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Original Contributions

Low-grade fibromyxoid sarcoma: a clinicopathologic study of 18 cases, including histopathologic relationship with sclerosing epithelioid fibrosarcoma in a subset of cases☆

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Abstract Low-grade fibromyxoid sarcoma (LGFMS) is an uncommon tumor with diverse histopathologic features. It has been found to be histopathologically and genetically related to hyalinizing spindle cell tumor with giant rosettes. Lately, sclerosing epithelioid fibrosarcoma (SEF) has been identified as another rare variant of fibrosarcoma. Very few studies have addressed the aspect of its histopathologic relationship with LGFMS. The present study was conducted to critically analyze the clinicopathologic features of a series of LGFMS cases, including identification of cases with histopathologic similarity with SEF. During a 7-year period, 18 LGFMS cases were diagnosed in 9 male and 9 female patients, had ages ranging from 10 to 69 years (median, 32.5 years), and were most commonly identified in the lower extremities (8 cases, or 44.4%). Most cases (16, 88.8%) showed "classic" features of LGFMS with mild (13 cases, or 72.2%) to moderate atypia (5 cases) and nil mitosis (12 cases, or 66.6 %). Variable features included whorling tumor growth pattern, small rosettes, perivascular hyalinization, and amianthoid-like collagen, along with epithelioid differentiation and nuclear pseudoinclusions within tumor cells. Four cases (22.2%) with large collagenous rosettes were diagnosed as hyalinizing spindle cell tumor with giant rosettes. Distinct SEF-like areas were observed in 6 cases (33.3%). On immunohistochemistry, consistent vimentin positively reinforced fibroblastic lineage of the tumor. Therapeutically, all 4 of 7 cases with available follow-up details, which underwent wide excisions, have been free of disease at 5 to 61 months. Eight excisions with unclear margins included 3 cases free of disease (24, 36, and 52 months) and 1 case with recurrence and metastasis. Two cases of marginal excision had tumor recurrences, including 1 case that recurred after 10 years. Low-grade fibromyxoid sarcoma is an uncommon sarcoma with diverse histopathologic features. Histopathologic relationship exists between LGFMS and SEF in a few cases. An LGFMS is optimally managed with surgical wide excision and follow-up.

Keywords: Low-grade fibromyxoid sarcoma; Sclerosing epithelioid fibrosarcoma; Fibrosarcoma; Uncommon soft tissue sarcomas

1. Introduction

Low-grade fibromyxoid sarcoma (LGFMS) was first described by Evans [1] as a deceptively bland soft tissue tumor (STT) on histopathology but with a relatively aggressive clinical disease course. After the first description of his 2 cases that were initially diagnosed as "fibromatosis" and a "fibroma," he published another set of 12 LGFMS cases in another study, highlighting the salient morphologic features of this rare tumor [2]. Subsequent studies along with the World Health Organization classification of STTs have confirmed this relatively uncommon tumor as a discrete subtype of a fibrosarcoma [3-6]. Lately, studies on genetic analysis have unraveled a characteristic underlying recurrent, balanced translocation t(7; 16) (q32-34; p11), resulting in the formation of *FUS-CREB3L2* and *FUS-CREB3L1* fusion genes in this sarcoma [7,8]. Lane et al [9] identified a hyalinizing spindle cell tumor with giant rosettes (HSCT) as

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a variant of LGFMS. This relationship was further confirmed with identification of the similar translocation in cases of HSCT [10]. Two years before the description of an HSCT, Meis-Kindblom et al [11] described another rare, discrete STT, namely, sclerosing epithelioid fibrosarcoma (SEF). Subsequent studies have also confirmed SEF as a distinct STT [12,13]. Antonescu et al [13] described the histopathologic resemblance of SEF with LGFMS in 25% of SEF cases. Areas resembling LGFMS were also described in the original description of SEF by Meis-Kindblom et al [11]. On genetic analysis, very few cases of "pure" SEF have been observed to display the similar translocation as noted in an LGFMS, thereby suggesting a genetic "link" between these 2 sarcomas in a small subset of cases [14,15]. Recently, we published 2 cases of SEF, with 1 of them showing focal areas resembling LGFMS and also displaying *FUS* gene rearrangements, as noted in an LGFMS [16].

The present study describes a spectrum of histopathologic features of 18 cases of LGFMS, including their critical evaluation for areas resembling a SEF, for possibility of a histopathologic similarity between these 2 sarcomas in certain cases.

2. Materials and methods

The records of the Department of Pathology, Tata Memorial Hospital, Mumbai, were searched for cases diagnosed as LGFMS, low-grade spindle cell sarcoma, low-grade fibrosarcoma, and spindle cell sarcoma (myxoid type) during a period of 7 years. On a review by B.R. and M.D., a total of 18 cases that fulfilled the diagnostic criteria of LGFMS were included in the present study [1,2].

Overall, there were 17 surgical excision specimens, including 7 cases with wide excision (R0), 2 cases with marginal resection (R1), 8 cases of tumor excision with unclear margins (Rx), and 1 case with only biopsy. Seven cases with R0 included 1 case that was initially marginally excised (R1).

Conventional hematoxylin and eosin–stained sections were available in all the cases. Special histochemical stain like the Masson trichome was performed in some cases.

The cases were extensively sampled and critically evaluated for histopathologic features of LGFMS. The diagnostic criteria for LGFMS were according to the histopathologic features described by Evans [1,2] and by authors in subsequent studies [3-6]. The number of slides from the tumor that were studied in each case were 4, 5, 9,1, 6, 4, 6, 10, 8, 6, 14, 3, 1, 19, 5, 5, 10, and 8, respectively, with an average close to 7 slides per case. The diagnostic criteria for SEF-like areas were according to the morphologic features of SEF, described by Meis-Kindblom et al [11] and by other authors in different studies [12,13].

Immunohistochemistry (IHC) was performed by immunoperoxidase method using MACH 2 Universal HRP-Polymer detection kit (Biocare, Yorba Linda, CA), including 3′-3′-diaminobenzidine tetrahydrochloride as the chromogen. Various antibody markers applied in different cases have been listed in Table 1.

Clinical outcome data were available in 10 cases (55.5%). In addition, a single, recently diagnosed case is on follow-up.

3. Results

Of 18 cases of LGFMS, 9 cases were identified in male and 9 in female subjects (male/female ratio, 1:1). The age ranged from 10 to 69 years with a mean age of 33 years and a median of 32.5 years. Location-wise, most cases were deep seated, including 8 cases (44.4%) in the lower extremities, followed by 2 cases in the face/jaw, 2 cases in the back, and 1 case, each, in the neck, axilla, chest wall, abdominal wall, retroperitoneum, and the paraspinal area, respectively.

Grossly, tumor dimensions, available in 11 (61.1%) of 18 cases that included tumor size varying from 2 to 22 cm, with a mean of 9.9 cm, in the largest dimension.

On histopathologic examination, most cases (16, or 88.8%) showed a tumor displaying swirling pattern of

Table 1
List of antibody markers used in various cases

Sarcoma no.	Antibody marker	Clonality, clone	Dilution	Antigen retrieval (buffer)	Manufacturer
1	EMA	Monoclonal, E29	1:200	Heat (Tris-EDTA), pascal	Dako, Produkionsveg, Glostrup, Denmark
2	Cytokeratin (CK)	Monoclonal, MNF116	1:200	Heat (Tris-EDTA), pascal	Dako
3	Desmin	Monoclonal, D33	1:200	Heat (Tris-EDTA), pascal	Dako
	SMA	Monoclonal, 1A4	1:400	Heat (Tris-EDTA), pascal	Dako
4	Myogenin	Monoclonal, MyF4	1:50	Heat (sodium citrate), pressure cooker	Novocastra, Burlingame, Calif
5	MyoD-1	Monoclonal, 58A	1:40	Heat (Tris-EDTA), pascal	Dako
6	BCL-2	Monoclonal, 124	1:50	Heat (Tris-EDTA), microwave	Dako
7	MIC2/CD99	Monoclonal, 12E7	1:100	Heat (Tris-EDTA), pascal	Dako
8	Vimentin	Monoclonal, V9	1:400	Heat (Tris-EDTA), microwave	Dako
9	Calponin	Monoclonal, CALP	1:50	Heat (Tris-EDTA), microwave	Dako
10	CD34	Monoclonal, QBEnd10	1:200	Heat (Tris-EDTA), microwave	Dako
11	S-100P	Polyclonal	1:1500	Heat (Tris-EDTA), pascal	Dako
12	H-caldesmon	Monoclonal, h-caldesmon	1:100	Heat, (Sodium citrate), pressure cooker	Dako
13	c-KIT/CD117	Polyclonal	1:300	Heat, (Sodium citrate), microwave	Dako
14	Ki-67	Monoclonal, MIB-1	1:200	Heat (Tris-EDTA), pascal	Dako