Annals of Diagnostic Pathology 28 (2017) 60–67

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Low-grade fibromyxoid sarcoma: Clinical, morphologic and genetic features

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ARTICLE INFO

Keywords:
Low-grade fibromyxoid sarcoma
Hyalinizing spindle cell tumor with giant rosettes
Sclerosing epithelioid fibrosarcoma
Genetics
Pathology
Gene rearrangement
Translocation
FUS-CREB3L2
FUS-CREB3L1
EWSR1-CREB3L2

ABSTRACT

Low-grade fibromyxoid sarcoma (LGFMS) is a bland spindle cell neoplasm that typically arises in the deep soft tissues of the proximal extremities or trunk of young adults. The majority of LGFMS are characterized by a recurrent (7;16)(q34;p11) translocation, resulting in the *FUS-CREB3L2* fusion gene, which generates a chimeric protein with transcriptional regulatory activity. Small numbers harbor a *FUS-CREB3L1* fusion resulting from t (11;16)(p11;p11), whilst rare cases harbor the *EWSR1-CREB3L1* fusion. LGFMS is of low to moderate cellularity and consists of bland spindle cells with small, angulated nuclei and scant, wispy cytoplasm, arranged in a whorled growth pattern and typically showing abrupt transition from myxoid to fibrous areas. Immunohistochemical expression of MUC4 is a consistent finding. Hyalinized spindle cell tumor with giant rosettes (HSCTGR) is a morphological variant of LGFMS that shares the same balanced translocation, and is also immunoreactive for MUC4. A potential relationship between LGFMS and sclerosing epithelioid fibrosarcoma (SEF), a rare fibroblastic neoplasm that most commonly arises in the deep soft tissues of the lower extremities, limb girdles or trunk, has also been suggested. SEF is classically composed of nests and cords of epithelioid cells with clear or eosinophilic cytoplasm embedded within densely sclerotic stroma. In some cases, areas indistinguishable from LGFMS are present, and these have been shown to contain *FUS-CREB3L2* fusion transcripts. The majority of pure SEF tumors harbor *EWSR1* rearrangements, with *EWSR1-CREB3L1* and more rarely *EWSR1-CREB3L2* gene fusions more common than those involving *FUS*. MUC4 immunoreactivity is also seen in approximately 70% of SEF. Surgical resection of these tumors with clear margins is the treatment of choice. Correct diagnosis is important because of the significant potential for recurrence and late metastatic spread. We review LGFMS and SEF, discussing morphology and immunohistochemistry, genetics and molecular findings, and the differential diagnosis.

1. Introduction

Low-grade fibromyxoid sarcoma (LGFMS) is a malignant, often late-metastasizing tumor with a misleadingly bland histological appearance that typically arises in the deep soft tissues of the proximal extremities or trunk of young adults. It was first proposed as a distinct entity by Evans in 1987 [1] who described two variably cellular neoplasms composed of alternating fibrous and myxoid areas containing bland spindle or stellate cells showing a swirling, whorled pattern of growth. Both tumors occurred in women in their late twenties and were located in the shoulder/trunk area. Lung metastases were present in both cases. Six years later, Evans expanded his original series with 10 more cases, also noting that 'dedifferentiation' occurred in one of the cases [2]. In 1997, Lane et al. described a tumor composed of hypocellular hyalinizing collagen cores rimmed by minimally atypical spindle cells in a fibromyxoid background [3]. This was initially thought to be a distinct neoplastic entity and was termed hyalinizing spindle cell tumor with giant rosettes (HSCTGR). However, it was noted that both tumors shared similar morphologic features and it was therefore proposed that HSCTGR should be considered a histological variant of LGFMS. This notion was further supported by a large series of LGFMS cases that found collagenous rosettes in tumors with otherwise classic histological features of LGFMS [4]. The majority of LGFMS and HSCTGR cases have since been shown to harbor a common t(7;16)(q34;p11), resulting in a chimeric fusion protein derived from the *fused in sarcoma* (*FUS*) gene of chromosome 16p11 and the *cAMP responsive element-binding protein 3-like 2* (*CREB3L2*) gene of 17q33 [5]. A minority of cases have been shown to display a *FUS-CREB3L1* fusion resulting from t(11;16)(p11;p11) [6] whilst the *EWSR1-CREB3L1* fusion has been reported in two cases [7].

It has also been suggested that there may be a relationship between LGFMS and sclerosing epithelioid fibrosarcoma (SEF) [8]. This is a rare fibroblastic neoplasm, first described in 1995 by Meis-Kindblom et al. [9], that most commonly arises in the deep soft tissues of the lower

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http://dx.doi.org/10.1016/j.anndiagpath.2017.04.001

extremities, limb girdles or trunk, where it is often closely associated with fascia or periosteum. Infiltration into adjacent structures, including bone, is common. Less frequently, SEF can arise in bone, usually in the head and neck region [10]. It typically occurs in middle-aged adults and can pursue an aggressive clinical course with more than half of patients developing local recurrences and distant metastases [9]. SEF is classically composed of nests and cords of epithelioid cells with clear or eosinophilic cytoplasm embedded within a densely sclerotic stroma. In some cases, areas indistinguishable from LGFMS are present [11]. The earliest observation of LGFMS cases with areas resembling what is now known as SEF was provided by Evans in 1993 [2], which was interpreted as evidence of 'dedifferentiation.' A subset of SEF, including some with hybrid LGFMS features, has been shown to contain *FUS-CREB3L2* fusion transcripts or *FUS* gene rearrangements [11,12]. Furthermore, the immunohistochemical expression of MUC4, which is a consistent finding in LGFMS, is also seen in approximately 70% of SEF [13], lending further weight to the possibility of a close relationship between these tumors.

1.1. Clinical features and management

The incidence of LGFMS has been reported as 0.18 per million [14]. It can affect patients of all ages but has a peak incidence in young adults, with a mean age of 33 years and a median of 32.5 years (age range 10 to 69 years) [15]. 13–19% of cases occur in patients younger than 18 years of age [4,16]. LGFMS is extremely rare in children younger than 5 years of age [17] with only nine cases reported in the literature to date [18]. The male to female ratio has been reported to be 7:2 in infants (0–5 years of age) and 8:5 in young adolescents (6–15 years of age) [18]. In adult cases, the male to female ratio was reported to be either equal [6,15] or 3:1 [19]. The majority of LGFMS cases present as painless, slow growing and deep seated masses within the proximal extremities and trunk, although superficial LGFMS is reported to be more common in the pediatric population [20]. Rarely, LGFMS can also arise as primary disease at other anatomic sites, including the head and neck (with reported cases in the malar area, palate, masseter muscle, face, thyroid and brain) [21-26], and visceral organs such as small and large bowel [27,28], heart [29,30] and kidney [31]. LGFMS can present with late metastases, most commonly to the lungs [32], with rare reported cases of metastases to the prostate [33] and liver [34]. Patients presenting with metastatic disease may have a decades-long history of a primary mass in the extremity or trunk [4]. It has been postulated by Maretty-Nielsen et al. [14] that LGFMS is not expected to be very chemo- or radiosensitive due to its low nuclear grade and infrequent mitotic activity. In their study, the best response to chemotherapy was short-term stabilization of disease progression with trabectedin. Another study by le Cesne et al. [35] suggested that trabectedin could offer some benefit in translocation-related soft tissue sarcomas such as LGFMS. However, surgical excision with clear resection margins remains the first line treatment option.

In one series of patients in whom medium term follow-up was achieved [19], no instances of local recurrence or metastasis occurred during the follow up period, even though two thirds of patients had a marginal resection. In a larger series, Folpe et al. [4] reported a local recurrence rate of 9%, metastasis rate of 6%, and 1% of patients dying of LGFMS at a mean of 38 months and median of 24 months follow-up. Guillou et al. [11] reported a smaller series with substantially longer follow-up. Their recurrence rate and metastasis rate were both 21% for those cases presenting with only local disease, with an overall metastasis rate of 27%. Their median times to local recurrence and metastasis were 276 months and 132 months respectively, with 83% of metastatic cases occurring beyond nine years follow up [11]. Moreover, in Evans' most recent comprehensive study of 33 LGFMS cases with long term follow-up (mean of 14 years), half of the patients developed metastases and 42% died of disease [36]. Thus, the potential for late recurrences and metastatic spread is high, necessitating long-term follow-up for all patients with LGFMS. Superficial LGFMS has generally been associated with a good prognosis, which is better than that for deep-seated neoplasms [20]. No specific histologic features of LGFMS, other than 'dedifferentiation', have been shown to correlate with prognosis, although small tumor size (< 3.5 cm) might represent a favorable prognostic factor [36].

SEF affects patients in an older age group with mean and median ages reported as 46 and 48 years, respectively (age range 10 to 78 years) [37]. While no significant gender difference in incidence has been observed in large series [9,12,37], the recent series of Prieto-Granada et al. has shown a striking female predominance (90% of patients) in tumors with morphology of pure SEF [38]. The most common anatomic site is the lower limb, followed by the trunk, retroperitoneum, paravertebral region, neck, upper limb, abdominal cavity and thoracic cavity [37,39]. Primary renal [40-42] and bone involvement (most frequently the long bones of the extremities) [43] have also been documented. Surgical excision with clear resection margins is the treatment of choice. The outcome of patients with SEF is highly variable. Like LGFMS, some neoplasms are characterized by a relatively protracted clinical course with metastases developing several years after surgical excision [9], whilst others exhibit more aggressive behavior with a high metastatic rate and a high proportion of tumor-related deaths [8]. The mortality rate between patients with pure SEF and those with hybrid SEF/LGFMS has been shown to be roughly similar, at 44% and 37% respectively (with a mean overall follow-up period of 66 months) [38].

1.2. Ultrastructure

LGFMS consists of slender spindle cells with long, narrow, delicate and mostly non-branching cell processes, embedded in a variable amount of collagenous stroma. The tumor cells have irregular nuclear outlines with finely clumped chromatin and inconspicuous nucleoli. Intra-nuclear cytoplasmic invaginations are found in some nuclei. Most cells have a variable number of cytoplasmic organelles, including free ribosomes, intermediate filaments and rough endoplasmic reticulum cisternae, which may be poorly, mildly or moderately well developed. The cisternae of the endoplasmic reticulum are often dilated and contain finely granular contents. Some cells may consist of ovoid cytoplasmic structures with a fibrillary content, consistent with angulate lysosomes [44,45]. Nielsen et al. [46] reported the ultrastructural findings of 3 cases of HSCTGRs. The neoplastic cells showed fibroblastic features with long branching rough endoplasmic reticulum complexes. In all tumors, deposits of amorphous basal lamina-like substance were admixed with abundant extracellular collagen fibers and were also seen within the dilated cisternae. Ultrastructurally, the tumor cells of SEF have fibroblastic features, such as well-developed networks of rough endoplasmic reticulum, abundant cytoplasmic intermediate filaments, and lack of basement membranes [9].

1.3. Genetics

LGFMSs are characterized in the majority of cases by a balanced translocation, t(7;16)(q34;p11), resulting in fusion of the *FUS* and *CREB3L2* genes, with a small minority of cases showing a variant *FUS-CREB3L1* fusion resulting from t(11;16)(p11;p11) [6,11,47-49] The *FUS* gene, located at the chromosomal band 16p11, encodes an RNA-binding protein, and is fused to another transcription factor gene, *CREB3L2*, which is a member of the OASIS DNA-binding and basic-leucine zipper family located at 7q34. The resulting fusion gene exhibits both transcription activating and oncogenic properties [50]. Gene sequencing has shown that fusion points can vary within *FUS*, *CREB3L1* and *CREB3L2* genes, with the insertion of variable numbers of intron sequences or nucleotides from the *FUS* and *CREB3L2* genes, or whose origin is unknown [11]. Exon 6 of *FUS* and exon 5 of *CREB3L2* are the most involved breakpoints [11]. In addition to the translocation t(7;16)