THE FALL AND RISE OF FIBROSARCOMA

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Bullet points

• Fibrosarcoma was a common diagnosis until the 1960s. It became a diagnosis of exclusion as evolving techniques facilitated recognition of other sarcoma subtypes. Pleomorphic forms became categorized as malignant fibrous histiocytoma.

• From the 1990s, several clinicopathologic subtypes of fibrosarcoma were characterized by cellular morphology or stromal patterns.

• Fibrosarcomas can be differentiated or pleomorphic. Pleomorphic fibrosarcoma subsumes many tumors previously characterized as malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma.

• A variable proportion of myofibroblasts can be found in some types of fibrosarcoma.

• Fibrosarcomas are defined by electron microscopy and identifiable by light microscopy. Immunohistochemistry is useful mainly to exclude other sarcomas.

• Some subtypes of fibrosarcoma have specific and consistent genetic abnormalities which are of diagnostic value.
**Historical Introduction**

The definition and classification of fibrosarcoma are related to its stroma. Fibrosarcoma was defined by Rokitansky (1842) as a tumor with varieties dependent on “the form and arrangement of the fibers”, and Mallory (1908) defined the fibroblast by its production of extra-cellular fibers. Fibrosarcoma was included in subsequent classifications by Wilks (1849) (as fibroplastic) and Borst (1902)(as fibroma sarcomatosum). Later, following the views of Ewing (1922) and of Quick and Cutler (1927), many deeply located fibrogenic spindle cell sarcomas were assumed to be of nervous origin; neurogenic sarcoma became a common diagnosis, though no specific criteria were given. Indeed, Warren and Sommer (1936) considered 63/118 (53%) of their ‘fibrosarcomas’ to be of neurogenic origin because of their herringbone and interlacing patterns.

Stout dismissed neurogenic sarcoma as a term with as little meaning as spindle cell sarcoma. In Cancer vol 1 (1948), he defined fibrosarcoma as “a tumor composed of spindle shaped fibroblasts and connective tissue fibers which are wrapped around all the cells rather than forming long wires”, but emphasized that before rendering a diagnosis of fibrosarcoma it was necessary to exclude all other diagnoses especially in cellular, fiber-deficient tumors. Stout found a low metastatic rate of 8% in fibrosarcoma but 76% of his cases were well-differentiated and included many examples of dermatofibrosarcoma. In the first AFIP Fascicle on soft tissue tumors (1953), the term “non-metastasizing fibrosarcoma” appears under the heading of fibromatosis, and dermatofibrosarcoma under fibrosarcoma. Both were removed from these headings in the 2nd edition (1966). By this time, the concept of the facultative fibroblast had taken hold: and Stout pointed out (p 101) that “after the so-called differentiated fibrosarcomas have been set aside, and malignant tumors of other types composed of cells acting as facultative fibroblasts, are omitted, the number of true malignant fibroblastic tumors capable of metastasizing shrinks very markedly”. Gabbiani described the myofibroblast in 1971.

Subsequently, with the recognition of fibromatosis and numerous benign fibroblastic/myofibroblastic lesions, the identification of specific sarcoma subtypes such as monophasic synovial sarcoma, and the categorization of many pleomorphic sarcomas as malignant fibrous histiocytoma (see below), fibrosarcoma became a rare diagnosis. In the last decade, however, the advent of newer techniques and methods of investigations has led to the definition of several fibrosarcoma subtypes and to the reassessment of the roles of the fibroblast and myofibroblast in pleomorphic sarcomas.

**Fibroblastic Sarcomas**

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Sclerosing epithelioid fibrosarcoma
Myxoinflammatory fibroblastic sarcoma
Pleomorphic fibrosarcoma (MFH)

**Adult fibrosarcoma**

Classical fibrosarcoma can be seen as a component of other subtypes of fibrosarcoma but its incidence as a pure tumor is rare; it probably accounts for around 1% of adult sarcomas. It is most common in middle-aged and older adults with equal sex incidence. Fibrosarcomas involve deep tissues of extremities, trunk, and head & neck; reports of occurrences in visceral organs and retroperitoneum are questionable. Some arise following therapeutic irradiation, and rarely following implantation of foreign material but the nature of these tumors is not always certain.

The typical fibrosarcoma has sweeping herringbone fascicles of spindle-shaped cells with tapered darkly staining nuclei, small nucleoli, and scanty cytoplasm with variable mitotic activity. The cells have prominent rough endoplasmic reticulum and absence of myofilaments, external lamina or intercellular junctions, and (apart from vimentin) usually lack markers except focal CD34 and SMA in some cases. An occasional cell has peripheral filament bundles suggestive of myofibroblastic differentiation; tumors in which this is prominent are myofibrosarcomas. Inflammatory fibrosarcoma is currently included with inflammatory myofibroblastic tumor, although it might properly be applied to malignant variants of the latter. Higher-grade tumors have more densely staining nuclei, and can display focal round cell change and multinucleated cells, but sarcomas with marked pleomorphism are classified as malignant fibrous histiocytomas. The stroma varies from a delicate intercellular network to paucicellular areas with diffuse or “keloid-like” sclerosis or hyalinization, or fibromatosis-like foci. Myxoid change and osteochondroid metaplasia can occur.

Fibrosarcomas metastasize to lungs and bone, especially the axial skeleton, and rarely to lymph nodes. Metastasis occurs in 9-63% of patients and is time- and grade-dependent. 5 year survival is 39-54%. Poor prognostic factors include high grade, high cellularity with minimal collagen, mitotic rates >20/10hpf, necrosis, and little collagen.

Fibrosarcoma can arise in dermatofibrosarcoma both de novo and in recurrent lesions. It is characterized by greater cellularity with fascicular architecture and increased mitotic activity. CD34 can be positive or negative in the fibrosarcomatous area. The fibrosarcomatous component behaves more aggressively, with local recurrence in >50% and metastasis in 15% of cases. Adequate local control of DFS with fibrosarcomatous changes, with clear surgical margins, can reduce both local recurrence and the incidence of metastasis. The reciprocal translocation of DFSP, t(17;22)(q22;q13) (with a supernumerary ring chromosome), resulting in fusion of the genes COL1A1-PDGFB (with a supernumerary ring chromosome) results in fusion of the genes COL1A1 and PDGFB (22q13), has also been shown in FS-DFSP. COL1A1-PDGFB fusion transcripts have also been detected in four of six superficial adult fibrosarcomas (but not deep ones) without a component of DFSP, implying possible origin from DFSP.
**Myxofibrosarcoma**

The term myxosarcoma was originally applied to myxoid change in fibrosarcoma (Warren and Sommer illustrate this – labelled edema - in their Fig 7) but Stout did not regard this as a separate entity and opposed the use of the term. The modern concept of myxofibrosarcoma was introduced in studies from Sweden in 1977-79. Higher grades of myxofibrosarcoma were considered to be equivalent to the contemporaneously described myxoid MFH, and there have been recent large clinicopathological series.

Although Merck (1983) suggested that myxofibrosarcoma was fibrohistiocytic, most ultrastructural and immunohistochemical studies have suggested that myxofibrosarcoma is a fibroblastic (not myofibroblastic) lesion. In fact, the term myxoid fibrosarcoma would be more appropriate as it would then be in line with myxoid liposarcoma, chondrosarcoma, leiomyosarcoma, etc. The proportion of myxoid change required to define this tumor has not been agreed. It has varied between >10% of tumor area, >30% of the whole tumor (or <20% of solid areas), at least half of the tumor, and wholly or almost wholly myxomatous; the current WHO classification refers to ‘variably myxoid stroma’.

Myxofibrosarcoma occurs mostly in the limbs of older subjects, and has a tendency to superficial location, as a multinodular subcutaneous unencapsulated mass which is usually slowly-growing. Within the myxoid nodules, spindle-shaped cells with hyperchromatic nuclei are irregularly dispersed. Nuclear pleomorphism is always present at least focally, but this is highly variable, and in areas the cells can look remarkably bland. Mitotic figures are usually found relatively easily, especially in the pleomorphic areas, and abnormal forms are seen. Higher grade lesions have an increasing proportion of non-myxoid tumor and pleomorphism as in storiform-pleomorphic MFH. These initially form solid cellular areas between the myxoid nodules, and can be fibrous, hemorrhagic or necrotic. Vessels are typically fairly numerous, short, separate, curved and relatively thick-walled rather than delicate; a plexiform vascular pattern is lacking and the tumor cells are not closely related to the blood vessels. A few scattered cells can be actin-positive, implying possible myofibroblastic differentiation and there is sometimes focal immunoreactivity for the fibroblastic marker CD34. Ultrastructurally, there are fibroblasts, with myofibroblastic differentiation appearing in higher grade or pleomorphic areas. The genetic abnormalities vary; some tumors are polyploid with complex karyotypes, and other have ringn chromosomes, 6p-or 9q+ or 12q+.

This lesion was originally defined as having four grades of which the lower ones are relatively bland angiomyxoid lesions, while higher ones have features of pleomorphic sarcomas. Prognostic factors include size (for metastasis, but not recurrence - 60% recur locally, often with grade progression), and depth: tumors in subcutis may recur but do not metastasize, whereas those involving deep fascia or muscle are more likely to recur and metastasize. The likelihood of metastasis is inversely proportional to the amount of myxoid change.
Low grade fibromyxoid sarcoma (LGFMS)

This was first described by Evans with 2 cases in 1987 and 10 more in 1993. It occurs in deeper soft tissues of young adults (with a subset located superficially) and is characterized by benign-looking histology, but a prolonged history of multiple recurrences and eventual metastasis. Histologically, the neoplasm shows predominantly fibrous and focally myxoid areas with a swirling or loosely whorled growth pattern. The appearance of fibrous areas and abrupt myxoid whorls is characteristic. Cellularity is low to moderate, and the stromal cells are bland with very rare mitoses, although there is focally minimal nuclear pleomorphism. The nuclei are not tapered but are ovoid or rectangular in places. The stroma is not markedly vascular, but tumor cells sometimes aggregate around vessels and a plexiform vascular pattern is occasionally seen. Subsequent recurrences are more cellular and mitotically active, and ultimately pleomorphic. The cases described by Evans recurred one to several times, usually over a period of many years, and eventually metastasized, most frequently to lung.

Hyalinizing spindle cell tumor with giant rosettes (HSCT) was described in 1997, as a painless, slowly growing, deeply situated mass of the proximal extremities (age 14-65 years, mean 38; 68% in males). 14 tumors were in skeletal muscle, and three in subcutis and most were circumscribed with occasional infiltrative borders microscopically. Histologically, they are composed of short fascicles of bland fusiform to spindled cells with minimal mitotic activity, situated in a hyalinized to myxoid stroma, often with “cracking” artefact in the collagen. In places there are more cellular areas sometimes with atypia. A characteristic feature is scattered large rosette-like structures that often merge with serpiginous areas of dense hyalinization. The rosettes, which vary from few and inconspicuous to multiple and prominent, consist of a central collagenous core surrounded by an irregular rim of rounded cells morphologically and immunophenotypically different from the cells of the spindled stroma. Lane et al suggested that this entity was similar to low-grade fibromyxoid sarcoma and a larger study from the same group of 73 cases of LGFMS and HSCT, supported this view and widened the spectrum of LGFMS. Epithelioid areas were present in 45% and rosettes in 30%. A number of LGFMS were also found to possess inconspicuous collagen rosettes indicating that these two tumors form a common spectrum. In fact, a specific chromosomal translocation, t(7;16)(q34;p11) resulting in a fusion gene FUS-BBF2H7 (also known as CREB3L2, or CREB3L1 in some cases), has recently been described in both LGFMS and HSCT, proving their identity and their nature as a distinct entity.

The spindle cells are immunoreactive in some examples for EMA and rarely for SMA and S100pr. The cells around the rosettes can express S-100 protein NSE and Leu 7 (11/13), and occasionally CD34. Ultrastructurally, both cell types appear fibroblastic with rare focal myofibroblastic differentiation.

Follow up (54 cases; range, 2-192 mos; median, 24 mos; mean, 38 mos) showed 5 recurrences, 3 metastases, and 1 death. Two of the metastatic tumors were LGFMS and one was a HSCT. HSCT, like LGFMS, are low-grade sarcomas with metastatic potential. The presence of focal areas of intermediate- to high-grade sarcoma does not relate to a worse outcome in the short term. LGFMS was initially reported to have a higher
metastatic rate than HSCT. However, Evans’ cases of LGFMS were initially selected because they eventuated in metastasis (and have frequently been misdiagnosed as fibromatosis), whereas in the large series of HSCT many cases were diagnosed prospectively as sarcomas and treated aggressively.

**Sclerosing epithelioid fibrosarcoma**

This was described in 1995 and occurs in deep muscle, around fascia or periosteum in the lower limb, trunk, shoulder and neck. Around 60 cases have now been reported. The tumors are circumscribed and can be up to 14.5 cm in diameter. They are sometimes multinodular, and cyst formation and calcification can be seen. Histologically, there are carcinoma-like nests or cords of rounded, epithelioid or fusiform cells, many of which have angulated nuclei within clear cytoplasm. Foci of more typical fibrosarcoma, with spindle cells in fascicles can be present elsewhere in the tumor. The cells are usually bland but can be pleomorphic, with mitoses up to 4/10 hpf and sometimes necrosis. The stroma has myxohyaline areas with metaplastic bone/cartilage, and a focal pericytomatous pattern. Some show positivity for CK, EMA, S100 protein, and bcl2, and the ultrastructure is interpreted as fibroblastic. Amplification of 12q13 and 12q15 sequences has been described in one case. Antonescu et al (2001) described a further series of 16 cases (3 of which had previously been reported) (6M, 10F, mean age 40) involving limbs and girdles, penis, chest wall and head and neck, with tumors between 3.7 and 22 cm. Only vimentin was expressed (though 5/12 had weak focal EMA), and again the ultrastructure was fibroblastic. These authors also describe some overlap with other fibrosarcoma patterns, including fascicular, and low-grade fibromyxoid sarcoma.

The tumor was initially described as low grade with 75% 5 year survival, but 53% persisted/recurred and 43% metastasised to lung or bone. In the series of Antonescu et al, the tumor appears to be of higher grade malignancy, with persistent disease or LR in 50% and metastasis in 86%, and 57% dead of disease 16 to 86 months after diagnosis. The aggregate of published cases indicates persistent/recurrent disease in 40%, and metastasis in 47% of cases.

**Myxoinflammatory fibroblastic sarcoma/inflammatory myxohyaline tumor**

This is a low-grade fibrosarcoma described from three centers in 1998, which arises in digits, wrist, and ankle regions, and predominantly in the subcutis. Montgomery et al described 51 cases, which occurred over a wide age range (4–81 years) and affected the sexes equally. 35 were in fingers, hand, wrist or arm, and 13 in toe, foot or lower leg. Many of the patients were treated aggressively but recurrences were noted in six of twenty-seven patients with follow-up. Almost simultaneously, a series of 44 apparently similar tumors in patients aged between 20 and 91 years was reported as “acral myxoinflammatory fibroblastic sarcoma” by these authors also noted a relation to tendon sheaths and joints in some cases. There was local recurrence in two thirds (67%) and several patients required amputation after repeated local recurrences. There was histologic documentation of metastasis to lymph node in one case. 5 tumors of the hand reported as “inflammatory myxoid tumor of the soft parts with bizarre giant cells by Michal, also in 1998, appear to be the same entity. There are now about 132 published cases, including 7 non-acral examples.
These tumors form infiltrative multinodular masses characterized by dense inflammation merging with myxoid to collagenous stroma. The myxoid zones contain (multi)vacuolated lipoblast-like fibroblasts, as seen in other myxoid fibroblastic lesions and representing stromal mucin within dilated RER. The inflammatory zones have scattered bizarre cells with vesicular nuclei and large inclusion-like nucleoli with abundant focally vacuolated cytoplasm, reminiscent of Reed-Sternberg cells or “virocytes”, some of which contain phagocytosed neutrophils. Other components include eosinophils, neutrophils, lymphocytes, plasma cells, Touton giant cells and siderophages, and fibrosis (including sclerosed and hyalinized areas). Normal and atypical mitoses are seen among the bizarre cells, and some cases displayed focal necrosis.

Immunostains are positive for vimentin and negative for CD30, CD15, and S100 protein; 4 of 13 cases were cytokeratin positive, but this was focal and weak and interpreted as aberrant. PCR for EBV was negative in 6/10 cases and positive at low levels (suggesting latent rather than active viral infection in 4). In the Swedish series, 7 of 25 were CD34 positive, 2 were SMA positive in occasional bizarre cells, and Ki67 labeling index was less than one per cent. Ultrastructural studies in this series demonstrated fibroblastic characteristics, and the ganglion-like cells are interpreted as modified fibroblasts. Clonal chromosome changes have been described in one case, which showed a complex karyotype with a reciprocal translocation t(1;10) (p22;q24) in addition to the loss of chromosomes 3 and 13.

Of the 132 published cases, 40% have recurred but only 3 have metastasized. Of the 4 non-acral cases with follow up information, only one has recurred (after 5 years).

**Pleomorphic Fibrosarcoma and Myofibrosarcoma**

Pleomorphic sarcomas have been subject to numerous revisions. Until the 1960s, they were categorized as pleomorphic rhabdomyosarcoma, fibrosarcoma, or undifferentiated pleomorphic sarcoma. At this time, based on tissue culture studies, it was considered that histiocytes of the reticuloendothelial system could under the correct circumstances become facultative fibroblasts. In 1963 Stout and coworkers examined a heterogeneous collection of soft tissue tumors (supposedly histiocytomas and fibrous xanthomas) with tissue culture and concluded that the fibroblastic elements were derived from histiocytes. The term malignant fibrous histiocytoma (MFH) was formalized as a type of malignant histiocytic tumor in the 1967 AFIP fascicle. A clinico-pathologic series of MFH, published in 1972, was soon followed by studies defining further morphologic types of MFH: giant cell, inflammatory, myxoid and angiomatoid. MFH became the most common diagnosis among adult soft tissue sarcomas, and pleomorphic fibrosarcoma essentially disappeared.

The fibrohistiocytic concept was later challenged and rebutted by the sequential application of new investigative modalities. Immunohistochemistry showed absence of marrow-derived histiocytic antigens and presence of antigens associated with mesenchymal cells, including intermediate filaments. Careful morphologic observation combined with immuno-histochemical and genetic studies allow separation of other
pleomorphic sarcomas such as pleomorphic liposarcoma or dedifferentiated liposarcoma. The residual tumors (synonym: MFH) formed a genetically heterogeneous group of fascicular or storiform neoplasms composed of atypical spindle and polygonal cells which show no specific line of differentiation. In fact, the constituent cells, whether fusiform or plump and histiocyte-like, have ultrastructural features of fibroblasts, with much rough endoplasmic reticulum. In addition, myofibroblastic differentiation has been observed since electron microscopy was first employed on examples of MFH. Typically, there are subplasmalemmal aggregates of cytoplasmic filaments, and a neoplastic cell with a fibronexus has been recorded in a pleomorphic myofibrosarcoma of bone. The proportion of pleomorphic sarcomas which display myofibroblastic differentiation increases with sample size and length of search. In one study, 56% of MFH of all types had detectable myofibroblasts, with a mean of 3% (range 0 - 22%) of myofibroblasts per case. Some low-or intermediate-grade myofibrosarcomas have recurred as pleomorphic tumors. Pleomorphic MFH and pleomorphic myofibrosarcoma are morphologically indistinguishable but the latter (like pleomorphic sarcomas with myogenic differentiation) have a worse outcome in the relatively few cases with clinical and follow up data.

Immunohistochemically, both SMA and desmin have been described in pleomorphic sarcomas with ultrastructurally confirmed myofibroblastic differentiation. None of the pleomorphic myofibrosarcomas examined expressed h-caldesmon, which implies that they are not merely poorly differentiated leiomyosarcomas. However, both actin and desmin have been demonstrated in pleomorphic sarcomas without ultrastructural features of myofibroblastic or smooth muscle differentiation. Ultrastructural examination reveals variable myofibroblastic differentiation.

As recently suggested, pleomorphic MFH, since it is primarily composed of fibroblasts with or without myofibroblastic modulation, can be regarded as the pleomorphic form of fibrosarcoma.

Conclusions

- Fibrosarcomas can be cellular or modified by stromal changes
- They can be differentiated or pleomorphic. Pleomorphic fibrosarcoma subsumes many tumors previously characterized as malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma.
- They can contain a variable proportion of myofibroblasts
- They are defined by EM and identifiable by LM. Immunohistochemistry is chiefly of value in excluding other tumors.
- Some have specific and consistent genetic abnormalities which are of diagnostic use.

References