Soft Tissue Tumors with Lipocytic Differentiation

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Lipomatous tumors are among the most commonly encountered tumors in soft tissue pathology. Although the vast majority of such lesions are lipomas and easily diagnosed, there are a number of lipomatous tumors (both benign and malignant) that are diagnostically challenging to the general surgical pathologist and the dermatopathologist. In fact, dermatopathologists very frequently encounter difficult lipomatous neoplasms, and it has been my own personal experience that a high proportion of consultation cases I review are unusual or difficult to diagnose lipomatous neoplasms excised by dermatologists and reviewed by dermatopathologists.

There are a number of benign lipomatous tumors that have unusual features which can make the pathologist believe one is evaluating a liposarcoma (or possibly even some other type of sarcoma). Similarly, there are some malignant lipomatous tumors (e.g. atypical lipomatous tumor/well-differentiated liposarcoma) that are easily mistaken for a lipoma. This presentation will focus on some of the more commonly encountered problems in the diagnosis of lipomatous neoplasms (particularly well-differentiated lipomatous neoplasms) to the general surgical pathologist/dermatopathologist.

**Lipoblasts: are they necessary for a diagnosis of liposarcoma?**

Virtually any time one discusses lipomatous tumors, the topic of lipoblasts is discussed. As a general rule, I do not look for lipoblasts for a number of reasons. First, lipoblasts are not required for a diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma. As discussed below, the identification of enlarged, atypical, hyperchromatic nuclei is the prerequisite for rendering a diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma. In fact, one may not be able to identify any definite lipoblasts in an atypical lipomatous tumor/well-differentiated liposarcoma, even if one is meticulous about searching for these cells. Second, lipoblasts can actually be identified in benign lipomatous tumors. For example, I have seen a number of examples of pleomorphic lipoma with unequivocal lipoblasts. Therefore, the
recognition of a lipoblast does not necessarily mean that a given tumor is malignant. Finally, and probably most important, there is simply too much interobserver variability in the recognition of lipoblasts. In my opinion, "lipoblasts are in the eye of the beholder," and there are a number of cells that are essentially histologically indistinguishable from lipoblasts which are not ("pseudolipoblasts"). For example, one can encounter lipoblast-like cells in atrophic fat which are essentially indistinguishable from the most perfect lipoblasts one might encounter in a myxoid liposarcoma. One can also encounter lipoblast-like cells in lipomas with fat necrosis or hibernomas. In addition, I have seen a number of examples of neoplasms that infiltrate the surrounding subcutaneous tissue, isolating individual cells which are indistinguishable from lipoblasts. Therefore, one should not have to rely on the identification of lipoblasts to separate a benign from malignant well-differentiated lipomatous neoplasm.

**The nomenclature of well-differentiated lipomatous neoplasms**

Unfortunately, the nomenclature of well-differentiated lipomatous tumors has been fraught with confusion. Before 1979, differentiated lipomatous tumors characterized by atypical stromal cells intermingled with mature fat and variable numbers of lipoblasts were all designated as well-differentiated liposarcomas, whether they were found in the subcutaneous tissue, the deep soft tissues of the extremity, or the retroperitoneum. However, in 1979, Evans et al proposed a change in nomenclature because of the variability of clinical behavior depending on site. These authors evaluated 30 well-differentiated lipomatous lesions, all of which were histologically similar but varied according to site. Nine cases were found within the subcutaneous tissue, and none of these cases recurred, dedifferentiated, metastasized, or resulted in patient death. Of 13 lesions in the deep soft tissue (intramuscular) of the extremities, 9 cases (69%) recurred, although similar to the subcutaneous lesions, none dedifferentiated, metastasized, or resulted in patient death. Of the 8 retroperitoneal lesions, 5 recurred (62%), and although none of the cases
dedifferentiated or metastasized, 3 patients (37%) died of their disease. Based upon these data, Evans et al proposed that the lesions in the subcutaneous tissue be called "atypical lipoma," and the intramuscular extremity lesions be called "atypical intramuscular lipoma," given their lack of associated morbidity or mortality. However, he proposed that the term "well-differentiated liposarcoma" be retained for histologically identical lesions of the retroperitoneum, given their propensity to recur and occasionally result in patient death.

In 1987, Azumi and colleagues performed a similar study on 69 well-differentiated lipomatous lesions. Similar to Evans' study, none of the 17 subcutaneous lesions recurred, dedifferentiated, metastasized, or resulted in patient death. Although 29% (7/31 cases) of the deep soft tissue lesions recurred, none resulted in significant morbidity or mortality. Of 21 retroperitoneal lesions, 14 recurred (67%) and 5 dedifferentiated (23%). Although none of the cases metastasized, 9 patients (43%) died of disease. Thus, these authors proposed that the subcutaneous and deep soft tissue lesions be called "atypical lipoma" and opted to retain the term "well-differentiated liposarcoma" for the retroperitoneal lesions.

In 1992, Weiss and Rao re-analyzed a large group of well-differentiated lipomatous tumors with a minimum follow-up of 2 years, and found that behavior was strongly influenced by location, with retroperitoneal lesions having the worst prognosis, deep soft tissue lesions having the best prognosis, and inguinal lesions having a prognosis in between. Although their data on retroperitoneal lesions is similar to the other studies (recurrence rate: 91%; dedifferentiation: 17%; metastasis: 17%; death due to disease: 33%), 3 of 46 cases from the deep soft tissue of the extremities (6%) showed areas of dedifferentiation. These authors concluded that dedifferentiation is not a site-dependent, but rather a time-dependent phenomenon, and is observed in locations with a high likelihood of clinical persistence of disease. Thus, they recommend the use of the term "well-differentiated liposarcoma" for lesions in all locations, except those located in the subcutis, which are usually easily cured at initial excision and do not
have the opportunity to dedifferentiate. They proposed the term "atypical lipoma" for these subcutaneous lesions. Finally, there are some who propose calling all of these neoplasms, regardless of location, "atypical lipomatous tumors," since they are histologically indistinguishable and vary only with respect to location/depth. Therefore, one's preferred nomenclature depends upon whether one is a "lumper" or a "splitter." In the end, what is of paramount importance is the communication that occurs between the pathologist and the clinician in terms of the necessity for complete excision of a given neoplasm.

**Problematic benign lipomatous tumors**

The vast majority of benign lipomatous tumors are straightforward and do not cause the pathologist any difficulty. However, there are a number of benign lipomatous tumors that, on occasion, can have histologic features which might suggest one is dealing with a sarcoma. Although dermatopathologists do not typically encounter such lesions, the **intramuscular lipoma** can be an exceedingly difficult diagnosis to make with certainty. In general, the larger and deeper the well-differentiated lipomatous neoplasm, the more likely the lesion is to be malignant. However, there are large and deep benign lipomatous tumors - i.e. the intramuscular lipoma. As implied by the name, these lesions arise as large intramuscular masses, typically in the deep soft tissue of the thigh or buttocks. In general, these lesions need to be extensively sampled (at least one section per cm of tumor) in order to exclude the possibility of an atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL). The interdigitation of mature adipose tissue and skeletal muscle is a strong indication that one is dealing with an intramuscular lipoma, as opposed to an ALT/WDL, since the latter entity generally pushes aside the skeletal muscle to the periphery of the lesion. One must be wary of atrophic skeletal muscle fibers, which can closely mimic the enlarged, hyperchromatic nuclei diagnostic of ALT/WDL.
Angiolipomas are relatively common lesions and often occur in "crops" in one general anatomic location. These lesions are composed of an intimate admixture of mature adipocytes and slit-like blood vessels, some of which contain fibrin thrombi. The classic angiolipoma is not difficult to diagnose, but on occasion one may encounter a cellular variant of angiolipoma that can be worrisome for an angiosarcoma. I have seen such lesions arise in the soft tissue near the breast, where one already has a heightened awareness of angiosarcoma. These lesions are generally small and very well circumscribed, and the vascular structures do not infiltrate into the surrounding soft tissue as one would expect for an angiosarcoma. Less cellular zones of classic angiolipoma are also a useful finding. Chondroid lipoma is fortunately an exceedingly uncommon neoplasm, but this lesion can cause difficulty in diagnosis, since it can be mistaken for either a myxoid liposarcoma or a myxoid chondrosarcoma. Grossly, these lesions have a yellow-brown appearance similar to classic lipoma. The presence of cartilage-like areas can either be focal or occupy most of the lesion and in the latter circumstance can cause confusion with respect to another type of sarcoma.

In my experience, the most common difficulty arises in diagnosing pleomorphic/spindle cell sarcoma. In 1981, Shmookler and Enzinger described 48 cases of a lipomatous lesion characterized by mature adipose tissue admixed with bizarre, pleomorphic, multinucleated giant cells. Many of these bizarre cells had a floret-like arrangement of nuclei, and were often associated with interlacing bundles of dense collagen. 83% of these lesions occurred in males, with a mean age of 57 years, and 78% of the cases occurred either on the shoulder, neck or back. None of the cases recurred, confirming the clinical benignancy of this lesion. Thus, pleomorphic lipoma is a unique variant of lipoma occurring in a particular clinicopathologic setting; that is, a well-circumscribed lesion in the subcutis of a middle-aged or elderly male in the shoulder, neck or back region.
Grossly, pleomorphic lipomas are typically well circumscribed and are sharply demarcated from the adjacent mature adipose tissue. Although the average size of this tumor is close to 4.0 cm, they may be significantly larger (up to 12 cm). Histologically, this lesion is characterized by multinucleated floret cells with a wreath-like arrangement of hyperchromatic nuclei. These cells are admixed with mature lipocytes and dense, birefringent collagen fibers. Occasionally, there is a prominent myxoid stroma composed primarily of hyaluronic acid. Lipoblast-like cells have been described in up to 50% of cases. Thus, this tumor does have overlapping features with well-differentiated liposarcoma. However, given the characteristic clinicopathologic setting and the superficial nature of the lesion, this tumor can be distinguished from ALT/WDL or pleomorphic liposarcoma.

In 1975, Enzinger and Harvey described a lesion (spindle cell lipoma) with a similar clinicopathologic setting as that seen in pleomorphic lipoma, but characterized histologically by a mixture of lipocytes and uniform bland spindled cells within a myxoid stroma and accompanied by dense collagen. Spindle cell lipoma is probably part of a spectrum with pleomorphic lipoma, given the similar clinicopathologic setting and overlapping histologic features. Up to 25% of cases of pleomorphic lipomas show areas indistinguishable from spindle cell lipoma. Furthermore, both spindle cell lipoma and pleomorphic lipoma typically stain diffusely for CD34. The spindle cells are often deposited in a prominent myxoid stroma composed primarily of hyaluronic acid, and in those cases in which the lipomatous component is inconspicuous, differentiation from other myxoid tumors, including myxoid sarcomas, may be difficult. Similar to pleomorphic lipomas, spindle cell lipomas are treated with local excision, and virtually never recur.

Cytogenetic studies have also linked spindle cell and pleomorphic lipoma, both of which generally show monosomy 16 or partial loss of the long arm of chromosome 16 in association with unbalanced alterations of the long arm of chromosome 13. These cytogenetic alterations
differ from those found in ALT/WDL (giant marker and ring chromosomes derived from the q13-15 region of chromosome 12), supporting the concept that these are histogenetically different lipomatous tumors. Other benign lipomatous tumors also reveal characteristic cytogenetic abnormalities. The most common cytogenetic aberration identified in solitary lipomas is a translocation between 12q13-15 and various other chromosomes. Hibernomas consistently reveal abnormalities involving chromosomes 11q and 10q22, and lipoblastomas consistently reveal deletions of the short arm of chromosome 8.
References


