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A case of low-grade fibromyxoid sarcoma with unusual central necrosis in a 77-year-old man confirmed by *FUS-CREB3L2* gene fusion

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ABSTRACT

INTRODUCTION: Low-grade fibromyxoid sarcoma (LGFMS) is a rare soft tissue tumor typically affecting young to middle-aged adults. Despite its otherwise benign histologic appearance and indolent nature, it can display fully malignant behavior, and recurrence and metastasis can occur even decades after diagnosis.

PRESENTATION OF CASE: Herein, we report a case of LGFMS in the buttock of a 77-year-old man. Magnetic resonance imaging uncovered a well-demarcated tumor measuring 27 × 20 mm with a slightly high intensity on T1-weighted images (WIs) and heterogeneously high intensity on T2-WIs. Histologically, the tumor was composed of bland spindle-shaped cells in a whorled growth pattern with alternating fibrous and myxoid stroma. The tumor stroma was variably hyalinized with arcades of curvilinear capillaries and arterioles with associated perivascular fibrosis. Unusual histology, such as central necrosis and cystic formation, was also noted. Reverse transcription polymerase chain reaction from a formalin-fixed, paraffin-embedded biopsy specimen revealed a *FUS-CREB3L2* gene fusion (exon6/int/exon5), leading to the diagnosis of LGFMS.

DISCUSSION: To the best of our knowledge, this is the second oldest patient to be diagnosed with LGFMS.

CONCLUSION: At the time of this report, the patient was alive with no evidence of the disease 4 months after diagnosis without any adjuvant therapy.

1. Introduction

Low-grade fibromyxoid sarcoma (LGFMS) is a rare soft tissue tumor that typically affects young to middle-aged adults.[1,2] A large series of LGFMS cases demonstrated that the median age of onset for this tumor is 34 years (range, 3–78 years).[3] Histologically, LGFMS is composed of bland spindle-shaped cells in a whorled growth pattern, arranged in alternating myxoid and collagenized areas, along with curvilinear capillaries and characteristic arterioles with perivascular fibrosis. Heterotopic ossification and cyst formation have also been reported in these tumors.[4,5] While LGFMS usually exhibits otherwise benign histologic appearance, a subset of tumors have been reported to show indolent progression, with many cases developing recurrence or metastasis decades later, mainly to the lung. Cytological atypia and tumor necrosis is absent in LGFMS.[6] However, approximately 30% of tumors have focal areas of intermediate- to high-grade sarcoma as shown by hypercellularity, nuclear enlargement, hyperchromatism, necrosis, and high mitotic activity (>5/50 high-powered fields), but the presence of these histologic features is not associated with patient survival.[3,5] Furthermore, approximately 40% of cases have focal areas of hypocellular collagen cores rimmed by epithelioid fibroblasts, referred to as collagen pseudo-rosettes. Cases of prominent collagen pseudo-rosettes are referred to as hyalinizing spindle cell tumors with giant rosettes.[7]

A diagnosis of LGFMS is often difficult by a small biopsy specimen that can lead to a misdiagnosis of malignant tumors as benign or as tumor-like lesions including nodular fasciitis, schwannoma, desmoid-type fibromatosis, neurofibroma, and myxofibrosarcoma.[8–10] A recent study reported up-regulation of the *mucin 4* (*MUC4*) gene in LGFMS compared to histologically similar tumors and lesions,[10,11] and MUC4 immunostaining was a sensitive and specific marker of LGFMS in appropriate morphologic context.[2,7] Several recent studies demonstrated that more than 90% of LGFMS have a balanced chromosomal translocation *t*(7;16)(q32–34;p11) leading to the fusion of the *FUS* and *CREB3L2* genes, while a minority of cases have a *t*(11;16)(p11;p11) translocation leading to the fusion of the *FUS* and *CREB3L1* genes.[1,2,7–9,12] In one report, a small number of LGFMS cases contained *EWSR-CREB3L1* gene fusions.[7,13]

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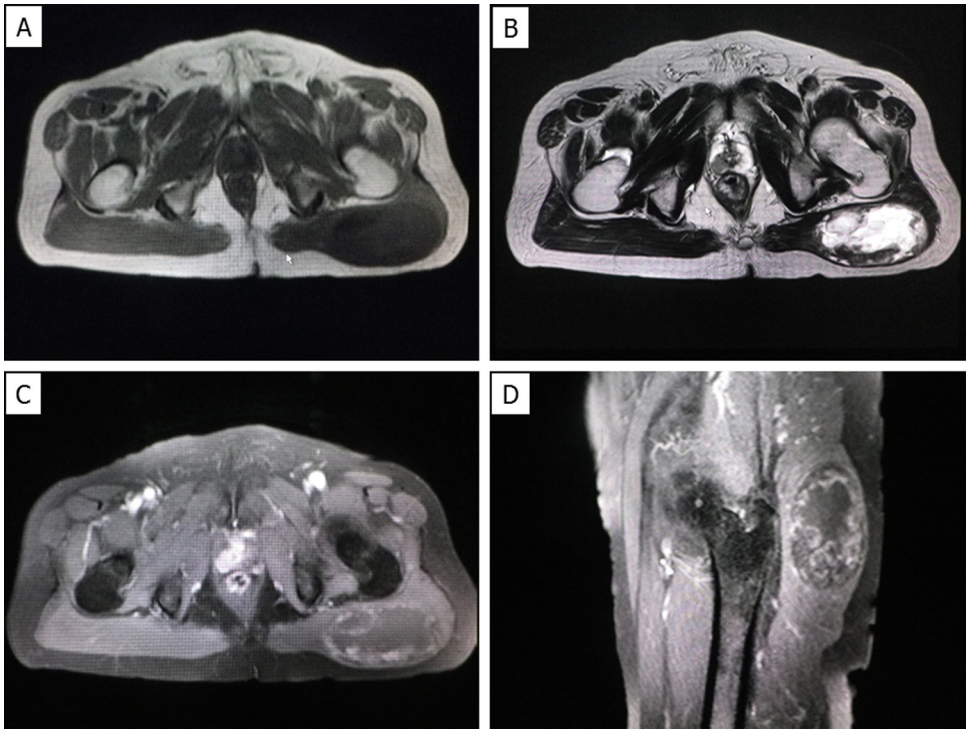

Fig. 1. Magnetic resonance imaging (MRI) of the left buttock of a 77-year-old patient. MRI revealed a well-defined mass in the left buttock. The mass showed low signal intensity compared to the skeletal muscle on T1-weighted images (WIs) (A) and heterogeneously high signal intensity on T2-WIs (B). The mass had heterologously mixed low to slightly high signal intensity compared to the skeletal muscle on fat-suppressed T1-WIs (C: coronal, D: sagittal).

Here, we report a rare case of LGFMS with central hemorrhagic necrosis in a 77-year-old male patient. Reverse transcription polymerase chain reaction (RT-PCR) from a formalin-fixed, paraffin-embedded (FFPE) biopsy specimen revealed *FUS-CREB3L2* gene fusion (exon6/int/exon5), leading to the diagnosis of LGFMS. To the best of our knowledge, this is the second oldest patient to be reported with LGFMS.

2. Case report

A 77-year-old man was referred to our hospital with a painless mass in the left buttock, which had been gradually growing since he first noticed it 10 years previously. A physical examination revealed an elastic hard mass in the left buttock, and magnetic resonance imaging (MRI) showed a well-demarcated tumor measuring 70 mm in maximum diameter with central hematoma formation. The mass showed low intensity on T1-weighted images (WIs), heterogeneously high intensity on T2-WI (Fig. 1A and B), and heterogeneously high signal intensity on fat-suppressed T1-WI (Fig. 1C and D). Chest and pelvic computed tomography (CT) revealed no evidence of metastatic lesion.

Histopathologically, the tumor was composed of bland spindle-shaped cells with a whorled growth pattern on biopsy specimen. The tumor stroma was fibrous, and alternating fibrous and myxoid stroma characteristic of LGFMS were unclear (Fig. 2A–C). The tumor showed no nuclear pleomorphism, high cellularity. Focally, tumor cells exhibited wavy appearance. Necrotic area was also observed at the edge of the specimen. Mitosis was not observed. Differential diagnosis on conventional hematoxylin and eosin staining included desmoid-type fibromatosis, schwannoma, and LGFMS. Immunohistochemically, the tumor cells were negative for S-100 protein (Fig. 2D) and nuclear staining of β-catenin, which are typically present in desmoid-type fibromatosis.

To determine the presence of *FUS-CREB3L1* or *FUS-CREB3L2* fusion genes in the tumor, we performed RT-PCR on FFPE tumor tissue. Briefly, five 10-μm thick paraffin sections were cut from the paraffin-embedded block. RNA was isolated using the RNeasy FFPE kit (QIAGEN, Hilden, Germany), purified, and reverse transcribed to cDNA using the Superscript first-strand synthesis system for RT-PCR (Invitrogen, CA, USA). The primer sequences used for the amplification in this study have been previously described.[14] The PCR product was separated on a 2% agarose gel, and the PCR product of the appropriate size was cut from the gel and sequenced. Sequencing confirmed the presence of a *FUS-CREB3L2* fusion gene in this tumor. This gene fusion occurred between the end of exon 6 of *FUS* and part of exon 5 of *CREB3L2* with a 4-bp insertion of unknown origin (Fig. 3A). Genomic DNA-based long PCR revealed a gene fusion between the part of intron 6 of *FUS* and part of exon 5 of *CREB3L2*. The 4-bp sequence at the end of intron 6 was identical to that of a 4-bp insertion of the *FUS-CREB3L2* fusion gene, suggesting that the 4-bp insertion was probably derived from the junctional region of the fusion gene (Fig. 3B). Thus, the fusion gene in this case was exon6/int6/exon5 of the *FUS-CREB3L2*.

A wide resection of the tumor was performed under a diagnosis of LGFMS. Macroscopically, the resected surface of the surgical specimen was whitish-gray with partial myxoid appearance (Fig. 4A). Central hemorrhagic necrosis was also observed. Pathological analysis of the resected tumor revealed characteristic alternating fibrous and myxoid stroma with occasional cystic formation (Fig. 4B–D). Four months after diagnosis, the patient was alive with no evidence of the disease without any adjuvant therapy.

3. Discussion

LGFMS can occur at any age, but typically affects young to middle-aged adults.[1,2] Two large studies on LGFMS reported that patient age at the time of diagnosis ranges between 6–52 years and 3–78 years, respectively.[3,5] In the current case, with the long duration of the tumor and cystic changes on MRI, the differential diagnosis on biopsy specimen included