Original paper

Low-grade fibromyxoid sarcoma of the extremities: a clinicopathologic study of 24 cases and review of the literature

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Low-grade fibromyxoid sarcoma (LGFMS) and hybrid sclerosing epithelioid fibrosarcoma (SEF)/LGFMS have a low potential for recurrence (10%) and metastasis (5%) but they are notorious for late occurring metastases. The aim of this study was to evaluate the outcome of LGFMS and review similar cases reported in the literature.

We retrospectively evaluated 24 LGFMS operated at a single Institution. All cases were histologically revised. Mean age was 34 years (range, 8 to 74). Two cases presented areas of SEF (hybrid tumours).

Three patients presented with metastasis at diagnosis. A strong cytoplasmic staining for MUC4 antibody was found in the majority of neoplastic cells. RT-PCR was feasible in 6 cases and it detected the presence of FUS-CREB3L2 fusion gene chimeric transcript.

Mean follow-up was 44 months (range, 6 to 217). Two patients developed lung metastasis after 9 and 26 months respectively.

Low-grade fibromyxoid sarcoma has a various histopathologic spectrum with few cases of LGFMS that share histopathologic resemblance with SEF, thereby reinforcing a possibility of a link within these two. It is of paramount importance an accurate and extensive sampling and examination of the whole specimen, in order to identify higher risk patients.

Key words: low-grade fibromyxoid sarcoma, Evans tumour, survival.

Introduction

Low-grade fibromyxoid sarcoma (LGFMS), also called Evans tumour, is a rare sarcoma that typically affects young adults and children. It is characterized by an indolent clinical course [1, 2, 3].

In some cases, more or less extensive areas reminiscent of sclerosing epithelioid fibrosarcoma (SEF) can be seen in combination with LGFMS areas: such tumours are known as hybrid SEF/LGFMS [4].

Although LGFMS has a much lower potential for recurrence (10%) and metastasis (5%) than SEF (> 50%) within the first 5 years, it is notorious for late occurring metastases [1]. Apart from tumour size and location, no strong predictive markers of metastasis have been identified [4, 5, 6].

Low-grade fibromyxoid sarcoma consists of slender spindle cells with long, narrow, delicate and mostly non-branching cell processes, embedded in a variable amount of collagenous stroma. On histological examination, LGFMS can be circumscribed or infiltrative, and is predominantly composed of bland-appearing spindle cells with small, angulated nuclei with inconspicuous nucleoli and scant, wispy cytoplasm [3]. Immunohistochemically, LGFMS characteristically shows strong and diffuse granular cytoplasmic

immunoreactivity with MUC4. It is highly sensitive for LGFMS [6].

However, the heterogeneous histological appearance makes the diagnosis challenging.

The majority of LGFMS cases have been shown to harbour a translocation between chromosome 7 and 16, 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 [3, 7]. A minority of cases have been shown to display a FUS-CREB3L1 [8].

Surgical excision with clear resection margins is the first line treatment option.

Maretty-Nielsen *et al*. [9] postulated that LGFMS is not very chemo- or radiosensitive due to its low nuclear grade and infrequent mitotic activity. However, another study by Cesne *et al*. [10] suggested that trabectedin could offer some benefit in translocation-related soft tissue sarcomas such as LGFMS.

The aim of this study was to evaluate the outcome of LGFMS and review similar cases reported in the literature.

Material and methods

From January 1999 to June 2018 a total of 28 patients received diagnosis of Evans tumour or hybrid SEF/LGFMS of the extremities at a single Institution (Rizzoli Orthopedic Institute, Bologna, Italy). All cases were histologically revised and classified according to the 2013 World Health Organization classification of STS [11] by experienced sarcoma pathologists of our Institute (AR). Immunohistochemical analysis with MUC4 antibody (Mouse Monoclonal Antibody, clone 8G7, Santa Cruz Biotechnology, 1 : 300 dilution) was done on all cases. Reverse transcriptase-polymerase chain reaction (RT-PCR) was carried out to detect t(11;22) EWSR1-CREB3L1, t(7;22) EWSR1-CREB3L2, t(7;16) EWSR1-CREB3L2 and t(11;16) EWSR1-CREB3L1 using RNA extracted from the frozen specimens, as previously described [12]. Fluorescent *in situ* hybridization (FISH) analysis for EWSR1 and FUS break-apart was performed to confirm the results of RT-PCR.

Four cases had a follow-up shorter than 6 months and were therefore excluded.

Tumour size was assessed on pre-operative MRI using the larger diameter as a reference and depths were divided into superficial (above the fascia) and deep (below the fascia). All patients underwent operation in order to obtain limb-sparing, function-sparing surgery with negative surgical margins, according to the Enneking classification [13].

The use of radiotherapy (RT) and chemotherapy (CT) was decided at the discretion of a multidisciplinary team (orthopedic surgeon, radiotherapist and oncologist). Radiation therapy and chemotherapy were administered according to STS guidelines [14].

A descriptive study is presented and data are presented in total frequencies and percentages. All analysis was completed using the Statistical Package for Social Science (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Informed consent was obtained by all the patients involved in the study.

All performed procedures were in accordance with the ethical standards of the local ethic committees and with the Helsinki Declaration of 1975, as revised in 1983.

Results

Of 24 cases of LGFMS (Table I), two cases (n. 12 and 21) presented some areas of SEF and were identified as hybrid tumours. Eight patients were male, 16 were female. Mean age was 34 years (range, 8 to 74).

Location-wise, most cases were deep-seated (18). Most of the tumours (15) were in the lower limb, 6 were in the pelvic girdle, one in the upper limb and one in the shoulder girdle.

Eleven LGFMS were small (< 5 cm), 11 were between 5 and 10 cm and two larger than 10 cm. Three patients presented with metastasis at diagnosis (two to the lungs and one to the spine). Histologically, vertebral metastasis of case 21 (hybrid tumour on primary lump) presented only features of SEF.

Apart from one patient in which an amputation was required, all other patients underwent excision of the tumour. Among these, 20 patients underwent wide surgical excision while three had marginal margins.

Macroscopically, all but two cases were well circumscribed with a white, fascicular appearance without areas of necrosis on cut section (Fig. 1A). Two cases showed infiltration of adjacent tissue. Morphologically, 8 cases showed "giant rosettes" characterized by hyalinixed collagenous nodular structures surrounded by palisading rounded or ovoid cells. In addition, nine cases evidenced markedly hypocellular and sclerotic areas with a misleading fibrotic appearance (Fig. 1B, C). Mitotic activity was low (mean one mitosis/10 high power fields) and necrosis was not evident in all cases.

A strong cytoplasmic staining for MUC4 antibody was found in the majority of neoplastic cells (Fig. 1D). In 6 cases, frozen neoplastic tissue was available to extract RNA. RT-PCR was feasible in all these 6 cases that detected the presence of FUS-CREB3L2 fusion gene chimeric transcript (Fig. 1E). All the other fusion chimeric transcripts examined (EWSR1-CREB3L1, EWSR1-CREB3L2, and EWSR1-CREB3L1) were not found. FISH analysis confirmed the RT-PCR

Table I. Patient's characteristics

Case	Age (years)	Sex	Location	Histology	Molecular (FUS-CREB3L2)	Depth	Size	DM at diagnosis	Surgery	Margins	Radiotherapy	Chemotherapy	LR	Time to LR (M)	DM	Time to DM (M)	Follow up (months)	Status
1	33	M	Thigh	Evans	–	Deep	< 5 cm	No	Excision	Wide	Adjuvant	No	No	NA	Lung	45	112	NED
2	18	F	Pelvic girdle	Evans	–	Superficial	< 5 cm	No	Excision	Marginal	No	No	No	NA	No	NA	22	NED
3	24	F	Thigh	Evans	–	Superficial	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	35	NED
4	48	M	Foot	Evans	–	Superficial	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	11	NED
5	8	F	Arm	Evans	–	Deep	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	15	NED
6	43	M	Pelvic girdle	Evans	–	Deep	> 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	11	NED
7	17	F	Thigh	Evans	–	Deep	> 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	96	NED
8	44	F	Leg	Evans	–	Deep	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	29	NED
9	67	F	Foot	Evans	–	Deep	> 5 cm	No	Amputation	Radical	No	No	No	NA	No	NA	27	NED
10	29	F	Shoulder girdle	Evans	–	Deep	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	15	NED
11	29	M	Thigh	Evans	–	Superficial	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	118	NED
12	17	M	Thigh	Hybrid	+	Deep	> 5 cm	No	Excision	Wide	NA	No	NA	1	No	NA	9	NED
13	40	F	Thigh	Evans	–	Deep	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	13	NED
14	40	F	Pelvic girdle	Evans	–	Superficial	< 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	83	NED
15	26	M	Thigh	Evans	–	Deep	> 10 cm	No	Excision	Wide	No	No	No	NA	No	NA	49	NED
16	17	M	Shoulder girdle	Evans	–	Deep	> 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	33	NED
17	29	M	Thigh	Evans	–	Deep	> 5 cm	No	Excision	Marginal	Adjuvant	No	No	NA	No	NA	26	NED
18	74	F	Pelvic girdle	Evans	–	Deep	> 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	6	NED
19	55	F	Pelvic girdle	Evans	–	Superficial	> 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	7	NED
20	34	F	Pelvic girdle	Evans	+	Deep	> 5 cm	No	Excision	Wide	No	No	No	NA	No	NA	8	NED
21	30	F	Thigh	Hybrid	+	Deep	> 5 cm	Yes (vertebra)	Excision	Wide	No	Neoadjuvant + Adjuvant	No	NA	Lung	9	19	DOD
22	34	F	Knee	Evans	+	Deep	> 5 cm	Yes (lung, breast)	Excision	Marginal	Adjuvant	Neoadjuvant + Adjuvant	No	NA	No	NA	11	DOD
23	47	F	Thigh	Evans	+	Deep	> 5 cm	No	Excision	Wide	Neoadjuvant	Neoadjuvant	Yes	83	Lung	26	217	AWD*
24	54	F	Thigh	Evans	+	Deep	>10 cm	Yes (lung)	Excision	Wide	Adjuvant	No	No	NA	No	NA	69	AWD*

**progression lung mets*
NED – no evidence of disease; DOD – died of the disease; AWD – alive with disease

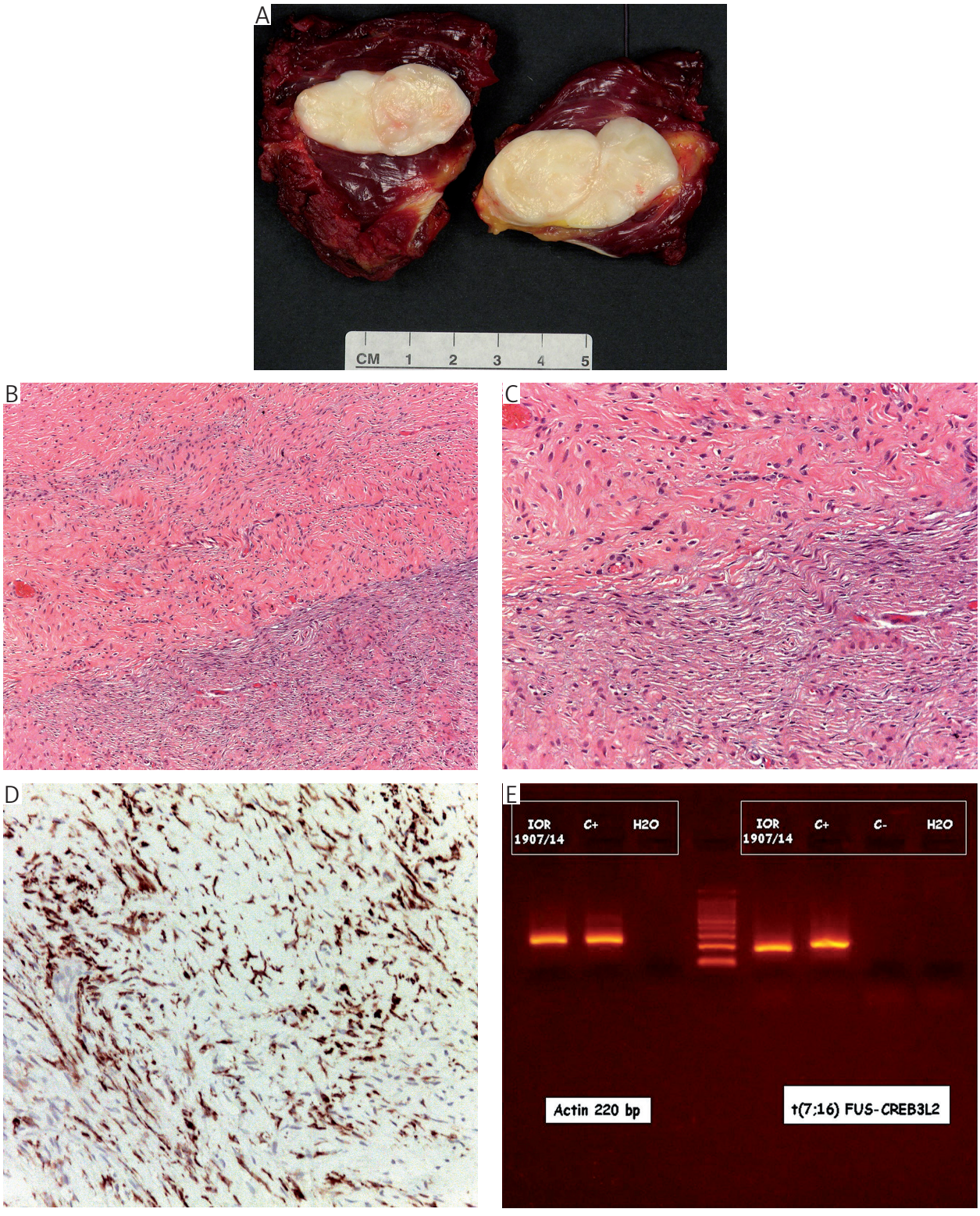

Fig. 1. A) An example of the macroscopy of a low-grade fibromyxoid sarcoma, showing a lobulated, glistening, leiomyoma-like, whitish mass. B, C) On hematoxylin and eosin, the tumor consists of very blande spindle cells embedded in a densely collagenous background, showing hypocellular and hypercellular areas (B: 100 × of magnification; C: 200 × of magnification). D) A strong immunohistochemical expression of MUC4 is evident in the majority of neoplastic cells (200 × of magnification). E) Chimeric FUS/CREB3L2 fusion transcripts, involving t(7;16) (q33;p11), is found in this tumor using RT-PCR analysis

Table II. Literature review

Authors	No. of cases	Age (years) (median, range)	LR (mean time to LR)	DM (mean time to DM)	Mean Follow up	Status
Lee *et al*. [18]	1	54	No	No	5 years	NED
Arnaoutoglou [19]	1	50	No	No	1 year	NED
Tay *et al*. [20]	1	85	No	No	17 months	NED
Evans [1]	21*	31 (6-52)	11 (5 years)	11 (7 years)	15 years	9 DOD 4 AWD 8 NED
Hisaoka *et al*. [5]	1	39	NA	NA	NA	NA
Folpe *et al*. [17]	73§	34 (3-78)	5 (NA)	3 (NA)	3 years	1 DOD
Indap *et al*. [22]	1	40	No	No	2 years	NED
Maretty-Nielsen *et al*. [9]	14	36 (8-65)	4 (8 months)	3 (4)	5 years	3 DOD 11 NED
Bajpai *et al*. [23]	1	22	No	No	5 years	NED
Papp *et al*. [24]	2	34 (18-50)	NA	NA	NA	NA
Kurisaki-Arakawa [27]	1	77	No	No	4 months	NED
Rekhi *et al*. [26]	9**	28 (10-45)	1 (NA)	1 (NA)	46 months (5-61)	1 AWD 4NED 4 NA
Kurisaki-Arakawa *et al*. [25]	1	5	NA	NA	NA	NA
Goodlad *et al*. [28]	11	45	6 (NA)	1 (lung)/NA	6 years (9/11 pts)	NA
Present study	24	34 (8-74)	1 (83)	3 (27)	44 months (6-217)	2 DOD 2 AWD 20 NED

** 21/33 cases located in the limbs*
***9/18 cases located in the limbs*
§ available follow up 54 cases
NED – no evidence of disease; DOD – died of the disease; AWD – alive with disease

results. FUS gene rearrangement was identified in the form of split signals in contrast to normal fused signals in all 6 cases examined. Conversely, EWSR1 gene rearrangement was not found in any cases.

Mean follow-up was 44 months (range, 6 to 217). Three patients (n. 1, 21 and 23) developed lung metastasis after 9, 26 and 45 months respectively. One of these (hybrid tumour) already presented vertebral metastasis. Local recurrence was observed in only one patient (n. 23) after 83 months. Overall, at last follow up twenty patients are alive with no evidence of disease. One patient (n. 1) is alive with no evidence of the disease after lung metastasectomy. Two patients (n. 21 and 22) who had metastasis at diagnosis died of the disease after 19 and 11 months, respectively. Two patients (n. 23 and 24) affected by synchronous or metachronous lung metastasis are still alive with slow progression of the disease after 191 and 69 months, respectively.

Among four patients with metastasis, only one was a hybrid case containing areas of SEF in the specimen.

Discussion

Low-grade fibromyxoid sarcoma is a low-grade distinctive variant of fibroblastic neoplasm with a metastasizing potential and, occasionally, long intervals between tumour presentation and metastasis.

In the present series only two out of 24 tumours presented areas of SEF. All tumours were extensively sampled and examined for identification of areas resembling SEF, including polygonal cells with eosinophilic to clear cytoplasm, arranged in cords and nests within a densely hyalinized stroma associated with a high mitotic activity and foci of tumoral necrosis [4, 5]. The mere presence of epithelioid cells was disregarded as a criterion for SEF-like morphology. A much higher proportion of such areas, more than 50%, would form a criterion for diagnosis of SEF, although there is no specific cut-off value for labelling pure and mixed SEF [7].

One out of two (50%) hybrid tumours presented with an aggressive clinical course (both synchronous vertebral and metachronous lung metastasis). Moreover, in the specimen of the vertebral metastasis, only areas of SEF were found. This might suggest a cells clone selection in the metastatic process. Noteworthy, only three out of 22 patients (11.5%) with "pure" LGFMS developed metastasis (either synchronous or metachronous).

Giant rosettes were found in 8 cases. This distinctive type of LGFMS containing rosettes was first described in 1997 [2] but the significance and pathogenetic mechanisms of the peculiar giant rosettes present in this type of fibroblastic neoplasm remain unclear. We did not find any correlation of rosettes with patients' prognosis.

Morphologically, because of its bland appearance, particularly evident in the cases with prevalent sclerotic areas, LGFMS could easily be confused with various benign soft tissue tumours, in particular on the biopsies, including desmoid fibromatosis, perineurioma, and cellular myxoma, as well as other low-grade sarcomas, especially low-grade malignant peripheral nerve sheath tumour and low-grade myxofibrosarcoma. Our series confirms that MUC4 is the best available marker for this tumour type because of very high accuracy to recognize LGFMS. Molecular analysis (RT-PCR and FISH) detecting FUS-CREB3L2 fusion gene chimeric transcript and FUS gene rearrangement confirms and supports the morphological and immunohistochemical results. It is interesting to observe that in all 6 cases examined with RNA available extracted from frozen tissue we found FUS gene rearrangement. Indeed, the proportion of LGFMS cases positive for the FUS break-apart reported in the existing literature varies considerably. Panagopoulos *et al*. [8] reported 12 positive cases out of 59 LGFMS patients; however, other studies have shown proportions of positive cases ranging from 81.1% to 96% [15, 16]. The large variation in the proportion of positive cases in different studies might be explained by differences in local practices and inclusion criteria. While the diagnosis of LGFMS "traditionally" is made based on the characteristic histological appearance and immunohistochemical features, some centres use the FUS break apart analysis as a part of the diagnostics, resulting in a, not surprisingly, variable proportion of positive cases.

Surgery, including wide excision with clear resection margins, remains the mainstay of treatment. In fact, due to the low grade of malignancy and therefore the low mitotic rate, LGFMS is not expected to be very chemo- or radiosensitive.

Recurrence and metastasis rate in the present study are similar to those previously reported by Folpe *et al.* [17]. We report a 4% rate of local recurrence (1 out of 24). Metastasis rate considering both synchronous and metachronous) was 21%. These data are similar to those reported a local recurrence rate of 9%, metastasis rate of 6%, and 1% of patients dying of LGFMS with a median of 24 months of follow-up. Guillou *et al.* [16] reported a smaller series with 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%. However, in Evans' most recent comprehensive study [1] of 33 LGFMS cases with long term follow-up (mean of 14 years), half of the patients developed metastasis and 42% died of disease. Thus, the potential for late recurrences and metastatic spread is high, necessitating long-term follow-up for all patients with LGFMS.

As for soft tissue sarcomas in general, superficial LGFMS has generally been associated with a good prognosis, which is better than that for deep-seated neoplasms [15]. All patients who developed metastasis in the present series had deep-seated tumours. However, Evans [1] reported that also small tumour size might represent a favourable prognostic factor in LGFMS.

Low-grade fibromyxoid sarcoma has a diverse histopathologic spectrum with a few cases of LGFMS which share histopathologic resemblance with SEF, thereby reinforcing a possibility of a link within these two. Even though even LGFMS can develop metastasis, it is of paramount importance an accurate and extensive sampling and examination of the whole specimen, in order to identify higher risk patients.

The authors declare no conflict of interest.

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