Perspectives on Low-grade Sarcomas: The Extraordinary Contributions of Sharon W. Weiss, MD

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Abstract: Soft-tissue pathology encompasses a wide spectrum of neoplasms that represent some of the most challenging and problematic tumors in surgical pathology. Owing to the intensive work of dedicated pathologists, this once esoteric field has become increasingly well defined. In this review, Dr Sharon Weiss’ monumental contributions to low-grade sarcomas, including low-grade fibromyxoid sarcoma, so-called hyalinizing spindle cell tumor, atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma, epithelioid hemangioendothelioma, and dermatofibrosarcoma protuberos with fibrosarcomatous transformation will be discussed.

Key Words: low-grade fibromyxoid sarcoma, atypical lipomatous tumor, epithelioid hemangioendothelioma, dermatofibrosarcoma protubers

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Sharon W. Weiss, MD, is someone who needs no introduction to anyone who practices surgical pathology. Dr Weiss has trained and mentored innumerable pathologists in the area of soft-tissue pathology, including her years at the University of Michigan (1989 to 1995) and at Emory University, where she has been since 1996. Between these 2 programs, Dr Weiss has trained 35 fellows in soft-tissue pathology, many of whom have made significant contributions themselves to this area of surgical pathology, in large part due to the guidance provided by Dr Weiss. The focus of this discussion will be on contributions that Dr Weiss made in conjunction with a number of her fellows to the area of low-grade sarcomas. Although her name can be seen associated with the literature on virtually all low-grade sarcomas, this review will focus on only a select few.

DISCUSSION

Low-grade Fibromyxoid Sarcoma and Hyalinizing Spindle Cell Tumor

In conjunction with 2 of her former fellows, Dr Andrew Folpe and Dr Kathy Lane, Dr Weiss has contributed significantly to our understanding of low-grade fibromyxoid sarcoma (LGFM) and the related lesion formerly known as hyalinizing spindle cell tumor with giant rosettes.

In 1987, Evans described a tumor that typically presents as a large, well-circumscribed mass in the deep soft tissues, most commonly occurring in the shoulder, thigh, and inguinal region, which he termed “low-grade fibromyxoid sarcoma.” Histologically, this lesion is composed of bland spindled cells of low to moderate cellularity deposited in an alternating fibrous and myxoid stroma. The cells often have a swirling growth pattern and occasionally condense in a perivascular location (Fig. 1A). Cytologically, there is little nuclear pleomorphism and mitotic figures are difficult to identify. Similar to other myxoid sarcomas, LGFM often has a rich, regular vascular network in the myxoid zones that is useful in its distinction from a benign lesion (Fig. 1B). Also, despite the gross circumscription, there is often microscopic infiltration of the surrounding soft tissues. Of the 12 patients described in Evans’ 1993 paper, 9 had local recurrences, 7 had evidence of distant metastasis, and 4 died of disease. By immunohistochemistry, this tumor tends to be negative for S100 protein, cytokeratins, and a number of other antigens, but a significant percentage of cases do stain for EMA. More recently, Doyle et al found that virtually all examples of this tumor stain for MUC4, a very useful marker in confirming this often difficult-to-diagnose tumor. At the molecular level, LGFM is characterized most commonly by a t17(t1;16), with fusion of the CREB3L2 gene on chromosome 7 with the FUS gene on chromosome 16. Less commonly, this tumor shows evidence of a t11;16 involving the CREB3L1 gene on chromosome 11. Recently, a novel gene fusion, EWSR1-CREB3L1, has been reported in 2 cases of LGFM, suggesting a wider spectrum of genetic alterations that characterize this tumor. We often utilize paraffin-embedded tissue for fluorescence in situ hybridization (FISH) with a FUS break-apart probe to confirm this difficult diagnosis, although we do this less often than in the past given the strong correlation between MUC4 positivity and the presence of this translocation.

In 2000, Folpe et al in conjunction with Dr Weiss made a major contribution to our understanding of the clinical behavior of this tumor. Of the 73 cases studied, 70 were initially diagnosed as LGFM. Three of these tumors presented with metastases and had previously been diagnosed as a “benign” tumor. The follow-up ranged from 2 to 192 months (mean: 38 mo), and local recurrences occurred in 9% of patients, with only 3 patients (6%) developing metastatic disease and 1 patient (2%) dying of their tumor, numbers far lower than previously reported. These authors emphasized that, when correctly diagnosed, this tumor can be excised completely with tumor-free margins, which seems to alter the clinical behavior of this tumor. Furthermore, many of the previous studies had relatively short follow-up periods. In 2011, Evans evaluated 33 cases of LGFM with long-term follow-up of at least 5 years. Twenty-one patients had recurrences after tumor-free intervals as long as 15 years, and 15 patients had metastasis after more than 45 years following initial diagnosis. Fourteen patients died of tumor, with intervals ranging from 3 to 42 years. In addition, Evans found that the only...
The histologic predictor of survival was dedifferentiation characterized by areas demonstrating anaplastic round cells with prominent mitoses. This study emphasized the pervasive nature of this neoplasm and the importance of long-term follow-up since complications from the tumor may occur many years after the initial diagnosis.

In 1997, Lane described the so-called hyalinizing spindle cell tumor with giant rosettes, a tumor which they noted shared a great deal in common with LGFMS. Although the most distinctive feature of this tumor is, as the name suggests, the presence of collagen rosettes, the authors noted that away from these rosettes the tumor was histologically identical to LGFMS (Fig. 1C). Subsequently, it became apparent these tumors were clearly related given the identical molecular genetic alterations present in hyalinizing spindle cell tumor with giant rosettes, as are found in LGFMS.

More recently, an overlap between LGFMS and selroosing epithelioid sarcoma (SEF) has been observed. In 2007, the French Sarcoma Group evaluated 63 cases of LGFMS and 66 of non-LGFMS for FUS-CREB3L2 and FUS-CREB3L1 using real-time polymerase chain reaction. They found that not only are these fusions highly sensitive for LGFMS, but that a subset of non-LGFMS (7/52) harbored these fusions, including 4 tumors diagnosed as SEF, suggesting a possible relationship between these 2 tumors. Rekhi et al found 6 of 18 cases of LGFMS to have SEF-like areas. In 2012, Wang et al found FUS rearrangements in pure SEF to be uncommon, with only 2/22 (9%) cases showing this gene fusion. There seems to be no prognostic impact of SEF-like areas in cases of LGFMS, but such studies admittedly have been few and characterized by short follow-up (5 to 52 mo). Of interest, MUC4 staining in pure SEF is observed in 69% to 90% of cases.

**Atypical Lipomatous Tumor/Well-differentiated Liposarcoma, and Dedifferentiated Liposarcoma**

Well-differentiated lipomatous tumors are among the most common soft tissue consultations we receive. Although the majority of these cases are actually benign lipomatous tumors that are thought to be malignant (most commonly pleomorphic lipoma or intramuscular lipoma), some however are atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDL) misclassified as lipomas. The vast majority of well-differentiated lipomatous tumors that all pathologists encounter are run-of-the-mills lipomas, which do not typically cause any diagnostic difficulty. Most of these lesions are small and superficial and, based upon those facts alone, are easily recognized as benign. However, there are a number of other benign lipomatous tumors that can cause diagnostic difficulty (intramuscular lipoma, lipoblastoma, hibernoma, chondroid lipoma, etc.). These cases can be further complicated by the tumor arising in an unusual location, such as the retroperitoneum, or large tumor size.

The nomenclature of well-differentiated lipomatous tumors has been fraught with confusion, and a variety of terms have been used for the same lesion. Before 1979, well-differentiated lipomatous tumors characterized by atypical stromal cells intermingled with mature fat and variable numbers of lipoblasts were all designated as WDL, regardless of whether they were found in the subcutaneous...
tissue, the deep soft tissues of the extremities 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 clinically according to location. 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 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. On the basis of these data, Evans and colleagues 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, they proposed the term WDL be retained for histologically identical lesions of the retroperitoneum given their propensity to recur and sometimes result in patient death.

In 1992, Weiss and Rao reanalyzed 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. Although their data on retroperitoneal lesions is similar to the other studies, 3 of 46 (6%) cases from deep soft tissue of the extremities 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 recommended 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 retaining the term “atypical lipoma” for these subcutaneous lesions. Others have proposed referring to all of these tumors as ALT, regardless of location. Historically, ALT/WDL is characterized by lipocytes that vary in size and shape, often divided into irregular lobules by dense fibrous septa (Fig. 2A). Within these septa and/or between lipocytes, there are scattered enlarged, hyperchromatic, atypical nuclei that are not seen in the usual type of lipoma (Fig. 2B). Lipoblasts, characterized by cytoplasmic lipid vacuoles that indent or scallop the nucleus, can be identified but are few in number and are not absolutely necessary for the diagnosis.

In conjunction with one of her former fellows, Dr Walter Henricks, Dr Weiss was also instrumental in our understanding of dedifferentiated liposarcoma (DDL). Traditionally, DDL has only been diagnosed when a dedifferentiated area resembles a high-grade sarcoma. However, it is apparent that there is a spectrum of histologic grade and extent of dedifferentiation within this group of tumors, but the effects of these parameters on clinical outcome had been largely unknown. To address this issue, Henricks and colleagues (under the guidance of Dr Weiss) studied 155 cases of DDL, 130 of which had clinical follow-up (median: 3 y). Although the majority of these tumors occurred in the retroperitoneum (68%), 21% of the cases were peripherally located, either on the trunk or within the deep soft tissues of the extremities. In most cases (86%), the dedifferentiated foci were present at the time of initial diagnosis (de novo dedifferentiation). In particular, the authors more fully described the nonlipogenic areas which were more cellular than classic ALT but had not yet reached the degree of cellularity, atypia, and mitotic activity characteristic of full-fledged high-grade dedifferentiation, and coined the term “low-grade dedifferentiation.” In many cases, these low-grade areas surrounded the high-grade areas, but in some cases, they represented the most histologically progressed area of the entire tumor, without any evidence of high-grade dedifferentiation. Overall, 41% of the patients developed recurrences, 17% developed metastases, and 28% died of tumor. Although the metastatic rate of DDL may seem low when compared with other high-grade sarcomas, it is important to keep in mind that DDLs, particularly those located in the retroperitoneum, often result in death by local extension and destruction before metastasis can become clinically evident. Henricks and colleagues found no significant difference in prognosis relative to the extent of dedifferentiation for the range examined (<25% of the tumor vs. ≥25% of the tumor). Furthermore, there was no significant difference in survival between patients with low-grade versus high-grade dedifferentiation. Thus, the authors proposed that the traditional definition of DDL be expanded to include liposarcomas with areas of low-grade nonlipogenic dedifferentiation (Figs. 2C, D).

Although most ALTs can be recognized by histologic features alone, a recent study by Dr Weiss and her colleagues evaluated the utility of FISH to detect amplification of MDM2 in difficult well-differentiated lipomatous tumors. The most common indications for performing FISH in this study included tumor size >10 cm (62%), equivocal cytologic atypia (48%), deep tumor location (28%), or history of recurrence (11%). Tumors which had more than one of the above indications were far more likely to show MDM2 amplification and therefore be diagnosed as ALT. In the end, the authors recommended FISH for recurrent well-differentiated lipomatous tumors, those with equivocal cytologic atypia, retroperitoneal, intra-abdominal, and pelvic tumors, and tumors >10 cm located in the deep soft tissues of the extremities, especially in patients older than 50 years of age. These authors also validated the existence of rare benign lipomas in the retroperitoneum, as reported by others.

Recently, these same authors evaluated MDM2 and CDK4 immunohistochemistry as a surrogate for MDM2 amplification by FISH in difficult lipomatous tumors. They found the sensitivity and specificity for MDM2 and CDK4 to be 45% and 41% and 98% and 92%, respectively. Given the relatively low sensitivity of these markers, the authors advocated the use of FISH as a superior technique for the evaluation of difficult well-differentiated lipomatous tumors.

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) of soft tissue is a vascular neoplasm of intermediate malignancy which can occur at almost any age and can be found in a variety of sites, most commonly the extremities. It usually arises as a solitary mass in either the superficial or deep soft tissue, but it can be found multifocally within a localized region of the body. Up to 50% are closely associated with or even seem to arise from a blood vessel.
Histologically, the tumor is comprised of strands or nests of epithelioid to slightly spindled endothelial cells, some of which have small intracellular lumina, the so called “blister cells” (Fig. 3A). The cells are deposited in stroma which varies from hyaline to myxoid (Fig. 3B). Immunohistochemically, the neoplastic cells stain strongly for vascular markers, including CD31, CD34, and ERG. Clinically, the tumor is capable of regional or distant metastases but at a rate which is significantly lower than that seen in epithelioid angiosarcoma. In a study by Deyrup et al,20 under the guidance of Dr Weiss, disease-specific survival was 81% at 5 years. In this series of 49 cases with follow-up (median: 58 mo), 31 patients (63%) were alive without disease, 5 patients (10%) were alive with disease, and 9 patients (18%) died of disease. Lymph nodes and lung were the 2 most common metastatic sites. These authors proposed a risk stratification scheme to help identify those patients with tumors which were more likely to progress and, therefore, could benefit from more aggressive targeted therapy. Tumors larger than 3 cm and having greater than 3 mitoses per 50 HPF were found to be high-risk lesions, and those lacking these features were described as low risk. Patients with high-risk tumors developed metastases in 32% of cases compared with 15% of patients

FIGURE 2. A, Atypical lipomatous tumor. Lipocytes of varying size and shape are divided into irregular lobules that are separated by dense fibrous septa. B, Atypical lipomatous tumor. At higher power, atypical cells with enlarged hyperchromatic nuclei can be seen scattered within the fibrous septa. C, Atypical lipomatous tumor component (on right) with high-grade dedifferentiation (on left) in a dedifferentiated liposarcoma. D, Atypical lipomatous tumor with area of low-grade dedifferentiation (adjacent atypical lipomatous tumor not pictured).

FIGURE 3. A, Epithelioid hemangioendothelioma (EHE) at high power, some of the epithelioid tumor cells demonstrate the small intracellular lumina called “blister cells.” Red blood cells can be seen accumulating within some of the intravascular spaces. B, EHE: cords of epithelioid cells can be seen embedded within a hyalinized stroma, but well-defined vascular channels are not seen.
with low-risk lesions. When compared with other hemangioendotheliomas, the metastatic rate for malignant EHE is considerably higher and, as such, the WHO suggested that malignant EHEs be grouped with angiosarcomas. Finally, this tumor is known to harbor a t(1;3) involving a novel gene fusion between \(WWTR1\) on chromosome 3 and \(CAMTA1\) on chromosome 1.21–23 This gene fusion is unique to EHE, reinforcing the importance of distinguishing this tumor from angiosarcoma. A small subset of EHE have recently been shown to harbor a gene fusion involving \(YAP1\) and \(TFE3\).21 Interestingly, these tumors can show a variation in the typical tumor morphology demonstrating prominent eosinophilic cytoplasm, increased atypia, and a distinct vasoformative growth pattern. Tumors with this gene fusion stain for TFE3 and while they appear clinically indolent, additional studies are needed to determine if their clinical course is significantly different from the typical EHE harboring the \(WWTR1\)-\(CAMTA1\) fusion.

**Dermatofibrosarcoma Protuberans/Fibrosarcomatous Dermatofibrosarcoma Protuberans**

Dermatofibrosarcoma protuberans (DFSP) is classified as a fibrohistiocytic tumor of intermediate malignancy that most commonly arises in young to middle-aged adults, usually as a slowly growing lesion most commonly on the trunk, proximal extremities, or head and neck. Rarely, they arise in infants and children, but they may not become clinically apparent until early adulthood.24 Histologically, DFSP is characterized by a uniform population of plump spindled cells arranged in a monotonous storiform pattern (Fig. 4A). Despite the gross circumscription of the tumor, DFSP is characterized by diffuse infiltration of the underlying subcutaneous tissue in a lace-like pattern. The lesion lacks cellular heterogeneity as well as secondary elements commonly seen in benign fibrous histiocytoma. Immunohistochemically, the neoplastic cells typically stain strongly and diffusely for CD34, although this marker lacks any degree of specificity. Although the adequacy of excision plays a major role in determining clinical behavior, up to 60% of patients develop 1 or more local recurrences.25

In a small percentage of cases of DFSP (approximately 10%), a portion of the tumor may resemble a fibrosarcoma [fibrosarcomatous (FS)-DFSP]. Historically, sarcoma arising in a DFSP was believed to be more common in a recurrent tumor, but studies have shown that when present it is most often a component of the original tumor. The FS component can be identified histologically by its increased cellularity and arrangement into longer fascicles, often with a herringbone growth pattern similar to that seen in deep soft-tissue fibrosarcoma (Fig. 4B). Most commonly, there is an abrupt transition between the less cellular monotonous storiform pattern of DFSP into the more cellular fascicular pattern of FS, often with the FS areas being found in the deeper portion of the tumor (Fig. 4C). In some cases, however, the transition from a storiform to a fascicular growth pattern can be gradual and difficult to recognize. The FS component has greater cytologic atypia and mitotic activity when compared with the surrounding DFSP, and it often shows decreased or even absent CD34 immunoreactivity when compared with the surrounding DFSP component. The clinical significance of sarcoma arising...
within a DFSP has until recently, not been well understood and studies have published conflicting data. In a study by Mentzel et al.\textsuperscript{26} in 1998, patients with FS-DFSP showed local recurrence in 64\% of cases, metastasis in 19\%, and death in 9\%, numbers that are far more striking than DFSP alone. However, in this study, only 4 patients actually underwent wide local excision with incomplete excision being noted in at least 23 patients. A more recent study in 2006 of 41 patients with FS-DFSP also showed an increased risk of tumor metastasis over pure DFSP.\textsuperscript{27} Of the 41 cases studied, 8 patients had local recurrences, 4 patients had metastasis, and 2 of the patients died from their tumor burden. However, all the tumors studied in this series had received local excision only with surgical margins positive in 22/39 of the cases. In a subsequent study of FS-DFSP by Goldblum et al.\textsuperscript{28} follow-up in 18 patients (median: 81.5 mo) revealed local recurrence in only 4 patients (22\%), with no patient developing metastasis or death. In all of these cases, the tumor was correctly diagnosed as FS-DFSP and was treated with wide local excision with tumor-free margins. As such, correct diagnosis and subsequent appropriate therapy does seem to impact clinical behavior.

**DISCUSSION**

In summary, this is not meant to be a comprehensive compendium of Dr Weiss contributions to soft-tissue pathology, as no review no matter how extensive could do that particular topic justice. However, this discussion was meant to highlight Dr Weiss major contributions to just a small subset of low-grade sarcomas. These outstanding contributions will serve as the basis for our further understanding of these and many other sarcomas in the future.

**REFERENCES**