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ORIGINAL ARTICLE

Undifferentiated myxoid lipoblastoma with *PLAG1–HAS2* fusion in an infant; morphologically mimicking primitive myxoid mesenchymal tumor of infancy (PMMTI)—diagnostic importance of cytogenetic and molecular testing and literature review

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Lipoblastoma is a benign myxoid neoplasm arising in young children that typically demonstrates adipose differentiation. It is often morphologically indistinguishable from primitive myxoid mesenchymal tumor of infancy (PMMTI), which is characterized by a well-circumscribed myxoid mass with a proliferation of primitive mesenchymal cells with mild cytologic atypia. PMMTI occurs in the first year of life and is known to have locally aggressive behavior. No specific genetic rearrangements have been reported to date. In contrast, the presence of *PLAG1* (Pleomorphic Adenoma Gene 1) rearrangement is diagnostic for lipoblastoma. We hereby demonstrate the combined application of multiple approaches to tackle the diagnostic challenges of a rapidly growing neck tumor in a 3-month-old female. An incisional tumor biopsy had features of an undifferentiated, myxoid mesenchymal neoplasm mimicking PMMTI. However, tumor cells showed diffuse nuclear expression by immunohistochemical (IHC) stain. Conventional cytogenetic and fluorescence *in situ* hybridization (FISH) analyses as well as next generation sequencing (NGS) demonstrated evidence of *PLAG1* rearrangement, confirming the diagnosis of lipoblastoma. This experience warrants that undifferentiated myxoid lipoblastoma can mimic PMMTI, and the combination of cytogenetic and molecular approaches is essential to distinguish these two myxoid neoplasms. Literature on lipoblastomas with relevant molecular and cytogenetic findings is summarized. Our case is the first lipoblastoma diagnosed with a *PLAG1* fusion defined by NGS technology.

Keywords Lipoblastoma, myxoid mesenchymal tumor, cytogenetics, *PLAG1* rearrangement, next generation sequencing

Introduction

The differential diagnoses of myxoid lesions of the soft tissue in newborns and infants comprise a broad range of conditions, including reactive lesions, hamartomatous lesions, and benign and malignant neoplasms (1). Lipoblastoma is a benign myxoid neoplasm typically arising in children before 3 years

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of age and often demonstrating adipose differentiation (2). Lipoblastomas are usually well circumscribed and superficially located, but infiltrative lipoblastomas (lipoblastomatosis), arising in the deep soft tissue, are also included in the category. Although most lipoblastomas are 3-5 cm in diameter, some exceed 10 cm. Lipoblastomas typically contain cells at a broad spectrum of maturation states from primitive mesenchymal cells, lipoblasts to mature adipocytes and often present with a myxoid background. Lipoblastomas are often indistinguishable from primitive myxoid mesenchymal tumor of infancy (PMMTI) which typically occurs in newborns and infants and is known to have locally aggressive behavior and may have low malignant potential (3,4). PMMTI is characterized by a well-circumscribed myxoid neoplasm with a proliferation of primitive immature mesenchymal cells with mild cytologic atypia. The tumor shows morphologic features overlapping with congenital infantile fibrosarcoma (CIFS) but it does not have the *ETV6* gene rearrangement, supportive of CIFS.

We hereby present a challenging case of a 3 month-old female with a rapidly growing left neck mass. An initial incisional biopsy demonstrated an undifferentiated mesenchymal neoplasm with a prominent myxoid background that mimicked a PMMTI. However, the tumor demonstrated diffuse nuclear *PLAG1* expression by IHC stain. Conventional chromosome analysis revealed a complex rearrangement involving chromosomes 8q and 11q. FISH analysis on metaphase spreads using a *PLAG1* break apart probe confirmed a *PLAG1* rearrangement. Further characterization using microarray and NGS revealed a more complete picture of this complex chromosome rearrangement resulting in *PLAG1–HAS2* fusion. This case illustrated that the cytogenetic and molecular analyses can play essential roles in making unequivocal diagnosis of undifferentiated myxoid lipoblastomas.

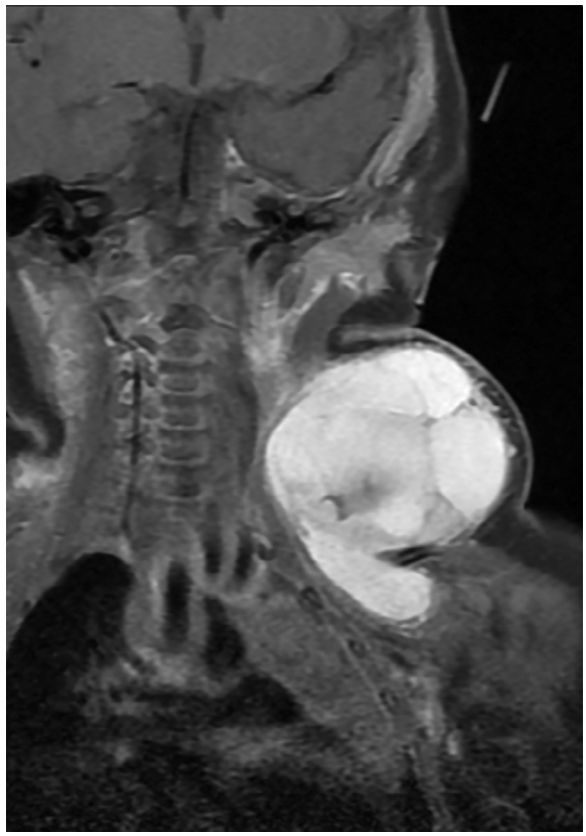

Figure 1 MRI imaging of the tumor mass. MRI imaging demonstrated a large solid left neck mass with relatively homogeneous enhancement with contrast.

Materials and methods

Patient clinical report

A previously healthy 3 month-old female with no abnormal prenatal/birth history presented with a 2 week history of a firm, rapidly growing, well defined left neck mass. A magnetic resonance imaging (MRI) demonstrated a homogeneous T2 hyperintense and T1 hypointense supraclavicular mass measuring $6 \times 5.5 \times 2$ cm (Figure 1). An incisional biopsy and a complete excision (3 weeks after the biopsy) were performed. No recurrence has been noted to date.

Histological analysis

Biopsy specimen

A small portion of the fresh biopsy tissue was submitted to cytogenetic analysis. Another small portion was fixed in cacodylate-buffered glutaraldehyde for electron microscopy. The reminder of tissue was entirely submitted for light microscopic examination. Formalin fixed paraffin embedded (FFPE) tissue was prepared. Routine hematoxylin and eosin (H&E) and IHC stains were performed on the FFPE sections of 4 mm at the CLIA certified histology laboratory at Cincinnati Children's Hospital Medical Center. IHC stains were performed on sections from an FFPE block containing abundant tumor tissue using the following antibodies: vimentin (mouse monoclonal antibody, Ventana, Tucson, AZ), CD34 (mouse monoclonal, Cell Marque, Rocklin, CA), SMA (mouse monoclonal, Cell Marque), S100 (rabbit polyclonal, Ventana), myogenin (mouse monoclonal, Cell Marque), CD99 (mouse monoclonal, Ventana), CD117 (rabbit monoclonal, Cell Marque) and Mib-1 (Ki-67, rabbit monoclonal, Ventana). Adequate positive and negative controls were stained along with the sample and were appropriately stained. The tissue submitted for electron microscopy was post-fixed in osmium tetroxide and embedded in epoxy resin. Ultra thin sections were stained with uranyl acetate/lead citrate. Detailed evaluation was made using a Hitachi transmission electron microscope.

Specimen from resection

The specimen of the entirely excised tumor was thoroughly sectioned and a routine H&E stain was performed on each FFPE tissue section.

Chromosome analysis

A soft tumor tissue of left neck (0.5×0.7 cm^2) was received and minced under a sterile condition. Then the tumor specimen was dissociated in collagenase B (Roche Diagnostics Indianapolis, IN) and the suspension was seeded on coverslips. The cells were cultured in RPMI-1640 (Fisher Scientific, Houston, TX) supplemented with 16% fetal bovine serum and Amnio Max supplemented media (Gibco Laboratories, Grand