Low-Grade Fibromyxoid Sarcoma
A Brief Review

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Low-grade fibromyxoid sarcomas are uncommon deep soft tissue neoplasms first described by Evans in 1987. They exhibit a deceptively benign appearance, with a whorled or linear arrangement of spindle-shaped cells showing few to absent mitoses. A characteristic, but not specific, feature is the presence of areas of myxoid stroma. Recurrences are common, and late metastases have been recorded. A closely related but morphologically distinct tumor, the so-called hyalinizing spindle cell tumor with giant rosettes, has also been described; both neoplasms share the same cytogenetic abnormality, a balanced translocation resulting in a FUS/CREB3L2 fusion gene. Because of similar clinical behavior and the common cytogenetic abnormality, some authors prefer to consider both lesions as a single entity within the spectrum of low-grade sarcomas. (Arch Pathol Lab Med. 2006;130:1358–1360)

Evans in 1987 described for the first time 2 cases of low-grade fibromyxoid sarcomas (LGFMSs), which are indolent but potentially metastasizing soft tissue tumors with a deceptively benign histologic appearance. A third case was reported by Devaney et al in 1990, and in 1993 Evans added 10 more cases to his original 2. This article provided long-term follow-up that indicated a high rate of local recurrence and eventual metastasis in just more than half the patients (7/12). However, even with metastasis, long-term survival was common. Occasional sporadic reports followed, and in 1995 Goodlad et al reported 11 similar cases. Recently Billings et al have reported a group of similar tumors confined to superficial soft tissue with similar histologic features.

These fibroblastic tumors typically occur in the lower limb/groin area but sporadically occur in other deep soft tissues. The patients are evenly divided among males and females in Evans’ group, but there was a striking male preponderance in the group reported by Goodlad et al. Their ages range from 6 to 51 years, but most are young adults, between the ages of 25 and 46. Most of the tumors are deceptively well circumscribed but not encapsulated, and resection is often incomplete.

The microscopic appearance of LGFMSs is somewhat variable, as the name suggests, consisting of bland fibroblasts with a whorled or linear arrangement (Figure 1), alternating with less cellular areas with a myxoid stroma (Figure 2). Tumor cells tend to be small, with poorly defined, palely eosinophilic cytoplasm and round to ovoid nuclei. Nucleoli are absent to indistinct. Mitotic figures tend to be absent to sparse. Nuclear anaplasia and necrosis are generally absent, although one of Evans’ cases became dedifferentiated (his terminology) at 30 years follow-up, with sheets of anaplastic rounded cells.

Immunohistochemical staining has been reported by a number of authors, with some conflicting results. Ugaí et al and Fukunaga et al showed positive staining with vimentin, but no immunoreactivity with antibodies to keratin, desmin, muscle specific actin, S100 protein, CD34, CD31, or epithelial membrane antigen. However, Goodlad et al reported occasional cases with immunoreactivity to actin, desmin, and cytokeratin, which they attribute to focal myofibroblastic differentiation.

Ultrastructurally, these tumors are generally characterized as fibroblasts with underdeveloped rough endoplasmic reticulum cisternae, scant cytoplasm with a paucity of organelles, long thin cell processes, and pinocytotic vesicles.

In 1997 Lane et al reported a variant of LGFMS, which was termed hyalinizing spindle cell tumor with giant rosettes. These tumors are characterized by a proliferation of rather bland spindle cells, with fibromyxoid areas (Figure 3). Scattered throughout the tumors are hyalinized acellular islands surrounded by oval and spindle cells in a palisading pattern, producing the distinctive pattern referred to by Lane et al as giant rosettes (Figure 4). They also noted intranuclear inclusions in a few of the rounded cells at the edge of the rosettes. The rosettes often coalesce into long serpiginous cords or bands of dense hyalinization. Elsewhere the spindle cells form irregular crisscrossing fascicles of fibroblasts and collagen, with a pattern resembling LGFMS, sometimes showing myxoid areas. Subsequently, Folpe et al compared a large number of LGFMSs (44 cases) and hyalinizing spindle cell tumor with giant rosettes (17 cases). Many of these cases were initially diagnosed and treated as fibrosarcomas, and indeed this group included tumors with enlarged nuclei, mitotic activity, and necrosis, features said to be absent in the original description of LGFMS.

The immunohistochemical profile, in particular of the rosettes, has suggested a neural phenotype. The cells...
forming the rosettes are Leu-7, S100, and pgp 9.5 positive, and the spindle cells are more consistent with fibroblasts. Electron microscopic studies by these same authors differ in that Nielsen et al.\(^{12}\) found that the cells surrounding the hyaline cores were similar to those comprising the majority of the tumors, whereas Bejarano et al.\(^{11}\) described distinctly different cells, some containing dense core granules.

Several investigators\(^{11,13-15}\) have identified a characteristic balanced t(7;16)(q34;p11) translocation in LGFMS and also in hyalinizing spindle cell tumor with giant rosettes, supporting the view that these 2 different morphologies represent the same neoplastic process. One case demonstrated an unusual ring chromosome\(^{16}\) containing material from chromosomes 7 and 16. Subsequently, Mertens et al.\(^{17}\) confirmed the finding of the FUS/CREB3L2 fusion gene in LGFMS in 22 of 23 cases, with a novel fusion gene FUS/CREB3L1 in the remaining case. Thus, cytogenetics appears to be an excellent tool for the differential diagnosis of LGFMS.

The microscopic differential diagnosis of LGFMS encompasses a number of entities characterized by spindle cell proliferations with myxoid morphologies. Several of the more commonly considered lesions might be low-grade myxofibrosarcoma, myxoid neurofibroma, perineurioma, myxoid solitary fibrous tumor, and fibromatosis. Low-grade myxofibrosarcoma typically has more uniform myxoid stroma, with less swirling of tumor cells and more cellular atypia. Myxoid neurofibroma has more slender wavy nuclei and consistently shows S100 positivity. Perineuriomas may show fibrous and myxoid areas and typically show diffuse staining for epithelial membrane antigen, whereas LGFMS may show only rare focal positivity. However, in a recent report by Hornick and Fletcher\(^{18}\) of a large series of perineuriomas, staining for epithelial membrane antigen was relatively weak in many cases and apparent only under high-power examination. Myxoid

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Figure 1. Medium power view of low-grade fibromyxoid sarcoma (LGFMS), showing bland fibroblasts arranged in a swirling pattern, with no nuclear pleomorphism or mitotic figures (hematoxylin-eosin, original magnification ×200).

Figure 2. Fibroblasts with myxoid stroma and a rich capillary network, again with little in the way of pleomorphism and no mitotic figures (hematoxylin-eosin, original magnification ×400).

Figure 3. Hypocellular area of hyalinizing spindle cell tumor, showing spindle cells with a similar appearance to low-grade fibromyxoid sarcoma (LGFMS) but with less of the whirling pattern (hematoxylin-eosin, original magnification ×200).

Figure 4. So-called giant rosette of hyalinizing spindle cell tumor with giant rosettes, with hyalinized central collagen surrounded by plump to oval cells (hematoxylin-eosin, original magnification ×200).
solitary fibrous tumor, as reported by Somerhausen et al, may resemble LGFMS but is uniformly immunoreactive for CD34. Although deep fibromatosis usually has a more fascicular architecture, there can be similarities with LGFMS, and recent studies by 2 different groups have suggested that immunohistochemical staining for nuclear β-catenin can distinguish deep fibromatosis from LGFMS.

A recent review by van Roggen et al provides an extensive overview of the differential diagnosis of myxoid tumors of soft tissue.

Although there are morphologic, immunophenotypic, and ultrastructural differences between LGFMS and hyalinizing spindle cell tumor with giant rosettes, Folpe et al have suggested that these lesions are morphologic variants of the same entity, that is, both are part of the spectrum of low-grade sarcomas, with a more indolent course than had previously been reported. These authors contend that, with improved recognition and treatment, cases prospectively diagnosed as LGFMS may have a better prognosis than previously reported. Nevertheless, they recommend prolonged follow-up because of the potential for late metastasis.

References