygeal teratomas.

Retroperitoneal germ cell tumors in adults can theoretically arise in this location or represent metastases from primaries in the gonads. Both types are much more common in males. The entire microscopic gamut includes seminoma (germinoma), embryonal carcinoma, teratocarcinoma, mature and immature teratoma, yolk sac tumor, and choriocarcinoma.

The chances of a retroperitoneal germ cell tumor in a male being metastatic from a small insidious testicular primary tumor are much higher than for a mediastinal tumor of the same type. The gross appearance of the tumor may give a clue in this regard: primary retroperitoneal neoplasms are formed by a single mass, whereas those metastatic from the testis tend to involve several nodes, often on both sides of the peritoneum. Also, seminomas are more likely to be primary than non-seminomatous germ cell tumors.

3.12 Other Primary Tumors and Tumorlike Conditions

3.12.1 Sympathetic Nervous System Tumors

Sympathetic nervous system tumors arise from adrenal sympathetic nervous system or outside the adrenal gland in the retroperitoneum, including neuroblastoma, ganglioneuroblastoma, ganglioneuroma and their variants. Retroperitoneal paragangliomas are originated outside of adrenal glands, accounting for 10% of paragangliomas. They may occur anywhere along the midline of the retroperitoneum.

3.12.2 Malignant Lymphoma

Malignant lymphoma can primarily arise from retroperitoneum and mostly belong to B-cell-derived non-Hodgkin's lymphoma. The major subtype is follicular lymphoma with prominent fibrosis.

3.12.3 Myelolipomas

Myelolipomas similar to those of the adrenal glands can be encountered in the presacral area. They are well circumscribed, can attain a huge size, and are composed of a mixture of fat cells and normal marrow hematopoietic elements.

3.12.4 Tumors of Mullerian Type

Tumors of mullerian type including mixed mullerian malignant tumor (mullerian carcinosarcoma) are occasionally seen as primary retroperitoneal masses in the pelvis or rectovaginal septum. They can be of serous, mucinous, or endometrioid subtype, either benign, borderline, or malignant.

3.12.5 Metastatic Tumors

Secondary neoplasms may appear in the retroperitoneal space as a result of local extension or lymph node involvement. The former is mainly represented by pancreatic carcinoma and primary bone neoplasms, notably sacrococcygeal chordoma.

The carcinomas most commonly giving rise to retroperitoneal lymph node metastases are those originating in the testis, prostate, pancreas, uterine cervix, endometrium, and kidney.

4 Grading and Staging of Soft Tissue Sarcomas

Besides histologic classification and subclassification, the grading and staging systems also provide important clues for predicting the biological behavior of soft tissue sarcomas. Grading is a useful tool for assessing the degree of malignancy based on histological indicators, whereas staging is determined by the scope of tumor involvement. Criteria for staging are relatively constant, whereas those for grading vary greatly depending on the types of tumors. For example, mitotic activity is important for the grading of leiomyosarcomas but not for the undifferentiated pleomorphic sarcomas.

4.1 Grading System of Soft Tissue Sarcomas

Grading of soft tissue tumors was first proposed specifically for fibrosarcomas by Borders et al. (1939). Studies over the years have emphasized the value of grading and identified necrosis and mitotic activity as its vital criteria. In a case study involving 1000 patients, the integration of grading with staging was proved to be an essential guide for predicating prognosis. Importantly, the study indicated that clinical staging would be determined basically by grading if no metastasis had occurred. Pitifully, a reliable grading system was not proposed in this study where grading was only judged subjectively according to the professional's experience. However, this study has proposed a concept that is still well-accepted today—some sarcomas are low grade in nature, while others are high grade essentially. This concept is not substantially fit for epithelial malignancies, in which precancerous lesions are commonly present.

Since then, a number of grading systems have been proposed internationally by Myrhe Jensen, Costa, Hashimoto, Van Unnik, Gustafson, and Markhede. Tumors are divided into two to four grades in some systems with individual strengths and weaknesses. None has been adopted by the World Health Organization (WHO), while the most common system used in China is the French grading which is proposed by Trojani et al. and improved by the French Federation of Cancer Centers Sarcoma Groups (FNCLCC), referred to as "FNCLCC grading" (Coindre et al. 1996; Stoeckle et al. 2001).

The FNCLCC grading system has integrated three parameters: tumor differentiation, mitotic index, and tumor necrosis. Grading is calculated by summing up the scores obtained for each of these parameters (Table 5.1). It has been shown that tumor grading is an independent and the most important prognostic factor. However, this system also has some limitations, including the determination of "differentiation score," due to difficulty in defining a well-differentiated vs. undifferentiated sarcoma, especially for specimens in response to chemotherapy.

Table 5.1 FNCLCC grading system

Parameter	Criteria
Tumor differentiation	Tumor differentiation
1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., well-differentiated liposarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of uncertain type (e.g., undifferentiated pleomorphic sarcoma)
Mitosis count	/10HPF
1	0–9
2	10–19
3	≥20
Tumor necrosis (under microscopy)	
0	No necrosis
1	≤50% tumor necrosis
2	>50% tumor necrosis
Histologic grade	Sum/total score
1	2–3
2	4–5
3	6–8

Additionally, none of the grading systems can be widely accepted because of specific characteristics of sarcomas. As mentioned before, it seems unnecessary to categorize some sarcomas of either low-grade malignancy or high-grade malignancy in nature. For example, well-differentiated liposarcoma itself is a low-grade and nonmetastatic tumor, whereas alveolar rhabdomyosarcoma itself is highly malignant. Another limitation of the system is the difficulty in grading rare sarcomas, such as epithelioid sarcomas. Moreover, clinical features of some tumors have more prognostic significance than histologic grading. Thus, the relevance between grading and biological behavior is significantly reduced. For example, the number and size of the lesions play a more important role than grading in predicting the prognosis of skin angiosarcomas.

Nevertheless, grading remains the most effective and economical tool in assessing the prognosis of sarcomas. Tumor specimens should be obtained prior to neoadjuvant therapy in order to avoid the effects of chemotherapy on grading parameters.

4.2 Staging System of Soft Tissue Tumor

Staging system refers to stratification of similar tumors based on histological grade, size, and location of tumors, as well as the presence or absence of distant metastases, to facilitate both prognostic evaluation and efficacy assessment. For adults with soft tissue sarcomas, the AJCC staging system developed by the American Joint Committee on Cancer is commonly used, which classifies soft tissue sarcomas with tumor size, lymph node involvement, presence of distant metastases, histologic subtype and grade, as well as invasive depth. Other staging systems include the Musculoskeletal Tumor Society staging system and the SIN staging system.

The disadvantage of the AJCC system is the difficulty in comparing various tumors originating from different sites, because it classifies tumors based on their individual lesions. The extent of resection during the surgery varies with the specific site of the tumor. Staging of soft tissue sarcomas requires a close multidisciplinary cooperation.

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