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Case study

Deceptively benign low-grade fibromyxoid sarcoma: array-comparative genomic hybridization decodes the diagnosis

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Summary Low-grade fibromyxoid sarcoma (previously known as Evans tumor) is a rare soft tissue neoplasm characterized by a deceptively bland appearance despite the potential for late metastasis or recurrence. We describe a 13-year-old patient with a popliteal fossa mass initially thought to be benign that, because of array-comparative genomic hybridization findings and subsequent immunohistochemistry, was diagnosed as low-grade fibromyxoid sarcoma. The array-comparative genomic hybridization demonstrated a loss of 11p11.2p15.5 and a gain of 16p11.2p13.3 with breakpoints involving the *CREB3L1 (cAMP responsive element-binding protein 3-like 1)* and *FUS (fused in sarcoma)* genes, respectively. Subsequent fluorescence in situ hybridization analysis of a dual-labeled break-apart *FUS* probe on interphase cells was positive. Our case highlights the importance of using genetic information obtained via array-comparative genomic hybridization to classify accurately pediatric soft tissue tumors.
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1. Introduction

Low-grade fibromyxoid sarcoma (LGFMS), first described by Evans in 1987, is a deceptively benign-appearing lesion that is known to recur frequently and/or metastasize late [1,2]. Cytogenetics has played an increasingly important role in the diagnosis of LGFMS with the discovery that between 88% and 96% of LGFMS demonstrate a characteristic translocation t(7;16) resulting in fusion of the *fused in sarcoma* (*FUS*) and *cAMP responsive element-binding protein 3-like 2* (*CREB3L2*) genes [2]. A rare variant of this translocation is t(11;16) (fusing the *FUS* and *cAMP responsive element-binding protein 3-like 1* [*CREB3L1*] genes) and has been described in only 4 patients, excluding our case [3,4]. We describe a case of a 13-year-old boy with a popliteal fossa mass that was initially thought to be a benign desmoplastic fibroblastoma based on the histology. Ultimately, the mass was diagnosed as a LGFMS when array-comparative genomic hybridization (array-CGH) showed a copy loss of chromosome 11p11.2p15.5 and a gain of

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16p11.2p13.3 with breakpoints involving the *CREB3L1* and *FUS* genes, respectively. The involvement of the *FUS* gene was confirmed by fluorescence in situ hybridization (FISH). Traditionally, the t(7;16) is a balanced translocation that may fail to be detected using array-CGH. However, the present case appears to have a derivative chromosome 11 made up of 16p and 11q (leading to loss of 11p and gain of 16p), which made it detectable by array-CGH.

Our finding of an unbalanced t(11;16) is unique and supports the 5′*FUS*/3′ *CREB3L1* gene product as being the critical fusion behind the formation of the tumor. In addition, immunohistochemistry for MUC4 (prompted by array-CGH findings) was positive, supporting both the cytogenetic findings and the recent literature that indicates that MUC4 is a sensitive and specific marker for LGFMS [5]. This case highlights the usefulness of array-CGH in the evaluation of tumors in pediatric pathology especially when tumor cell culture fails to grow in vitro and pathology findings indicate a benign tumor.

1.1. Clinical course

Our patient is a 13-year-old boy who was found to have an enlarging right popliteal fossa mass and who had been followed for 5 years. Physical examination showed a firm, nodular, mobile, nontender mass. A magnetic resonance imaging demonstrated a soft tissue lesion intimately associated with the common peroneal nerve, and the clinical diagnosis was a peripheral nerve sheath tumor. The clinical picture was not typical of a malignant process, but a neoplasm could not be definitively ruled out without a tissue sample. The family elected to proceed with excisional biopsy of the lesion with the understanding that the nerve may be at risk based on intraoperative findings. The tumor was removed en bloc as a marginal resection, requiring “peeling off” the common peroneal nerve. Preliminarily, the lesion was thought to be a desmoplastic fibroblastoma; however, because of the cytogenetic testing and immunohistochemistry, the final diagnosis was LGFMS. The tumor was noted to extend to the surgical margin. Based on the diagnosis, the patient obtained a chest computed tomography, which was negative for metastatic disease.

Because LGFMS has the potential for late local or systemic recurrence [1], the patient and family discussed current and long-term treatment options, which included the following: surgical re-excision, adjuvant radiation therapy, or active surveillance. The family ultimately elected to proceed with active surveillance.

2. Materials and methods

Array-CGH: Genomic DNA was isolated from the right popliteal fossa mass using the Qiagen DNeasy Blood and Tissue kit (Qiagen, Valencia, CA). DNA purification was performed with 25:24:1 phenol:chloroform:isoamyl alcohol in conjunction with 5′ Phase-Lock Gel tubes. The purified DNA was diluted to a working concentration of 50 ng/μL. The tumor and control DNA were labeled with cyanine 3 and 5 dyes using the Roche Nimblegen Dual-Color labeling kit (Roche Diagnostics, Germany). Both DNAs were combined and hybridized onto a custom 12-plex 180K-feature whole-genome oligonucleotide slide designed by Signature Genomic Laboratories (Spokane, WA) and manufactured by Roche NimbleGen (Madison, WI). The array was scanned with a Molecular Devices GenePix 4000B scanner (Sunnyvale, CA), which uses the GenePix Pro 6.0 Software. The resulting text (.txt) file was analyzed and visualized using Signature Genomic’s Genoglyphix software (Signature Genomic Laboratories).

FISH: Based on array-CGH findings, the breakpoint on 16p appeared to involve the *FUS* gene. To confirm this finding, FISH was performed using a *FUS* probe ordered from Abbott Molecular (Abbott Park, IL) on interphase cells derived from fresh solid tumor. The LSI FUS (16p11) probe is a dual-color break-apart probe consisting of a 500 kilobase (kb) 3′ telomeric side labeled in spectrum green and a 270 kb 5′centromeric side labeled in spectrum orange. A 2-fusion signal pattern indicates no rearrangement involving the *FUS* gene, whereas a distant separation between orange and green signals indicates *FUS* gene involvement. FISH was performed in accordance with the manufacturer’s instructions. Hybridization signals were evaluated under a fluorescence microscope (Olympus BX41; Applied Imaging) using the appropriate filter sets.

2.1. Pathologic findings

Grossly, the mass was a 2.7 × 1.7 × 1.2 cm well-circumscribed ovoid piece of pink-white firm tissue (Fig. 1A). The cut surface was fibrous-appearing, firm, white, and whorled. Histologically, the lesion was paucicellular and generally well circumscribed. The lesional cells were embedded in a hyalinized paucicellular eosinophilic matrix with a slightly wavy character (Fig. 1B). The nuclei were small and angulated without atypia or mitotic activity (Fig. 1C). The neoplastic cells labeled with antibody to vimentin and MUC4 (Fig. 1D) but were negative with antibodies to desmin, smooth muscle actin, epithelial membrane antigen, CD34, CD68, CD57, S-100 protein, or neurofilament.

2.2. Molecular cytogenetic findings

Based on the pathology department of Cardinal Glennon Children’s Hospital, pediatric neoplasms are routinely sent for cytogenetic analysis. After conventional methods, the tumor was processed for culture and direct harvest. However, the culture failed to yield dividing cells. Therefore, tumor DNA was processed for an array-CGH. Results showed 2 significant abnormalities: a loss of 11p and a gain of 16p

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