

More Than a Diagnosis: How the Surgical Pathologist Should Deal with a Soft Tissue Tumor.

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Bullet points:

- Use a team approach – be familiar with the clinical and radiographic findings and treatment implications.
- Triage the tissue thoughtfully so necessary ancillary studies can be performed.
- Subclassify and appropriately grade sarcomas.
- Carefully dissect excision specimens and determine the status of resection margins and measure their clearance.

Introduction

“My early training has always impressed on me that the Surgical Pathologist’s chief function is service, to be useful and helpful to the therapist . . .”. (1) This was Stout’s credo, and it remains, as it should, one of the important philosophical underpinnings of our medical specialty. Being useful and helpful to the ‘therapist’ in the treatment of soft tissue tumors is essential for optimal patient outcome, and these responsibilities should be fulfilled by the pathologist in a careful, deliberate, and thoughtful manner which incorporates the remarkable advances made in our understanding of soft tissue neoplasia.

How the surgical pathologist deals with a soft tissue tumor has significant impact on the information that can be derived from the specimen. Key to the appropriate handling of a soft tissue tumor specimen is the utilization of an integrated approach that assesses and correlates the clinical, morphologic, immunophenotypic, molecular and biologic attributes of the lesion, as well as, the treatment effect, and status of resection margins. In most instances, this is best accomplished when the pathologist is a participatory member of a multidisciplinary group, which includes oncologic sarcoma surgeons, musculoskeletal radiologists, and clinicians who specialize in the treatment of patients with these tumors. This team of physicians works together to diagnose the lesion and design an optimal treatment strategy that incorporates the type, grade, and stage of the tumor and the prognosis and medical condition of the patient.

Assessing soft tissue tumors in isolation without pertinent information is inappropriate and predisposes to diagnostic errors that may have dire consequences for the patient. Clinical information such as the age of the patient, relevant past medical history, length of time the tumor has been noted, and the anatomic location, depth, and size of the tumor can help paint a portrait of the neoplasm that assists the pathologist in generating an appropriate differential diagnosis.

Soft Tissue Tumor Specimens

Tissue from soft tissue tumors is retrieved to make a primary diagnosis, eradicate the neoplasm, document recurrence or metastasis and assess treatment effect. The tissue is usually obtained in the form of fine-needle aspiration cytology (FNA), needle cores, open biopsy or an en bloc resection. It is best that the specimens be sent to the pathology laboratory immediately after it is removed from the patient and should be kept in the fresh state until it is evaluated by the pathologist. In many instances, gross inspection, dissection and frozen section analysis can be useful in providing immediate important information.

Role of Intraoperative consultation, tissue triage, and preparation

Intraoperative consultation can be a valuable tool in the handling of soft tissue tumor specimens. The pathologist should always be aware of the implications of every diagnosis made by frozen section analysis. Regarding diagnostic specimens (needle core, open biopsy or resection), performing a frozen section allows the pathologist to render a working diagnosis, and importantly, triage pieces of tumor for all of the necessary ancillary studies required to make a definitive diagnosis. This includes the consideration of submitting fresh tissue for karyotypic analysis and snap freezing and storing tumor for molecular analysis usually in search of tumor-specific translocations, performing touch preps for FISH, mincing small pieces and placing them in gluteraldehyde for electron microscopy, and processing adequate amounts of tissue for routine histologic evaluation.

Intraoperative consultation is also very important in evaluating tumor resection specimens (see below). It affords the pathologist the opportunity to become familiar with the orientation of the specimen, as well as, assess the relationship of the tumor to important normal structures and the margins of resection. When necessary, the individual margins can undergo frozen section analysis to confirm their status microscopically.

Fine Needle Aspiration (FNA)

Fine needle aspiration cytologic evaluation has been reliably and successfully utilized for many years in the investigation and diagnosis soft tissue tumors (2-8). FNA of soft tissue tumors, however, is challenging because of the morphologic heterogeneity of the tumors and their relative rarity. Regardless, this technique is important because of its minimally invasive nature, speed, and low cost.

The utility of FNA in the evaluation of soft tissue lesions has been demonstrated by a favorable comparison of its accuracy rate to that achieved by other available biopsy techniques (2-9). FNA diagnosis of soft tissue tumors has been reported to have a high accuracy rate (> 90%)

when the goal is distinguishing benign from malignant lesions ((2-8). Cytopathology is significantly less accurate, however, when precise subclassification of tumors or grading of a sarcoma is required (2-10). Specific problematic areas include distinguishing amongst the different types of myxoid tumors, low grade fibroblastic neoplasms, differentiating reactive pseudosarcomas from sarcomas, to name a few.

FNA evaluation is most successful when stained smear preparations are used in conjunction with hematoxylin and eosin-stained cell block material. Cell block specimens facilitate the assessment of architecture and provide tissue for special studies including immunohistochemistry, FISH, and molecular analysis. Some authors, who I agree with, feel core biopsy in conjunction with FNA optimizes diagnostic accuracy (7). I also think it is important that cytopathologic preparations be interpreted by pathologists with experience and expertise in the technique and soft tissue pathology.

Needle Core Biopsy

If a tumor is being diagnosed via needle biopsy, which is frequently performed with CT guidance, we recommend that 3 cores of tumor-bearing tissue be obtained. In most instances, a frozen section can be performed on 1 core to confirm that diagnostic tissue has been received, provide provisional diagnostic information, and facilitate triage of the remaining tissue. This core can be kept frozen for immunohistochemical and molecular studies, if needed. The second core can be used to generate 3-5 touch prep slides and should then be fixed in formalin and processed routinely for the production of standard hematoxylin and eosin stained slides. Portions of the third core can be submitted for electron microscopy, cytogenetics, or molecular analysis, if such ancillary techniques are warranted.

Open Biopsy

Open biopsy for primary diagnosis is being performed less frequently. These specimens are also amenable to frozen section analysis. The tissue can be frozen to construct a working diagnosis and allow for the appropriate triage of tissue. If the biopsy is going to be immediately followed by a definitive procedure during the same operation, then all of the tissue submitted for initial diagnosis should undergo frozen section analysis so that errors based on sampling can be avoided. Portions of specimens not frozen should be fixed and processed in their entirety, if this can be accomplished with 10 cassettes.

En bloc resections

En bloc resections are performed for both benign and malignant neoplasms. Unfortunately, there is no standardized protocol for evaluating soft tissue tumor resection specimens, and each institution likely completes the task in a different fashion. The following are suggestions based on my experience in evaluating soft tissue tumor resection specimens.

1. During the resection the surgeon should identify and mark important landmarks or aspects of the orientation of the specimen. This can be easily accomplished by using different length or color sutures.

2. Once the specimen has been removed from the patient the surgeon should review it and the pertinent imaging studies with the responsible staff pathologist. The surgeon should also indicate what margin, if any, is particularly close or of concern.
3. The pathologist should fully understand the orientation of the specimen and be able to identify all of the margins and important landmarks. We have found that when handling a resection specimen, if the tissue overlying the neoplasm is soft and movable the margin in that area is likely to be negative. Tissue planes fixed to the tumor implies infiltration by the neoplasm and the relevant margin is likely to be positive. For specimens in which the tumor is surrounded by fatty or soft and extremely mobile tissue we submerge the entire specimen in liquid nitrogen for 30 seconds – 1 minute to firm up the tissue at the margins, which facilitates slicing or bread loafing the margins at thin (0.3-0.5cm) intervals. For large specimens, the pathologist should bisect the inked specimen through both the greatest dimension of the tumor and the closest margin. The two halves can then be carefully serially sectioned perpendicular to the cut surface and the margins at 3-5 millimeter intervals. For smaller specimens such as a skin ellipse and underlying subcutis and deep fascia, the entire specimen is again inked, submerged in liquid nitrogen for 30 seconds to 1 minute and then serially cross sectioned perpendicular to the long axis of the specimen as 3-5 millimeter intervals. The margin(s) from both small and large specimens that are deemed the closest can be immediately sampled for frozen section analysis. If a margin is identified as being positive, the surgeon then has the opportunity to resect additional tissue during the ongoing operation. If the margins are considered negative, the pathologist can sample the margins for permanent section analysis according to the following guidelines: a) margin(s) that measure less than 2 mm. should be sampled so that one section per half centimeter is submitted; b) margin(s) that measure between 2mm and 1 cm, should have 1 section submitted per centimeter submitted; c) margin(s) that measure greater than 1 centimeter should have 1 section per surface submitted. The tumor should then be thoroughly dissected and representative sections submitted at a minimum of 1 cassette per centimeter of tumor. If needed, fresh tumor can be frozen for both diagnostic purposes and tissue triage
4. Resected tumors that have been treated with preoperative chemotherapy may require determination of the percent of tumor necrosis. To accomplish this, a central slab of tumor can be Xeroxed and then blocked out in its entirety. A section of tumor per centimeter (as determined by its greatest dimension) should be processed from each of the remaining 2 hemispheres of the specimen. During histologic review, the amount of tumor necrosis on each slide can be estimated and these scores can then be averaged to calculate the overall percent tumor necrosis. The location of the areas of viable and necrotic tumor can then be located on the map of the slab section, if necessary.

Clinical Reporting of Soft Tissue Tumor Specimens

The surgical pathology report is the documentation and distillation of the clinical and pathological information derived from the pathologist's evaluation of a soft tissue tumor. (11, 12) The report should include the appropriate patient identifiers, important clinical findings, anatomic site, anatomic depth (dermal, subcutaneous, fascial, intramuscular, intra-abdominal, retroperitoneum), type of specimen (FNA, needle core, incisional, excisional) and number of

specimens and pieces of tissue. The macroscopic evaluation should include orientation data, descriptive characteristics of the neoplasm (size, color, texture, cystic change, hemorrhage), pattern of growth (well circumscribed/infiltrative), and relationship to normal structures and distance from margins.

For benign tumors the diagnosis should include the histologic classification of the tumor, and its anatomic location and relationship to normal structure and surgical margins, if relevant. (13) Results of all ancillary studies including frozen sections, and clinical correlations should be included, as well.

For sarcomas the diagnosis should include the histologic classification and grade of the tumor. The grade of the sarcoma has been shown to be the single most important prognostic feature of the tumor and represents the pathologists attempt to predict biological behavior based on morphologic grounds. (13-17) The grade of the sarcoma is also important because in certain situations (large and deep seated tumors) it may have a bearing on whether or not chemotherapy is incorporated into the treatment plan. The two most common grading systems used are the French Federation of Cancer Centers Sarcoma Group (FNCLCC – see below) and National Cancer Institute (NCI) systems. (18,19) These grading schemes are 3 tiered and incorporate the degree of differentiation or histologic type, cytologic feature, necrosis and mitotic activity into a numeric grade. They were derived from studies using abundant representative tissue from either incisional or excisional biopsy specimens. However, most soft tissue sarcomas are now being diagnosed on much smaller volumes of tissue from needle core biopsies. This introduces challenges to the process of grading because of the potential of problems in sampling in which necrosis may be absent and mitotic activity limited. In these situations, for most sarcomas, I rely on the degree of cellularity and cytologic atypia to determine the grade. If there is a discrepancy between the clinical and radiographic findings (large deep-seated heterogeneous mass with areas of likely necrosis) and the grade (tumor appears low grade) then recommending another biopsy for additional sampling of the tumor should be considered, if the grade of the tumor is going to influence the next step in the treatment scheme.

Other information in the report of a sarcoma should include the anatomic location and relationship to normal structures and surgical margins, if relevant. Mitotic activity, presence or absence of necrosis, presence or absence of vascular invasion and lymph node metastases, treatment effect, and the results of all ancillary studies including frozen sections, and clinical correlations should be included, as well. (11)

This information helps provide the information to stage the patient. The TNM Staging System for soft tissue tumors of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is commonly used and provides information for treatment and prognosis. (21,22)

FNCLCC Grading (Modified from Ref 11).

The FNCLCC grade is based on 3 parameters: differentiation, mitotic activity, and necrosis. Each of these parameters receives a score: differentiation (1–3), mitotic activity (1–3), and necrosis (0–2). The scores are summed to produce a grade.

Grade 1: 2 or 3

Grade 2: 4 or 5

Grade 3: 6 to 8

Differentiation.—Tumor differentiation is scored as follows:

Tumor Differentiation	
Histologic Type	Score
Well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrosarcoma	2
Myxofibrosarcoma (myxoid MFH)	2
Typical storiform MFH (sarcoma, NOS)	3
MFH, pleomorphic type (patternless pleomorphic sarcoma)	3
Giant cell and inflammatory MFH (pleomorphic sarcoma, NOS with giant cells or inflammatory cells)	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly differentiated/pleomorphic/epithelioid leiomyosarcoma	3
Biphasic/monophasic synovial sarcoma	3
Poorly-differentiated synovial sarcoma	3
Pleomorphic rhabdomyosarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Ewing sarcoma/PNET	3
Malignant rhabdoid tumor	3
Undifferentiated sarcoma	3

Score 1: Sarcomas closely resembling normal, adult mesenchymal tissue

Score 2: Sarcomas of certain histologic type

Score 3: Synovial sarcomas, embryonal sarcomas, undifferentiated sarcomas, and sarcomas of doubtful tumor type

Tumor differentiation is the most problematic aspect of the FNCLCC system. Its use is subjective and does not include every subtype of sarcoma. Nevertheless, it is an integral part of the system, and an attempt should be made to assign a differentiation score.

Mitosis Count.—The count is made in the most mitotically active area in 10 successive high-power fields (HPFs) (a high-power field $\times 400 = 0.1734 \text{ mm}^2$) (use the 40 \times objective).

Score 1: 0 to 9 mitoses per 10 HPFs

Score 2: 10 to 19 mitoses per 10 HPFs

Score 3: 20 or more mitoses per 10 HPFs.

Tumor Necrosis.—Determined on histologic sections.

Score 0: No tumor necrosis

Score 1: Less than or equal to 50% tumor necrosis

Score 2: More than 50% tumor necrosis

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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 Rokitsky (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 extracellular fibers.¹ Fibrosarcoma was included in subsequent classifications by Wilks (1849) (as fibroplastic) and Borst (1902)(as fibroma sarcomatosum)². Later, following the views of Ewing (1922)³ and of Quick and Cutler (1927)⁴, 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)⁵ 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”⁶, 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 1971⁷.

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

Adult fibrosarcoma
in dermatofibrosarcoma
in solitary fibrous tumor
Infantile fibrosarcoma
Myxofibrosarcoma
Low grade fibromyxoid sarcoma/hyalinizing spindle cell tumor with rosettes
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.⁸ 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 CD34⁹ and SMA in some cases. An occasional cell has peripheral filament bundles suggestive of myofibroblastic differentiation; tumors in which this is prominent are myofibrosarcomas.¹⁰ 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%^{11,12}. 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* (17q21-22) and *PDGFB1*(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.¹³

Myxofibrosarcoma

The term myxosarcoma was originally applied to myxoid change in fibrosarcoma (Warren and Sommer illustrate this – labelled edema - in their Fig 7⁵) but Stout did not regard this as a separate entity and opposed the use of the term⁶. The modern concept of myxofibrosarcoma was introduced in studies from Sweden in 1977-79¹⁴⁻¹⁶. Higher grades of myxofibrosarcoma were considered to be equivalent to the contemporaneously described myxoid MFH¹⁷, and there have been recent large clinicopathological series^{18,19}. Although Merck (1983)²⁰ 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 area¹⁹, >30% of the whole tumor (or <20% of solid areas)¹⁸, at least half of the tumor²¹, and wholly or almost wholly myxomatous²⁰; the current WHO classification refers to 'variably myxoid stroma'.²²

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 polyploidy with complex karyotypes, and other have ring 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.^{23, 24} It occurs in deeper soft tissues of young adults (with a subset located superficially²⁵) and is characterised 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 1997²⁶, 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 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 group²⁷ 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 entity²⁸⁻³⁰.

The spindle cells are immunoreactive in some examples for EMA²⁵ 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.³¹

Follow up (54 cases; range, 2-192 mos; median, 24 mos; mean, 38 mos) showed 5 recurrences, 3 metastases, and 1 death.²⁷ 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 1995³² 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)³³ 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 al³⁴ 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”³⁵. 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”³⁶. 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.³⁵ 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 13.³⁷

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.³⁸ Careful morphologic observation combined with immuno-histochemical and genetic studies allow separation of other pleomorphic sarcomas such as pleomorphic liposarcoma or dedifferentiated liposarcoma.³⁹ 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.⁴⁰ 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.⁴¹ 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.⁴² 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^{43, 44}, 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.

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HEMANGIOPERICYTOMA, TRUE PERICYTIC TUMORS AND MIMICS

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Bullet points

- Diagnostic criteria for the diagnosis of hemangiopericytoma have shifted since Stout's first description.
- Very many tumors may show a branching pericytoma-like vascular pattern, as a consequence of which the diagnostic term 'hemangiopericytoma' has often been loosely applied.
- The majority of tumors formerly diagnosed as so-called hemangiopericytoma have nothing to do with pericytes.
- The single largest subset of lesions formerly known as hemangiopericytoma (at all sites) would nowadays be classified as solitary fibrous tumors.
- There exists a group of truly pericytic neoplasms, known as myopericytoma, which are being increasingly defined and represent a continuum between myofibroma(tosis), glomus tumor and angioleiomyoma.

Hemangiopericytoma was first described and introduced as a diagnostic concept by Stout and Murray in 1942.¹ They described a series of 9 cases characterized by perivascular proliferation of rounded cells, which they believed to be Zimmermann's pericytes. They chose the term hemangiopericytoma to contrast with hemangioendothelioma, a type of vascular tumor in which the dominant proliferating component (whether benign or malignant), was endothelial cells. In 1949, Stout published an additional 25 new cases with the purpose of further characterizing and defining the 'entity'.² At this time he noted that the tumor cells consistently grow outside the reticulin sheath of vessel walls, that "the exact nature of these so-variable cells" was uncertain and that it was not possible to distinguish benign and malignant examples of hemangiopericytoma on morphologic grounds. Just 4 years later, in 1953, he stated, during a slide seminar in New York, that it was his "general attitude in regard to hemangiopericytoma to reject it as a diagnosis if he could think of any other reasonable explanation for a tumor."³ He already feared that it might represent a possibly heterogeneous tumor type but, nevertheless, he described a further series of 31 cases in pediatric patients, identified from among a total of 307 cases of hemangiopericytoma (at all ages) which he had accumulated by that time.⁴ Among these 31 cases, 10 were congenital and more than 50% developed before the age of 5 years. Two patients had multifocal lesions.

In succeeding years, however, the concept of hemangiopericytoma shifted and, in the major series published by Enzinger and Smith in 1976,⁵ the definition shifted away from describing cells with rounded glomus-like morphology and a perivascular growth pattern to focus on ovoid-to-spindle-shaped cells arranged in a haphazard fashion in association with variably dilated branching or staghorn vessels.

The proposal that these tumors were composed of perivascular contractile cells was based mainly on the architectural pattern with tumor cells surrounding branching blood vessels, and was supported to some extent (at least in the past) by ultrastructural studies.⁶⁻⁸ However, immunohistochemistry has failed to support this theory, as most tumors (at least in adulthood) stain only (and non-specifically) for vimentin and CD34⁹ but not for actin or other myoid markers.^{8,10,11}

Traditionally, hemangiopericytoma has been classified into adult and infantile variants which have little in common, either clinically or histologically, except for the presence of a branching "pericytomatous" vascular pattern, a feature that is also shared with many other tumors.¹²⁻¹⁴ Most common among those tumors which consistently share this pattern are solitary

fibrous tumor, synovial sarcoma, infantile myofibromatosis, low-grade endometrial stromal sarcoma, mesenchymal chondrosarcoma, deep benign fibrous histiocytoma and infantile fibrosarcoma.

In recent years it has become clear that infantile and adult hemangiopericytoma are two completely independent “entities”, the former being closely related to infantile myofibromatosis and the latter being of disputed nature but, in most cases, essentially synonymous with solitary fibrous tumor.

Among the lesions formerly diagnosed as hemangiopericytoma in adults there seems to have been considerable inhomogeneity, likely reflecting the absence of reproducible diagnostic criteria. In fact the personal opportunity, with Juan Rosai, to review some of Stout’s original cases has suggested that this “entity” may have been heterogeneous and relatively non-cohesive from the outset, as is easy to understand given the absence of more modern diagnostic techniques at that time. In this regard it is worth reminding ourselves that, by 1953, Stout himself indicated that he no longer made this diagnosis if he could come up with any alternative !

As a consequence, hemangiopericytoma has become (like so-called “malignant fibrous histiocytoma”) something of a wastebasket diagnosis, yet there remain discrete subsets (detailed below) for which there is no better name. In parallel with this realization, it is also increasingly appreciated that there probably exists a group of truly pericytic lesions (examples of which were included in Stout’s early work on this topic).^{1,2} These lesions, which include examples of so-called “myofibromatosis” occurring in adults,¹⁵ are best categorized as myopericytoma and are described in more detail below.

Clinical features

So-called adult hemangiopericytoma has traditionally been said to occur in middle to late adult life with an equal sex distribution.^{5,16} Probably the majority of the cases so classified in the past would nowadays be regarded as examples of solitary fibrous tumor at the more cellular end of that morphologic spectrum and this view was codified in the 2002 WHO Classification.¹⁷ This would also include the cellular lesions located in pelvis and retroperitoneum, seemingly most often in adult females, which may be associated with hypoglycemia due to secretion of insulin-like growth factor.¹⁸ A supposedly distinct group comprises those lesions which arise in the meninges (formerly often known as angioblastic meningioma but nowadays often labelled ‘*meningeal hemangiopericytoma*’).^{19,20} However, many would argue that these also are cellular or malignant

examples of solitary fibrous tumor and certainly there seem to be no convincing criteria for distinguishing these tumor types from one another. Although histologic grading of these so-called meningeal hemangiopericytomas is unreliable, many seem ultimately to pursue an aggressive course: a distinctive feature of considerable relevance to general pathologists is the propensity of meningeal lesions to give rise to osseous, intra-abdominal or (less often) pulmonary metastases, often after a prolonged latent period.

Sinonasal hemangiopericytoma is a histologically distinct subset composed of more obviously myoid (actin-positive) cells. These cells are short, spindled or ovoid, with uniform nuclear morphology and pale eosinophilic cytoplasm. They are typically arranged in sheets or nodules around small thin-walled vessels and form a submucosal mass which generally measures less than 2-3 cm. Such tumors occur principally in adults and are characterized by the tendency for local recurrence in 15-20% of cases, but not metastasis.²¹⁻²³

So-called infantile hemangiopericytoma can be congenital or else present in the first years of life as a solitary, most often deep dermal or subcutaneous mass.^{5,24,25} Some patients have multiple lesions,²⁵ further underlining the overlap with infantile myofibromatosis. Recurrence is common but the ultimate behavior is generally benign. Rare cases with metastasis have been reported;²⁶ however this might represent an unusual manifestation of multicentricity rather than true metastasis. The clinicopathologic features are virtually identical to those of infantile myofibromatosis and it is nowadays generally agreed that they represent different stages or patterns of the same entity.^{24,25,27}

Myopericytoma is the term we currently prefer to use to embrace lesions described as myofibromatosis in adults, glomangiopericytoma and myopericytoma.^{14,28,29} This is essentially the largest group of true pericytic neoplasms. We also believe that this is usually a more appropriate term for infantile myofibromatosis and solitary myofibroma in adults,²⁸ although general adoption of such changes in terminology is only occurring gradually. As a group, these lesions most commonly develop in superficial soft tissue of the extremities (particularly the distal lower limb) of adults, although often they have been noticed since birth or early childhood. The lesions may be solitary or multiple, are sometimes painful, and (in clinical terms) appear to recur locally in 10–20% of patients, although this probably represents multifocal (or “field change”) disease, rather than true recurrence of a previously excised lesion. A case of glomangiopericytoma associated with

oncogenic osteomalacia has been described.³⁰ Examples of malignant myopericytoma are very rare but seem to behave aggressively.³¹

Histologic appearances

Adult hemangiopericytomas (so-called) are indistinguishable from (and essentially the same as) cellular examples of solitary fibrous tumor. They are usually well circumscribed, often lobulated, and are composed of cytologically uniform small, basophilic, ovoid to spindle cells with an oval nucleus and ill-defined cytoplasm. These cells are arranged in a patternless fashion around numerous thin-walled ramifying blood vessels, which often adopt a typical staghorn configuration. Focal or diffuse myxoid change and stromal fibrosis can be a feature. A silver stain shows that the tumor cells are located outside the vascular spaces and are each surrounded by a reticulin sheath. Features that have been said to indicate malignancy are the presence of increased cellularity, necrosis, hemorrhage and more than 4 mitotic figures per 10 high-power fields,⁵ the latter being the most important feature – these are essentially the same criteria as are nowadays employed in solitary fibrous tumor.^{32,33}

So-called infantile hemangiopericytoma is a multinodular tumor in which the lesional cells tend to be more polymorphic and focally spindle-shaped or myoid in appearance. Mitotic figures and focal necrosis are common findings, as is subendothelial proliferation which may simulate vascular invasion. In essentially all cases it is possible to distinguish a second tumor cell population composed of micronodules and fascicles of plump spindle-shaped cells with myoid features that stain positively for smooth muscle actin. This creates a subtle zoning phenomenon, indistinguishable from (but often less marked than) that seen in myofibromatosis.

Myopericytoma encompasses a morphologic continuum of lesions ranging from those with the appearance of myofibromatosis to those, which almost resemble glomus tumor (but often with “pericytoma-like” vessels) or angioleiomyoma. All are composed of actin-positive perivascular contractile cells showing a variable degree of myoid (spindle-celled or glomoid) cytomorphology. In many cases there are admixed patterns that closely resemble myofibromatosis and so-called “hemangiopericytoma”, except that the perivascular spindle cells in these lesions are eosinophilic and clearly myogenic. It is common, particularly at the periphery of these lesions, to find perivascular proliferation of similar spindle-shaped cells (outside the main tumor nodule), as also occurs in glomus tumors and these cells may also proliferate in either the adventitial or subendothelial layers of vessel walls. The latter closely mimics true vascular invasion, except for

the intact overlying layer of endothelium, and this is the feature which has previously been well described in both infantile myofibromatosis and infantile hemangiopericytoma (which in reality are points on this same morphologic spectrum). Examples of true intravascular myopericytoma are seen occasionally.³⁴

Differential diagnosis

With the advent of immunohistochemistry the diagnosis of so-called hemangiopericytoma became one of exclusion since many neoplasms can show, at least focally, a pericytoma-like pattern.^{12,13} Most particularly these include:

- synovial sarcoma, which may show a biphasic pattern and is EMA and pan-keratin positive
- mesenchymal chondrosarcoma, which shows islands of mature cartilage
- deep benign fibrous histiocytoma, which is more polymorphic (showing a storiform pattern and inflammatory cells)
- phosphaturic mesenchymal tumor, which has a variety of histologic patterns and is often associated with calcification and osteoclast-like giant cells.

Other tumors which commonly show this vascular pattern are infantile fibrosarcoma and, in truth, almost any type of sarcoma may show focally a perfect resemblance to so-called “hemangiopericytoma” on occasion, hence this diagnostic term is falling into disuse and should only be employed with great caution and in specific clinical contexts. In the long run, it seems possible that the term may be reintroduced for the family of myopericytic neoplasms – but it seems prudent to ensure that the majority of pathologists (as well as relevant clinicians) understand the demise of the former usage before any such change is made.

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Problem-Prone Soft Tissue Lesions with a Potential for Litigation

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BULLET POINTS

1. Understand the incidence of serious errors in soft tissue pathology and how the method of ascertainment affects one's perception of the problem.
2. Develop an awareness of the most common situations and/or lesions in soft tissue pathology that give rise to potentially litigious errors.
3. Understand the reasons that underlie these mistakes and develop a strategy or approach to avoid them.

INTRODUCTION

Although there are numerous problem-prone situations in soft tissue pathology, this lecture will focus on those in which a misdiagnosis significantly alters therapy or prognosis such that a malpractice claim could arguably ensue. How one identifies this group of lesions and assesses their relative importance is influenced by the method of ascertainment. In other words, the manner in which a misdiagnosed case comes to one's attention can influence our perception of which lesions are problem-prone. For example, a retrospective study of sarcomas referred to a northwest England regional cancer registry found that 22% of cases were not sarcomas following review of an expert panel.¹ On the other hand, a large review of referral material submitted on patients undergoing therapy at a large tertiary care center, found that in 1.4% (86 of 6171) the diagnosis was changed.² Of these 86 cases only 1% involved soft tissue lesions, an incidence that roughly paralleled the incidence of soft tissue lesions in the group as a whole. This could be construed as indicating that significant misdiagnoses in soft tissue are a minor problem.

More recently Troxel has analyzed "diagnostic pitfalls" in surgical pathology based on an review of actual malpractice claims submitted to The Doctors Company, a physician-owned professional liability insurer of approximately 10% of pathologists in this country. Although approximately one half of claim cases displayed no error pattern and were therefore considered "random errors," the other half fell into a number of "repetitive" patterns indicating "systematic cognitive error."³ The most common systematic cognitive errors related to melanoma and breast biopsy diagnosis; each accounted for 15% of all claims. The diagnosis of sarcomas, also considered among systemic cognitive errors, accounted for about 5% of all malpractice claims and, therefore, are disproportionately represented relative to the rarity of the disease. Furthermore, litigation more often centered around the failure to diagnose malignancy (false negative diagnosis) than the over diagnosis of malignancy (false positive).

Claim cases, however, represent the end result of numerous failed opportunities to either diagnose the case correctly or to resolve the case short of a malpractice claim. The study by Arbiser et al, which analyzes soft tissue cases referred for expert consultation, gives a more balanced view of problematic lesions. The authors found that 25% of cases referred for consultation with an accompanying diagnosis underwent a diagnostic change. These could be broken down into the following categories: benign mesenchymal lesions diagnosed as sarcomas (45%), sarcomas

diagnosed as benign lesions (23%), non-mesenchymal lesions diagnosed as mesenchymal tumor (20%), and significant grading errors (12%). Interestingly, this study found that a relatively few number of lesions led to a majority of major diagnostic discrepancies (e.g. nodular fasciitis, desmoplastic melanoma) suggesting that heightened awareness of a few lesions could significantly reduce diagnostic discrepancies.

PROBLEM PRONE SITUATIONS

The following problem-prone categories will be discussed and illustrated with cases:

Low grade spindle cell sarcomas

One of the most common situations that leads to litigation is the failure to recognize a low grade spindle cell sarcoma as a malignant. The best example is the **monophasic synovial sarcoma**. In fact, in the study by Troxel one third of all claims involving false negative diagnosis of sarcoma were monophasic synovial sarcomas. In its classic form the synovial sarcoma is a densely cellular spindle cell sarcoma having a fascicular growth pattern and expressing EMA and cytokeratin in about 90% and 60% of cases respectively. The principal reasons for false negative diagnoses are:

- Long clinical duration such that the clinician has prejudged the lesion to be benign
- The lesions appears hypocellular because it is myxoid, densely hyalinized, calcified, or infiltrates between tendinous connective tissue.
- Immunostains for keratin and/or EMA are not performed or the presence of S100 protein, which occurs in about one third of cases, is interpreted as evidence of benign nerve sheath tumor

The common non-malignant diagnoses that are rendered for monophasic synovial sarcoma are fibroma, calcifying aponeurotic fibroma, fibromatosis, and neurofibroma

The diagnosis of monophasic synovial sarcoma should be suspected in low grade spindle cell proliferations on the extremities of young adults, especially if calcified. The appropriate immunostains should be ordered and confirmed by molecular genetic testing for the unique and specific $t(X;18)$ in questionable cases

Low grade fibromyxoid sarcoma (LGFMS), a relatively recently described lesion, usually develops in the deep soft tissue of the extremities of young to middle aged patients.^{5,6} Consisting of fibromatosis-like areas that merge with highly myxoid zones containing an arborizing vasculature they have a “mosaic” or marble-like appearance at low power. The cells vary from oval to spindled and in some cases encircle large nodules of collagen leading to the formation of giant collagen rosettes. Prior to the description of this tumor by Evans, the majority of LGFMS were probably diagnosed as fibromas or fibromatosis. The features that distinguish this tumor from fibromatosis are the mosaic architectural pattern, greater degree of nuclear atypia and hyperchromatism, and highly vascularized myxoid zones. Recently, a $t(7;16)$ ⁷ has been identified in this tumor and can serve as a molecular test to distinguish this lesion from other myxoid and fibroblastic lesions.⁸ Unlike fibromatosis which never metastasize, LGFMS metastasizes in about 10% of cases; therefore, failure to separate this lesion from fibromatosis may have untoward consequences.

Reactive Lesions

Reactive lesions are among the most common soft tissue lesions encountered in routine practice. They group include, nodular fasciitis and its numerous variants (cranial, intravascular, proliferative, ischemic) and bone-producing pseudotumors (myositis ossificans, panniculitis ossificans, reactive periostitis).⁹ The prototype of all of these lesions, nodular fasciitis, is classically a small (<3 cm) and superficially located lesion that evolves relatively rapidly and then stabilizes. It has a variegated appearance at low power consisting of short fascicles of mitotically active myofibroblasts alternating with myxoid and microcystic areas. The myofibroblast, common to all these reactive lesions, is a plump spindled cells with vesicular nuclear chromatin pattern and an eosinophilic to amphophilic cytoplasm. Misdiagnosis of nodular fasciitis as a sarcoma usually results when undue emphasis is given to the presence of mitotic figures without noting the lack of nuclear atypia or hyperchromatism or in assuming that the presence of actin within myofibroblasts is reflective of smooth muscle differentiation—hence a leiomyosarcoma. However, other pitfalls in the diagnosis of reactive lesions can be ascribed to unfamiliarity with the unique features of some of the variants—for example the large size of ischemic fasciitis, the sheet like proliferation of ganglion-like cells in proliferative fasciitis, or the intravascular growth of intravascular fasciitis.

Although more reactive lesions are probably called sarcomas, the converse situation also occurs. It is important to make certain that the diagnosis of a reactive lesion makes sense in the context of the case. For example, the diagnosis of nodular fasciitis should be seriously reconsidered if the lesion is large, deep, or recurrent. Since degenerated tumors can display “breakdown” changes that mimic fasciitis, be careful of making this diagnosis in degenerated material. Osteoid in bone-producing sarcomas may appear very mature and, therefore, this is an unreliable feature to use in making the diagnosis of myositis ossificans. Rather it is the quality of the cells producing the bone and the location of the bone (central vs. peripheral) which are more important determinants.

Non Mesenchymal Lesions Mimicking a Soft Tissue Tumor

About one fifth of significant errors in soft tissue relate to non mesenchymal lesions misdiagnosed as a sarcoma.⁴ The common scenarios are pleomorphic carcinomas interpreted as pleomorphic sarcomas (malignant fibrous histiocytoma), lymphoblastic or large cell lymphoma interpreted as round cell sarcomas (e.g. Ewing sarcoma, rhabdomyosarcoma, round cell liposarcoma), and desmoplastic malignant melanoma interpreted as a scar, fibromatosis, or neurofibroma. It is useful to keep in mind that pleomorphic tumors presenting in sites where carcinomas are known to occur should always be evaluated with that thought in mind. For example, it is reasonable to consider the diagnosis of a sarcoma and carcinoma for a retroperitoneal mass and to perform the appropriate immunostains, whereas it is less reasonable in the case of a deep thigh mass. Likewise, the differential diagnosis of round cell lesions should include in some instances lymphoid markers.

Desmoplastic melanoma is probably the most common non mesenchymal tumor that leads to litigation in the area of soft tissue pathology. The reasons for this are manifold. They are

uncommon variants of melanoma and present in a manner different from classic melanoma.¹⁰ White and scar-like in appearance they typically do not produce melanin or express melanin-associated markers. They may be biopsied with a superficial shave that reveals only a subtle desmoplasia of the papillary dermis. Alternatively, they may be pleomorphic lesions that resemble an atypical fibroxanthoma. Since the majority are associated with a precursor lesion, usually lentigo maligna, good clinical practice considers the diagnosis in all cases of lentigo maligna or in actinic-damaged skin having an underlying scar or desmoplasia.¹¹ Since S100 protein is strongly expressed by these lesions, it is wise to perform this stain on unusual cutaneous scar-like lesions of the head and neck of adults, particularly if accompanied by a prominent lymphocytic infiltrate, as well as lesions in which the diagnosis of atypical fibroxanthoma is being considered. However, since ordinary scars may occasionally contain small numbers of S100 protein positive cells,¹² one needs to evaluate the character of the cells in conjunction with the stain.

Summary

The foregoing discussion has focused on problem prone situations in soft tissue pathology with the potential to lead to litigation. However, it should be borne in mind that significant errors do not necessarily lead to litigation. Some errors are simply not preventable and therefore the actions of the pathologist or consultant do not fall below the “standard of practice.” It is also important to remember that serious errors are far easier to defend if accepted practices have been followed.³ This implies that difficult cases undergo peer review at consensus conferences, that the final report reflect this review, and that in cases of non-consensus an expert consultation be considered.

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