Spindle cell sarcomas of soft tissue; beyond herringbones and fibrosarcoma goals

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INTRODUCTION AND HISTORICAL BACKGROUND

Historically, a soft tissue tumor composed of a highly cellular proliferation of spindle cells, typically with a “herringbone” growth pattern was classified as fibrosarcoma. However, this diagnosis extended well beyond this narrow definition so that fibrosarcoma was one of the most common subtypes of soft tissue malignancy. One of the earliest reviews of the subject by Bick at Mount Sinai defined fibrosarcoma as a “malignant tumor of connective tissue in which the cells are non-osseous mesoblastic mesoblastic origin.” ¹ This definition included spindled, round and giant cells or a mixture, arising from fascia, blood vessels, nerve sheath or periosteum and almost certainly represented entities that would not be classified differently. At the Mayo clinic, the diagnosis of fibrosarcoma has decreased in incidence from a high of 66% in 1936 to <1% of adult soft tissue sarcomas by 2010. ², ³ This approximately mirrors the use of the diagnosis in the pathology literature over the same time period.

The decrease in fibrosarcoma incidence stems from improved diagnostic accuracy and classification of soft tissue sarcomas and a more strict definition of fibrosarcoma. The 2013 WHO defines fibrosarcoma as a “malignant tumor, composed of fibroblasts with variable collagen and, in classical cases, a herringbone architecture. It is a diagnosis of exclusion”. ⁴ Note that the emphasized clause at the end of the definition was added in the most recent edition of the WHO. Despite this important qualifier, the definition is still problematic since there is no morphologic, immunophenotypic or genetic “gold standard” for a neoplastic fibroblast. From a practical perspective, two question arise from these observations:

- How have tumors formerly known as fibrosarcoma been reclassified?
- Are there any true fibrosarcomas left?

To answer these questions, the current presentation will (1) review the soft tissue tumors that look like the classical definition of fibrosarcoma: namely spindle cells in a tightly packed fascicles, occasionally herringbone, pattern and (2) discuss the few remaining entities that are still called fibrosarcoma (irrespective of whether that designation is accurate in a biological sense).

MONOPHASIC SYNOVIAL SARCOMA

Apart from undifferentiated spindle cell sarcoma (discussed later), monophasic synovial sarcoma represents the most common mimic of fibrosarcoma.³ This is not surprising since monophasic synovial sarcoma is characterized by a highly uniform population of fusiform spindle cells growing in tightly packed fascicles. Although the herringbone
growth pattern is not always present, it can be seen in a subset of cases. Unlike biphasic synovial sarcoma, which demonstrates more overt epithelial differentiation in the form of pseudoglands, monophasic lacks this feature. Monophasic synovial sarcoma may demonstrate a branching, staghorn-like, vasculature and calcifications, which is not typical of fibrosarcoma. Keratin and EMA expression may be helpful to support the diagnosis of synovial sarcoma, but the monophasic type usually shows only very focal staining with these antigens or they can be entirely absent.\(^5\) TLE1 has shown promise as a helpful ancillary marker\(^6\) although, in our experience, specificity is not very high. Molecular or genetic methods to detect the \(t(X;18)\) translocation or resultant SS18 rearrangement has proven extremely helpful for definitive diagnosis.\(^7\) To the best of our knowledge, this translocation remains highly specific for synovial sarcoma.

Clinically, synovial sarcoma typically affects young adults, and although it can occur anywhere in the body, the lower extremity in the vicinity of the knee is most common. Incidentally, it is this anatomic predilection that is responsible for the name synovial sarcoma. They are high grade tumors that are treated with surgery and adjuvant chemotherapy. Five year survival is between 36 and 76% depending on the series. Some data suggest that small, superficial tumors and those with calcifications have better prognosis.\(^8,9\)

**MALIGNANT PERIPHERAL NERVE SHEATH TUMOR**

Malignant peripheral nerve sheath tumor (MPNST) is defined as a malignant neoplasm that either derives from, or differentiates toward, a peripheral nerve sheath cell type.\(^10,11\) Approximately half of cases arise in patients with Neurofibromatosis 1 (NF1). Familial NF1 cases more frequently arise from pre-existing benign nerve sheath tumors (usually neurofibroma) whereas sporadic cases arise *de novo*. In the absence of NF1 history or a pre-existing benign neurofibroma, the diagnosis is very difficult to make with certainty. This is because no “gold standard” morphologic, immunophenotypic or genetic changes have been identified to prove MPNST with certainty. In fact, one could argue that the clinical setting of NF1 is hardly sufficient evidence to diagnose every spindle cell sarcoma in these patients as MPNST. Low-grade MPNST have a high recurrence risk (~50%) whereas high-grade forms frequently metastasize.

Though MPNST can have a number of growth patterns, the most common tightly packed fascicular growth mimics “fibrosarcoma.” Unfortunately, there are no pathognomonic microscopic features unless a precursor benign nerve sheath tumor (usually neurofibroma) is present. The nuclei are hyperchromatic and fusiform but more tapered at their tips than synovial sarcoma. MPNST typically does not show calcifications or staghorn vessels as seen in synovial sarcoma. A peculiar hemiation of
tumor cells into the media or lumen of vessels has been described as a useful feature of MPNST. Mitotic activity and pleomorphism is generally higher than synovial sarcoma.

Immunohistochemistry can be helpful. Approximately half of MPNST express at least focal S100 or SOX10.\(^\text{12,13}\). Somewhat paradoxically, diffuse and strong S100 or SOX10 staining in a spindle cell neoplasm argues against MPNST and should raise the possibility of a spindle cell melanoma. Focal S100 can be seen in synovial sarcoma, but SOX10 is much less common.\(^\text{13}\) Unfortunately, about half of MPNST do not express either S100 or SOX10. Recently, loss of H3K27Me3 expression has been described as highly sensitive for MPNST.\(^\text{14}\) Currently, there are no reproducible genetic changes to confirm the diagnosis of MPNST.\(^\text{10}\) Mutations in the \(\text{NF1}\) gene are of course found in patients with Neurofibromatosis 1, but the finding is not specific. MPNST do not harbor rearrangements of the \(\text{SS18}\) gene.

**DERMATOFIBROSARCOMA PROTUBERANS and FIBROSARCOMATOUS PROGRESSION**

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive, dermal and subcutaneous neoplasm of fibroblasts.\(^\text{15}\) Although DFSP is composed of monomorphic spindle cells, the storiform growth and fat infiltration are so characteristic that, despite the “fibrosarcoma” name, its microscopic appearance is distinct from classic “fibrosarcoma” (i.e. fascicular, herringbone). However, DFSP can occasionally progress to a higher grade sarcoma, known as **fibrosarcomatous DFSP**. The latter tumors, like DFSP, arise on the trunk and proximal extremities of middle aged adults with either a synchronous or metachronous DFSP at the same site. There is some controversy whether a fibrosarcomatous component invariably carries a worse prognosis. Though a higher recurrence and metastatic risk was reported in earlier studies, a more recent study in which patients received wide local excision (as they would for conventional DFSP) did not show a worse prognosis if fibrosarcoma was present.\(^\text{16}\)

Both DFSP and fibrosarcomatous DFSP contain a monotonous population of spindle cells with scant cytoplasm, and hyperchromatic nuclei with tapered ends. Microscopically, compared to the storiform pattern of DFSP, the fibrosarcomatous component is fascicular with the classic herringbone pattern, more diffusely hypercellular and larger (>5 cm). Necrosis and abundant mitoses (> 7 / 10 hpf) are common. The residual DFSP can often be identified at the periphery of the lesion.

The tumors express CD34, albeit less intensely and diffusely than the precursor DFSP in a manner analogous to loss of S100 staining in MPNST compared to benign schwannoma. Fibrosarcomatous DFSP notably lacks keratin, S100 or desmin. Genetically, DFSP and fibrosarcomatous DFSP share the same \(t(17;22)(\text{q21;\text{q13}})\)
translocation and resulting \textit{COL1A1:PDGFβ} fusion. Such genetic confirmation is seldom necessary for classic DFSP, but for a dermal-subcutaneous spindle cell sarcoma lacking a DFSP precursor, it may be useful.

**INFANTILE FIBROSARCOMA**

Infantile fibrosarcoma is a very rare mesenchymal malignancy in neonates. It is almost never seen after 1 year of age.\textsuperscript{17} Although retaining the name “fibrosarcoma” for historical reasons, it is unclear whether the tumor is truly fibroblastic and, as with many translocation-driven sarcomas, it represents a clinicopathologic and genetic entity rather than a histologic subtype. Most tumors involved the distal lower extremity though the anatomic distribution is wide. Despite the high grade morphology, the tumors have a relatively good prognosis compared to other pediatric sarcomas such as rhabdomyosarcoma or adult fibrosarcoma. Therapy consists of either neoadjuvant chemotherapy to reduce tumor size and conservative excision or wide excision with or without adjuvant chemotherapy.\textsuperscript{18} The prognosis does not correlate with histologic grading.

Microscopically, the tumors are highly cellular. They consist of monotonous small spindled to ovoid cells usually with little intervening stroma. Although a herringbone pattern may be observed in some cases, sheet like or haphazard growth is more common in our experience. Pleomorphism is absent. Hemangiopericytomatous vasculature can be seen. Mitotic activity can vary within a given tumor sometimes exceeding 20 per 10 high power fields. However, as mentioned above, this is not prognostic. Rare cases have more fibrous stroma or a prominent lymphoid infiltrate (another feature typically absent in adult fibrosarcoma).

The tumors are negative for keratins, desmin, myogenin, S100 and CD34. Some weak SMA staining may be seen but this is a very nonspecific result among spindle cell sarcomas. The \textit{ETV6:NTRK3} gene fusion resulting from a \textit{t(12;15)} translocation is diagnostic. Interestingly, the same translocation is seen in congenital pulmonary fibrosarcoma and congenital mesoblastic nephroma.\textsuperscript{19, 20} These may be closely related lesions but the finding of the same translocation in some breast cancers and myeloid leukemias suggests the genetics are not entirely specific for congenital sarcomas.\textsuperscript{21, 22}

**ADULT FIBROSARCOMA / UNDIFFERENTIATED SPINDLE CELL SARCOMA**

As previously discussed, the diagnosis of adult fibrosarcoma has become a diagnosis of exclusion. Ostensibly, fibrosarcoma is defined as a malignant mesenchymal tumor with
fibroblastic differentiation that usually forms collagen matrix. This definition is problematic for several reasons. First, fibroblastic differentiation is very difficult to "prove" morphologically and immunophenotypically and ultrastructure is rarely evaluated in soft tissue tumors. Furthermore, the presence of patchy SMA expression in a subset of "fibrosarcomas" has led some to conclude that the category also includes myofibroblastic sarcomas. Third, collagen production is hardly specific for fibrosarcoma. Thus, one could argue that the diagnosis of undifferentiated spindle cell sarcoma (USS) is a more accurate term to describe these tumors. By analogy, the diagnosis of malignant fibrous histiocytoma (MFH) has largely been replaced by undifferentiated pleomorphic sarcoma (UPS) to denote the exact same degree of uncertainty regarding histotype. Whichever term (fibrosarcoma, USS or even UPS) is used, the definition of this category is similar.

Tumors typically arise in middle aged or older adults, involving the deep soft tissues of the proximal extremity or trunk. Superficial examples most likely represent fibrosarcomatous DFSP if analyzed at the genetic level. The prognosis is considerably worse than infantile fibrosarcoma (<55% 5 year survival). Treatment consists of wide excision with or without adjuvant (or intraoperative) radiotherapy and chemotherapy.

Adult fibrosarcoma consists of monomorphic spindle cells in short to intermediate length fascicles, in parallel arrays that produce the classic "herringbone" pattern. That some authors also include tumors with storiform or haphazard growth, fibromatosis like areas or extensive myxoid matrix underscores the lack of a strict definition for this tumor since these features are commonly seen in other, better characterized, subtypes of sarcoma. That said, fibrosarcoma is immunophenotypically negative for keratins, desmin, S100, CD34 but can show some weak SMA – essentially a "null" immunophenotype. Immunostains are, of course, helpful to exclude other spindle cell sarcomas discussed above. The usually show a genomic landscape that is complex.
SUMMARY

1. Adult fibrosarcoma is a diagnosis of exclusion
2. Some diagnoses that retain the diagnosis of “fibrosarcoma” are not uniformly herringbone
3. Most herringbone spindle cell neoplasms in adults can be classified as synovial sarcoma, MPNST or fibrosarcomatous DFSP
4. Immunohistochemistry and, in some cases, genetics are needed in most cases to classify these tumors

Table 1. Ancillary immunohistochemistry and genetic testing useful in the evaluation of monomorphic spindle cell sarcomas.

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<th>MPNST</th>
<th>FS in DFSP</th>
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<td>Weak, patchy</td>
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REFERENCES


