Fibrous and myofibroblastic tumors

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Introduction

In the past, a very wide variety of tumors were labelled as “fibroma” or “fibrosarcoma” without further qualification. With time, these generic terms have been shown to subsume a spectrum of numerous reactive and neoplastic lesions with striking clinicopathological differences and often different therapeutic implications. With the advent of electron microscopy and immunohistochemistry, it has become clear that these variants are functional variants of single cell type or whether there exist primarily myofibroblastic components; fibroma of tendon sheath, which generally arises in the hands or feet, is better circumscribed, often more cellular and contains slit-like vascular channels, and desmoid fibromatosis, which is usually deep-seated, more cellular and has a consistently fascicular growth pattern.

Collagenous fibroma (desmoplastic fibroblastoma)

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New entities in pathology of soft tissue tumors

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the distinction of giant cell angiofibroma from solitary fibrous tumor (SFT) and it is arguable that the giant cells and pseudovascular spaces in giant cell angiofibroma represent degenerative features in SFT. However, tumor cells in SFT tend to have more elongated wavy nuclei, and stromal keloid-like or stellate hyalinization is seen. The vascular pattern in SET is most often thin-walled and pericytoma-like.

**Cellular angiofibroma**

Cellular angiofibroma is a recently described benign vulval neoplasm which clinically is often mistaken for a Bartholin gland cyst (6). It occurs mainly in middle-aged women but comparable lesions have been described in male patients (7). Thus far, in our experience, no case has either recurred locally or metastasized.

Morphologically, cellular angiofibroma is generally a circumscribed neoplasm composed of uniform spindle cells arranged in short, irregularly intersecting fascicles with wispy stromal collagen bundles, numerous small to medium sized blood vessels which often show prominent hyalinization of their walls, and a varying proportion of mature adipocytes. The tumor cells have ill-defined cell borders, pale cytoplasm and oval or fusiform, bland nuclei, thus closely resembling tumor cells of spindle cell lipoma. They stain positively for vimentin and, in a few cases, for CD34 as well. Generally, these neoplasms are cellular and show quite frequent mitoses, but pleomorphism and tumor necrosis are absent. Stromal mast cells are common.

Because of the brisk mitotic activity, examples of cellular angiofibroma may be mislabeled as sarcoma, especially as leiomyosarcoma. However, smooth muscle tumors of the external genitalia have abundant eosinophilic cytoplasm and cigar-shaped nuclei, and they stain positively for myogenic markers. Because of its location, cellular angiofibroma also has to be distinguished from angio-myofibroblastoma, which is much less cellular and composed of rather rounded myoid tumor cells which stain positively for desmin. In contrast to cellular angiofibroma, spindle cell lipoma is more common in male patients and shows a predilection for the neck and upper back region. It typically contains ropey refractile collagen bundles and lacks numerous blood vessels with hyalinized vessel walls; tumor cells in spindle cell lipoma stain consistently for CD34.

**Hyalinizing spindle cell tumor with giant rosettes**

Hyalinizing spindle cell tumor with giant rosettes is a rather enigmatic lesion, first described by Weiss and coworkers in late 1997 (8), which has been said to resemble low grade fibromyxoid sarcoma. The original report included 19 cases and, since that time, there have been just occasional case reports (9,10), one of which described possible primary lung involvement (10). These lesions affect mainly young to middle-aged adults and present as a deep-seated slowly growing mass with predilection for the limbs. Most examples have measured less than 10 cm in diameter and, although follow-up data are limited so far, only one tumor has recurred locally and none has metastasized.

Grossly these are well-circumscribed, pale firm tumors but histologically they have infiltrative margins. They consist principally of uniform spindle cells with fibroblastic or neural-like morphology arranged in fascicles in a collagenous or myxoid matrix. Large zones of hyalinization are generally present and characteristically these may form nodules, surrounded in rosette-like fashion by more rounded or ovoid tumor cells in axial array. Pleomorphism is minimal and mitoses are scarce. Some cases show osseous or chondroid metaplasia and one case was reported to show transition to a more cellular fibrosarcoma-like pattern (8). Immunostains very often show positivity for variably specific neural crest antigens (S-100 protein, Leu7, neuron-specific enolase) but this has been claimed to be more striking in the rosette-like foci rather than the spindle cell fascicles.

The original authors proposed that this was a variant of low-grade fibromyxoid sarcoma, differing only in the presence of the giant rosettes, and predicted an indolent, potentially metastatic course. My personal experience has been that the spindle cell areas are usually S-100 protein positive and, while accepting that these lesions bear no resemblance to schwannoma or neurofibroma, I wonder if they might represent a form of low grade malignant peripheral nerve sheath tumor. Certainly similar rosettes can be seen in a variety of tumor types and future electron microscopic studies may help to better resolve the nature of these tumors.

**Inflammatory myofibroblastic tumor**

**Inflammatory fibrosarcoma**

The concept of reactive “tumorous” proliferations composed of fibroblasts, myofibroblasts and chronic inflammatory cells grew in popularity following Bahadori and Liebow’s seminal paper on plasma cell granuloma of the lung (11). Subsequently, such lesions were more often referred to as inflammatory pseudotumors or, more recently, as inflammatory myofibroblastic tumors to emphasize their major cellular constituent and, increasingly, to imply that such proliferations may represent benign neoplasms. They have been described in virtually all organs including the mesentery and retroperitoneum (12). In 1991, Meis and Enzinger (13) proposed that, especially in children, at least some of the intraabdominal lesions previously designated as inflammatory pseudotumor actually represent a true sarcoma which they called inflammatory fibrosarcoma. It is my experience that there is sufficient clinicopathological evidence to justify such a designation for at least a small minority of these lesions, but this is a controversial topic.

The originally published clinical data in Meis and Enzinger’s series described 38 cases. These arose predominantly in the mesentery and retroperitoneum of children (median aged 8.5 years), although comparable lesions in adults also occur. Over one-third of patients had multiple tumors. Among 27 patients with follow-up, 10 developed local recurrence (3 repeatedly) and 3 developed metastases. Overall, 6 patients died of their tumor, although interestingly most were adults. Microscopically, these lesions displayed a spectrum of histological appearances which incorporated two major components; plump spindle cells arranged in cellular fascicles or whorls and a prominent infiltrate of plasma cells and some lymphocytes. The spindle cells showed features of fibroblastic and myofibroblastic differentiation and, invariably, at least some showed nuclear irregularity and contained very large nucleoli. A variable number of ganglion-like cells were present. In common with inflammatory pseudotumor, some cases showed areas of myxoid change and/or marked hyalinization of collagen.

It soon became clear, however, that a significant number of pathologists felt uncomfortable with the designation of sarcoma for these lesions. Such concerns were based upon the fact that some examples were histologically indistinguishable from the reactive process, long known as inflammatory pseudotumor, and upon the possibility that so-called metastasis in fact represented multicentricity. This alternative point of view was supported by a large study of 84 cases from Coffin et al. (14). These authors again noted the predilection for children and location within the abdomen, although
they described cases at a wide variety of sites and occurring up to the age of 46 years. Frequently associated anemia was noted, as was the occasional presence of other systemic features such as elevated erythrocyte sedimentation rate or unexplained fever.

From the histologic point of view, Coffin et al. (14) described the three following principal patterns which were commonly intermixed: i) a myxoid fasciitis-like pattern with mixed inflammatory cells; ii) a more cellular pattern resembling fibromatosis or fibrous histiocytoma but with numerous admixed plasma cells; and iii) a hypocellular fibrous pattern resembling scar tissue, in which there were scattered chronic inflammatory cells and sometimes foci of calcification. Because some cases were multinodular, hard to eradicate and sometimes recurrent (approximately 25%), Coffin et al. further reaffirmed their preference for the designation “inflammatory myofibroblastic tumor”. They also noted four patients whose tumors regressed spontaneously and two patients who died of uncontrollable local disease. Importantly, they made no mention of nuclear or cytologic atypia in any of their primary lesions and none of their patients developed metastatic disease. They did, however, describe two cases in which local recurrence was associated with the development of areas having histological features of a histiocytoid malignant neoplasm. This phenomenon had been described previously in lung lesions by Spencer and conceptually is quite difficult to reconcile with an intrinsically reactive process.

My personal experience of more than 50 cases, based largely on consultation material with no pediatric bias, has revealed the same predilection for anatomic site and an age distribution of 2 months to 79 years, with 40% of cases occurring in patients older than 18. It has seemed to me that at least a minority of cases do show the nuclear atypia described by Meis and Enzinger – and when this is combined with high cellularity, this inevitably raises concern for malignancy. This concern has been substantiated by the development of liver metastases (by all usual criteria) in at least two patients (both children) and I am aware of other convincing clinically malignant cases in other people’s practices. Admittedly, this is a very small number of “malignant” examples and the majority of other cases are cytologically bland, more closely resembling either fascitis or the old-fashioned inflammatory pseudotumor.

Given this premise, are there any reliable histological features which allow accurate recognition of inflammatory fibrosarcoma from among the group of inflammatory myofibroblastic lesions as a whole? The major discriminant feature employed by Meis and Enzinger was that of nuclear atypia. In my experience, focally, there may also be very cellular, fascicular areas. Undoubtedly, reliable distinction (in prognostically useful terms) is very difficult but consideration of the nuclear detail of such tumors perhaps allows recognition of a more aggressive subset. Limited available cytogenetic data have revealed a variety of clonal aberrations in lesions of this type (15, 16), supporting their neoplastic nature, and the original protagonists in the dispute concerning the nature of these lesions have very recently moved towards a consensus viewpoint that they should all be regarded as low-grade sarcomas (17, 18).

Principal considerations in the differential diagnosis include fasciitis-like proliferations, fibromatosis, deep fibrous histiocytoma and inflammatory leiomyosarcoma. Some of the fasciitis-like lesions reported at visceral locations may in fact belong in the inflammatory myofibroblastic tumor category – but most cases show much less pronounced inflammation, a more tissue culture-like cytornorphology and they are generally smaller in terms of lesional size. Fibromatosis is more uniformly fascicular, generally lacks any significant degree of inflammation and very rarely has such plump nuclei with prominent nucleoli. Deep benign fibrous histiocytoma is an uncommon lesion and is especially rare in the abdomen or in children. It has a storiform rather than fascicular pattern and usually consists of a highly cellular admixture of short fibroblast-like cells and plumper histiocyte-like cells. Chronic inflammatory cells are relatively sparse. Inflammatory leiomyosarcoma is more cellular and more cytologically atypical than inflammatory myofibroblastic tumor and generally shows much more extensive actin immunostaining. Lymphocytes typically predominate in the inflammatory infiltrate.

**Low-grade myofibroblastic sarcoma**

For many years, the existence of myofibroblastic neoplasms (and especially myofibroblastic sarcomas) has been disputed, principally because the scientists who described this cell type felt strongly that this was not possible (19). Yet one of the prototypical myofibroblastic lesions, desmoid fibromatosis, is now known to be a clonal proliferation and a wide variety of benign neoplasms have been shown to have a myofibroblastic phenotype at the immunohistochemical and ultrastructural levels (e.g., infantile digital fibromatosis, intranodal myofibroblastoma, mammary myofibroblastoma and angiomyofibrolastoma). It has also become evident that a variety of more aggressive lesions show myofibroblastic differentiation, including inflammatory myofibroblastic tumor (also known as inflammatory fibrosarcoma), infantile fibrosarcoma and some cases of so-called “MFH” (20). To this list has been added more recently a distinctive group of lesions which we have designated as low-grade myofibroblastic sarcoma (21).

Low-grade myofibroblastic sarcoma (21) affects adults of either sex over a wide age range, with a peak incidence between the ages of 20 and 50. Overall anatomic distribution is wide but, strikingly, around 25% of cases occur in the oral cavity (especially the tongue). Most cases present as slowly growing peripheral or deep-seated masses which generally measure less than 5 cm (with larger exceptions). Although follow-up data are limited at present, local recurrence is a feature of 20-30% of cases (usually due to marginal or incomplete excision), and occasional patients develop indolent metastases.

Grossly, most lesions are firm, pale and fibrous with infiltrative margins, reminiscent of desmoid fibromatosis. Generally there is no hemorrhage or necrosis. Most cases are hypercellular throughout, usually being more cellular than a fibromatosis and, distinctively, these lesions typically show a diffusely infiltrative growth pattern within skeletal muscle (producing a pattern rather reminiscent of proliferative myositis). Focal stromal hyalinization is common. Tumor cells show usual myofibroblastic features, with variably wavy/tapering or plump/vesicular nuclei, and typically are arranged in a fascicular pattern. When compared to a fibromatosis there is distinctly more nuclear atypia, even if only mild and focal in extent. Scattered multinucleate tumor giant cells are occasionally seen and, in most cases, the mitotic rate does not exceed 5 per 10 high-power fields. Immunohistochemically around 65% of cases show diffuse desmin immunopositivity and a similar proportion of cases (although not necessarily the same ones) are smooth muscle actin positive. Electron microscopy shows typical myofibroblastic features.

Low-grade myofibroblastic sarcoma should be distinguished from fibromatosis, myofibromatosis, solitary fibrous tumor, other types of myofibroblastic sarcoma, fibrosarcoma and leiomyosarcoma. The fairly consistent hypercellularity and at least focal nuclear
atyia excludes fibromatosis, while myofibromatosis typically has a distinctive biphasic growth pattern with primitive pericytoma-like areas and myoid nodules or whorls (which are often hyalinized). Solitary fibrous tumor is well circumscribed, has a patternless architecture and is generally immunonegative for myogenic markers. Fibrosarcoma has paler (less eosinophilic) cytoplasm and lacks immuno or EM evidence of myoid differentiation. Leiomyosarcoma usually has more circumscribed margins, more eosinophilic cytoplasm and more cigar-shaped nuclei.

**Sclerosing epithelioid fibrosarcoma**

Sclerosing epithelioid fibrosarcoma, first described by Meis-Kindblom and colleagues from AFIP in 1995 (22), is an uncommon and probably poorly recognized type of sarcoma which has only slowly gained acceptance as a distinct entity. In part, this reflects the considerable morphological overlap between this and other tumor types, but the recent publication of additional cases (23, 24) is indicative of justifiably increasing recognition. These tumors affect mainly young to middle-aged adults of either sex, who present usually with a deep-seated mass in the lower limb, limb girdle or trunk. Almost all cases measure less than 10 cm in diameter and the growth rate is variable. Approximately 50% of patients develop local recurrence and/or distant metastasis, but systemic spread is usually delayed for 5 years or more.

These are generally well circumscribed, lobulated, rubbery masses which histologically are notably hypocellular with extensive stromal hyalinization. However, the cellular areas consist of nests, cords and strands of relatively small epithelioid cells which most often have clear cytoplasm. Other areas may have an alveolar growth pattern but, in addition, there are generally areas with a fascicular spindle cell appearance reminiscent of conventional fibrosarcoma. The densely hyaline stroma may simulate osteoid and there is often a pericytoma-like vascular pattern. Pleomorphism is minimal and mitoses often do not exceed 5 per 10 mean power frequencies. Published immunophenotypic findings (as well as personal experience with cases of this type) have been variable but it seems that at least some cases stain positively for epithelial membrane antigen and less often for keratin and S-100 protein. Ultrastructural studies have shown fibroblastic features and recent cytogenetic data in one case (25) showed nonspecific clonal aberrations.

The differential diagnosis includes principally metastatic carcinoma, ossifying fibromyxoid tumor, osteosarcoma and monophasic synovial sarcoma. In general, the combination of clinical context, focally distinctive cytoarchitectural features and careful use of immunohistochemistry resolve this problem so long as one is aware of the existence of this unusual tumor.

**References**