Diagnostically Challenging "Fatty" Retroperitoneal Tumors

Karen J. Fritchie, MD*

KEYWORDS

• Adipocytic • Fatty • Retroperitoneal • Sarcoma • Liposarcoma

ABSTRACT

A variety of benign and malignant retroperitoneal mesenchymal lesions may have a component of adipose tissue, including entities such as lipoma, myolipoma, angiomyolipoma, solitary fibrous tumor, genital stromal tumors, and well-differentiated/dedifferentiated liposarcoma. Although definitive diagnosis is usually straightforward on the complete resection specimen, it is often more difficult to workup these lesions on small biopsy samples. This review focuses on challenging diagnostic scenarios of retroperitoneal lesions with a "fatty" component and provides major differential diagnoses for commonly encountered morphologic patterns, clinicopathologic features of the various entities, and strategy for use of ancillary techniques, such as immunohistochemistry and cytogenetic studies.

OVERVIEW

One of the most commonly encountered specimens in soft tissue consultation practice is the biopsy or resection of a retroperitoneal mass. Oftentimes these specimens harbor a component of fat. Although the differential diagnosis of a "fatty" retroperitoneal tumor includes well-differentiated liposarcoma and dedifferentiated liposarcoma, it is also important to consider benign entities, such as lipoma, myolipoma, angiomyolipoma, the lipomatous variant of solitary fibrous tumor, and genital stromal tumors.

There are 4 main rules that pertain to this topic (Key Points). The first 3 are critical in the workup of any adipocytic tumor, and the fourth applies to retroperitoneal sarcomas. Not only do these rules provide a starting point in the evaluation of these cases, but they also keep the pathologist out of trouble. The first rule is location, location, location. Although not absolute, superficial fatty tumors are often benign, whereas those occurring in deep soft tissue (intramuscular, retroperitoneal, groin, mediastinum) are more likely to be malignant. This rule is especially true in the retroperitoneum, as well-differentiated/dedifferentiated liposarcoma should be on the differential diagnosis of virtually every lipomatous mass at this site.

Key Points

1. Location: Superficial (above the fascia) fatty tumors are typically benign, whereas those occurring in deep soft tissue (intramuscular, retroperitoneum, groin, mediastinum) are more worrisome for malignancy.
2. Do not look for lipoblasts. The diagnostic cell of well-differentiated liposarcoma is the atypical hyperchromatic stromal cell.
3. Most fatty tumors have recurrent cytogenetic aberrations.
4. The main differential diagnosis of a retroperitoneal sarcoma is well-differentiated liposarcoma, dedifferentiated liposarcoma, and leiomyosarcoma.

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Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street, Southwest, Rochester, MN 55905, USA

* Department of Anatomic Pathology, Mayo Clinic, Hilton 11, 200 First Street, Southwest, Rochester, MN 55905.

E-mail address: fritchie.karen@mayo.edu

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The second rule of fatty tumors is, do not look for lipoblasts. Searching for lipoblasts is a time sink that does more harm than good. Lipoblasts are neoplastic cells that recapitulate the development of normal fat (**Fig. 1**A). It is important to realize that lipoblasts may be found in both benign and malignant fatty tumors. Except for the diagnosis of pleomorphic liposarcoma, lipoblasts are not requisite for the diagnosis of liposarcoma. Furthermore, many cell types, including atrophic adipocytes (see **Fig. 1**B), vacuolated histiocytes (see **Fig. 1**C), and signet-ring cell carcinomas (see **Fig. 1**D), can mimic lipoblasts, leading to diagnostic chaos. The key cell of atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma is the atypical hyperchromatic stromal cell (see **Fig. 1**E).

Most lipomatous tumors harbor chromosomal aberrations, and the third rule is that we can often exploit these cytogenetic findings, especially on small biopsy specimens. Atypical lipomatous tumors/well-differentiated liposarcoma and dedifferentiated liposarcoma have giant and ring chromosomes with 12q13–15 amplicons containing genes such as *MDM2* and *CDK4*, whereas lipomas do not.[1] Consequently, the identification of *MDM2* amplification by fluorescence in situ hybridization (FISH) is a sensitive and specific tool in the evaluation of well-differentiated fatty tumors (lipoma vs atypical lipomatous tumor/well-differentiated liposarcoma), and this technique is especially helpful with limited tissue (**Fig. 2**).[2,3] Although *MDM2*/*CDK4* amplification also may be detected by immunohistochemistry, FISH studies may be preferable due to occasional nonspecific staining and lower sensitivity and specificity encountered with CDK4 and MDM2 immunostains.[3] Approximately 75% of lipomas have abnormal karyotypes, with translocations involving the region of 12q13–15 (*HMGA2* locus) being the most common finding; other benign lipomatous tumors that are occasionally found in the retroperitoneum, such as hibernoma, lipoblastoma, and myelolipoma, also have chromosomal aberrations.[4–7] Because it often is not possible to look for these abnormalities because of lack of readily available FISH probes, sending fresh tissue for cytogenetic analysis from the resection of any lipomatous neoplasm may yield helpful information.

The last important rule to consider is the differential diagnosis of a retroperitoneal sarcoma, and by far the most common entities include well-differentiated liposarcoma/dedifferentiated liposarcoma and leiomyosarcoma. Although other sarcomas may occur at this location, the pathologist should consider the former diagnoses before entertaining other ideas.

The remainder of this review emphasizes these key principles while discussing frequent morphologic patterns of retroperitoneal masses with an adipocytic component.

PATTERN 1: MATURE ADIPOSE TISSUE AND ATYPICAL HYPERCHROMATIC STROMAL CELLS

This scenario is commonly seen on biopsy and resection specimens of adipocytic lesions in the retroperitoneum. Morphologic review shows mature adipocytes admixed with variable amounts of atypical spindled cells with hyperchromatic and smudgy nuclei (**Fig. 3**A). Some of the atypical cells may have a floretlike multinucleated appearance (see **Fig. 3**B).

When one encounters a retroperitoneal mass harboring these features, it is helpful to recall the rules mentioned earlier. First, the fatty mass is at a deep site (retroperitoneum), which should trigger the pathologist to think about well-differentiated liposarcoma. Second, the diagnostic cell type (atypical hyperchromatic stromal cell) has been identified, confirming the diagnosis of well-differentiated liposarcoma. Note that in this situation we do not need lipoblasts or ancillary testing for diagnosis. Be aware that fat necrosis is common in lipomatous lesions and may raise concern for malignancy (Pitfall: Fat necrosis). Although foci of fat necrosis can be quite cellular, the components include histiocytes, fibroblasts, and inflammatory cells without cytologic atypia (**Fig. 4**).

Pitfalls

Fat necrosis

! Fat necrosis is common in adipocytic tumors

! Fat necrosis shows a mixed population of fibroblasts, histiocytes, and inflammatory cells without atypia

! Be careful not to misinterpret cells in fat necrosis as atypical hyperchromatic stromal cells

! Histiocytes are often positive for MDM2 by immunohistochemistry; therefore, it is advised that both MDM2 and CDK4 immunostains are used in conjunction, as histiocytes are negative for CDK4