Case Report

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Myxoid Lipoblastoma with New Fusion Transcript *PLAG1–CHCHD7* in an 18-Month-Old Girl Diagnosed by Target RNA Sequencing: A Case Report

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Abstract

Lipoblastomas are rare, rapidly growing benign tumors rising from embryonic white fatty cells that continue to *proliferate* in the postnatal period. We presented a case of a toddler with an undifferentiated myxoid neoplasm with features of a minimally differentiated lipoblastoma. Our patient was an 18-month-old female with a painless solid tumefaction in the middle third of the right leg. *Histopathologically*, the nodular tumor mass consisted of lipobastic cells embedded in a myxoid stroma. Immunohistochemistry showed strong diffuse positivity for vimentin, S100, CD34, CD56, NSE and rare Ki67+ cells. FOXO1 polyploidy was detected in 30% of cells by FISH. Using target RNA sequencing, we detected a fusion gene, *CHCHD7-PLAG1*, in the tumor sample. Sequence analysis showed that the first exons of *CHCHD7* were fused to either exon 2 or exon 3 of *PLAG1*. Our case demonstrates that due to the histomorphologic overlaps, the molecular diagnostics is essential for confirmation of lipoblastomas.

Keywords: *PLAG1;* lipoblastoma; toddler; chromosomal rearrangement; RNA sequence

1. Introduction

Lipoblastomas are rare, rapidly growing benign soft-tissue tumors rising from embryonic white fat cells that continue to *proliferate* in the postnatal period [1]. This *tumor* primarily affects children younger than 3 years of age (75 - 90%), but can also occur in older children and very rarely in adulthood [2]. Lipoblastoma are well-encapsulated mass and no malignant degeneration and metastasis has been documented to date. The long-term prognosis for lipoblastoma is often excellent. They are usually located in the subcutaneous tissue of the trunk and extremities, however other less common tumor sites such as head and neck, mediastinum, mesentery, retroperitoneum, inguinoscrotal or labial region are also reported [1]. Thus, depend on tumor location, the rapid growth of the soft palpable mass causes the broad range of clinical features. The main pathophysiological mechanism of lipoblastoma is the continuous proliferation and differentiation of embryonic white adipocytes during the postnatal period [1]. Macroscopically, lipoblastoma is a lobulated, soft, and encapsulated mass of yellow or creamy white color. *Histopathologically*, lobular architecture of lipoblastoma is characterized by *spectrum* of the fat cells at different stages of *maturation ranging* from stellate or spindled mesenchymal cells, mono- or multivacuolated lipoblasts, to immature and mature adipocytes. Lipoblasts are cells that contain a hyperchromatic nucleus and a lipid-rich cytoplasm, which may be mono- or multivacuolar. The nucleus may be located eccentrically if a single large fat droplet is present, or centrally with smaller depressions formed by the interaction of multiple small lipid droplets [3]. Fat cells are separated by fibrovascular septa and

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areas of myxoid matrix with primitive stellate or spindled mesenchymal cells and plexiform vascular network [4,5]. Lipoblastoma with late resection may show fibrolipomatous changes with no presence of lipoblasts [6]. According to histopathological and clinical features, there are two types of lipoblastoma: limited and diffuse lipoblastoma. Limited lipoblastoma is more common in clinical practice, it is encapsulated and most often found in the subcutaneous tissue of the limbs. Diffuse lipoblastoma, more commonly known as lipoblastomatosis, occurs less frequently and is characterized by infiltrative and diffuse growth, deep localization and absence of capsule [7]. The goal of treatment is complete surgical resection of the tumor, however, this is difficult to achieve in lipoblastomatosis. In these cases, especially in newborns, conservative treatment is used [8,9]. To date, no spontaneous resolution or reduction of lipoblastoma has been reported, and recurrence rates of 14% and 25% have been reported with incomplete excision.

Gene fusions or chromosomal rearrangements are a main class of somatic alterations in lipoblastoma and can have important roles in the initial steps of tumorigenesis [10]. Genetic anomalies in lipoblastoma includes structural alteration of 8q11–q13, leading to a rearrangement of the pleomorphic adenoma gene 1 (*PLAG1*) in chromosome 8. Pleomorphic adenoma gene 1 was first described in pleomorphic adenomas of the salivary glands and belongs to the PLAG family of transcription factors along with PLAG-*like* 1 and PLAG-*like* 2 genes [11]. *PLAG1* oncogene encodes a zinc finger transcription factor, broadly expressed during fetal development and only at very low levels postnatally [12]. *PLAG1* transcriptional up-regulation in lipoblastoma is associated with the gene rearrangements leading to the promoter swapping and bringing the *PLAG1* gene under the transcriptional control of a more active promoter [13]. In particular, exon 2 or 3 of *PLAG1* combines with exon 1 of the N-terminal side of the partner genes, causing the increased transcription of the fusion gene [14]. To date, different *PLAG1* fusion partners have been described, including *COL1A2, COL3A1, HAS2, RAD51L1, RAB2A, BOC, CHCHD7, SRSF3, HNRNPC, PCMTD1, EEF1A1, YWHAZ, CTDSP2, PP2R2A, DDX6, KLF10*, and *KANSL1L* [13].

Here, we describe the diagnostic workup of a pediatric patient with lipoblastima due to *PLAG1* rearrangements, and compare these findings with other reports of this rare disease. Our case demonstrated that the molecular analyses play essential role in making unequivocal diagnosis of undifferentiated myxoid lipoblastomas in infants. To the best of our knowledge, this is the first case of lipoblastoma due to break points in chr8:57124396-chr8:57083748 and chr8:57124396-chr8:57092072 regions.

2. Results

2.1. Clinical and Histopathological Features

Echosonographically, in the region of the tumor, in the anterior part of the right leg, an oval hyperechoic change (dominantly central hyperechoic) was detected at about 6.3 mm from the skin level, measuring about 12x30x16 mm, which was at the level of the associated muscle. The hyperechoic zone did not involve bone (data not shown). Radiographic analyses confirmed intact bone. Laboratory analysis revealed resulting *values* within the *normal range*.

Under conditions of analgosedation and regional block, the tumor was completely removed and sent for histopathological verification. The operative and immediate postoperative course were uneventful, with no immediate complications.

The soft tissue fragment of white-yellowish color was resected. Histopathological analysis showed lobules with spindle-shaped, stellate and light cells of lipoblastic appearance separated by fibrous septa. Zones of myxoid matrix were present in the tumor, which in places had a chondroid appearance. The tumor had a nodular type of growth, surrounded by a pseudocapsule that is missing in places (**Figure 1**).

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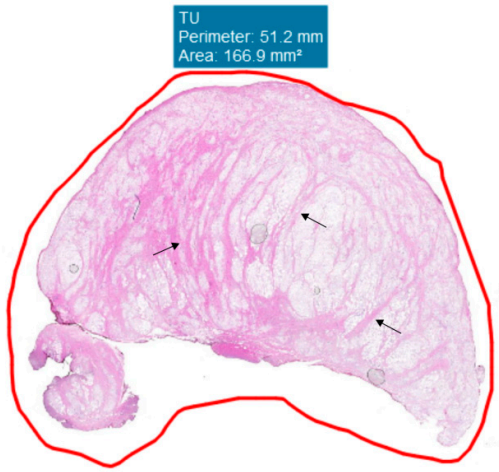


Figure 1. Hematoxylin and eosin (H&E) staining. H&E showed lobules of mature fat cells and lipoblasts separated by fibrous septa (black arrow). The tumor is pseudo-encapsulated with nodular growth pattern. The lipobastic cells are embedded in a myxoid stroma which in places has a chondroid appearance.

Tumor immunophenotype: immunohistochemistry showed strong diffuse positivity for vimentin (+++), S100 (+++), CD34 (++), CD56 (+++), NSE (+++) and rare Ki67+ positive cells (<1%). Myogenin, Myo D1, Rb, LCA, SOX10, alpha SMA, and caldesmin were negative (data not shown).

2.2. Cytogenetic and Molecular Features

In the analyzed sample, the presence of FOXO1 rearrangement was not observed, while FOXO1 polyploidy was detected in 30% of cells by FISH analysis (data not shown). Based on morphology (fatty component present), the immunophenotype, as well as the FISH analysis, the diagnosis of a mesenchymal tumor of the myxoid lipoblastoma type, infantile subtype was made.

In the sample of the known myxoid lipoblastoma from 19.10.2023. tumor driver *CHCHD7-PLAG1* was identified using the NGS Somatic tumor panel (TUM01) panel (not evidently therapeutically relevant). RNA sequencing revealed *CHCHD7-PLAG1* fusion (on RNA level), resulting from a cryptic intrachromosomal rearrangement at 8q12 (**Figure 2**).

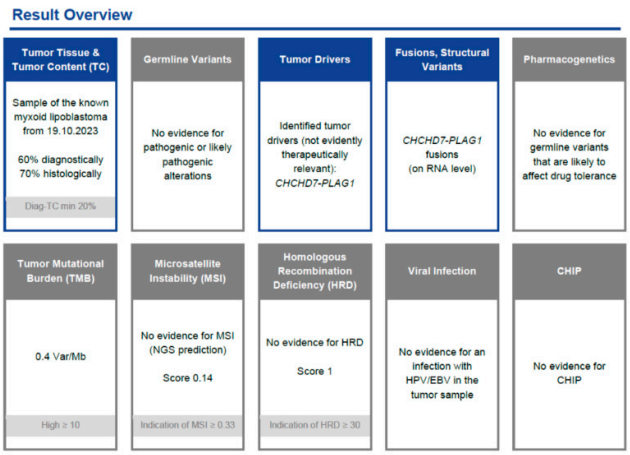


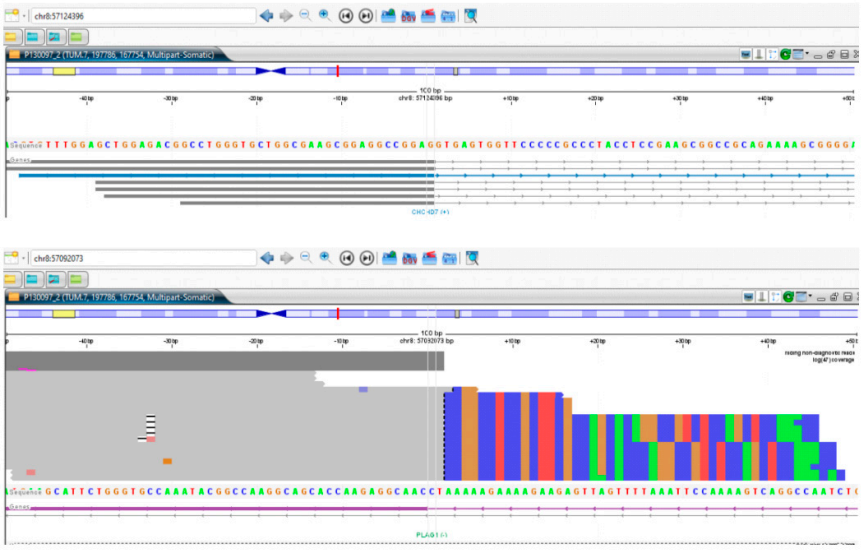
Figure 2. Somatic molecular genetic analysis of tumor tissue sample - TUM01 tumor panel. RNA fusion (STR) panel analysis for identification of gene fusions.

 doi:10.20944/preprints202603.0558.v1

The focal somatic copy number alterations and structural alterations detected in the tumor sample are presented in **Figure 3**. Both *PLAG1* fusions identified in this study involved the 5′ untranslated regions of both PLAG1 and a fusion partner gene. In *CHCHD7-PLAG1*, *CHCHD7* (NM_001011671.3) exon 1 fused to *PLAG1* (NM_002655.3) exon 3 (**Figure 3A**), and *CHCHD7* (NM_001011671.3) exon 1 fused to *PLAG1* (NM_002655.3) exon 2 (**Figure 3B**). Consequently, all fusions resulted in having the entire *PLAG1* coding sequence, which begins in exon 4, placed under the transcriptional control of promoter regions of fusion partner genes (promoter swap).

A

Gene	Functional category	Transcript-ID
CHCHD7-PLAG1 chr8:57124396-chr8:57083748	fusion CHCHD7 5'UTR (exon 1), PLAG1 5'UTR (exon 3)	NM_001011671.3, NM_002655.3



B

Gene	Functional category	Transcript-ID
CHCHD7-PLAG1 chr8:57124396-chr8:57092072	fusion CHCHD7 5'UTR (exon 1), PLAG1 5'UTR (exon 2)	NM_001011671.3, NM_002655.3

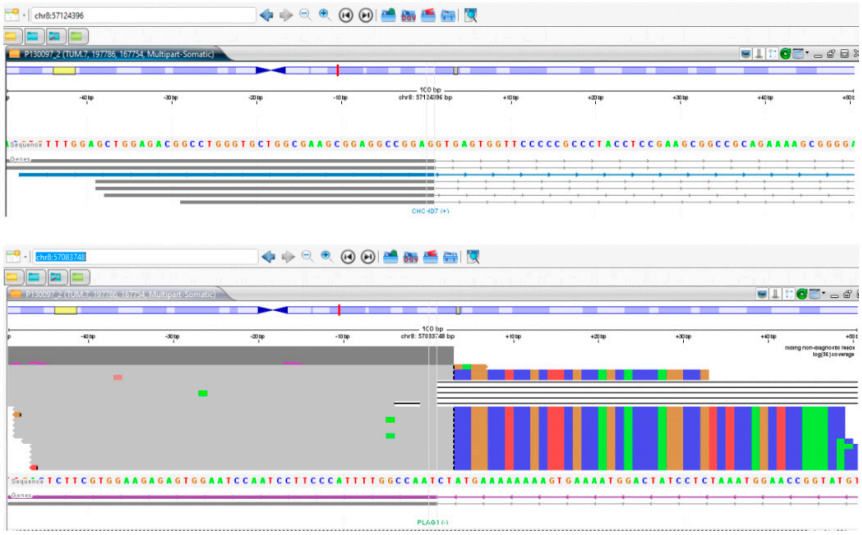


Figure 3. Focal somatic copy number alterations and structural alterations detected in the tumor sample. (A) CHCHD7-PLAG1, CHCHD7 (NM_001011671.3) exon 1 fused to PLAG1 (NM_002655.3) exon 3. (B) CHCHD7 (NM_001011671.3) exon 1 fused to PLAG1 (NM_002655.3) exon 2.

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Our sequencing data do not provide evidence for the presence of potentially relevant copy number alterations of large genomic segments. There is no evidence for the presence of homozygous deletions or strong amplifications of single therapeutically relevant genes.

3. Discussion

Pediatric lipoblastoma commonly presents as a painless subcutaneous soft tissue mass, however, the differential diagnosis is broad and includes sarcoma, vascular tumor, myofibroma, and other fibromatoses [15]. Clinical evidence indicates that differentiating between the soft tumor subtypes is crucially important, and can assist with the treatment plan influencing the disease prognosis and survival. This paper describes the diagnostic algorithm important to distinguish undifferentiated lipoblastoma from other lipomatous and myxoid lesions.

The diagnostic procedure to identify lipoblastomas includes clinical and histopathological features, immunophenotype, cytogenetic and molecular approaches. Although histomorphology and immunohistochemistry play an important diagnostic role for most mesenchymal neoplasms, due to the histomorphologic overlaps, molecular diagnostics with identification of *PLAG1*- rearrangement is essential for confirmation of lipoblastomas.

Here, we presented a case of a toddler with an undifferentiated myxoid neoplasm with features of a minimally differentiated lipoblastoma. Vast majority of lipoblastomas are characterized by cytogenetic rearrangement of the *PLAG1* gene, leading to *PLAG1* overexpression and tumorigenesis [16]. Using target RNA sequencing, we detected a fusion gene, *CHCHD7-PLAG1*, in the tumor tissue sample. Sequence analysis showed that the first exons of *CHCHD7* were fused to either exon 2 or exon 3 of *PLAG1*. *PLAG1* has a genomic fusion breakpoint in intron 1, resulting in alternative splicing of exon 2. The start codon of *PLAG1* is located in exon 4, and the coding sequences of *PLAG1* are preserved in the *CHCHD7-PLAG1* fusion gene. Based on the review of the available literature, we came to the conclusion that the frequency of this tumor is not that high in the population of children. The **Figure 4** represents the number of published case reports related to pediatric lipoblastoma in the period from 1990 to December 2025 (PubMed). It can be noted that the total number of published manuscripts is 159, which confirms the rarity of this tumor.

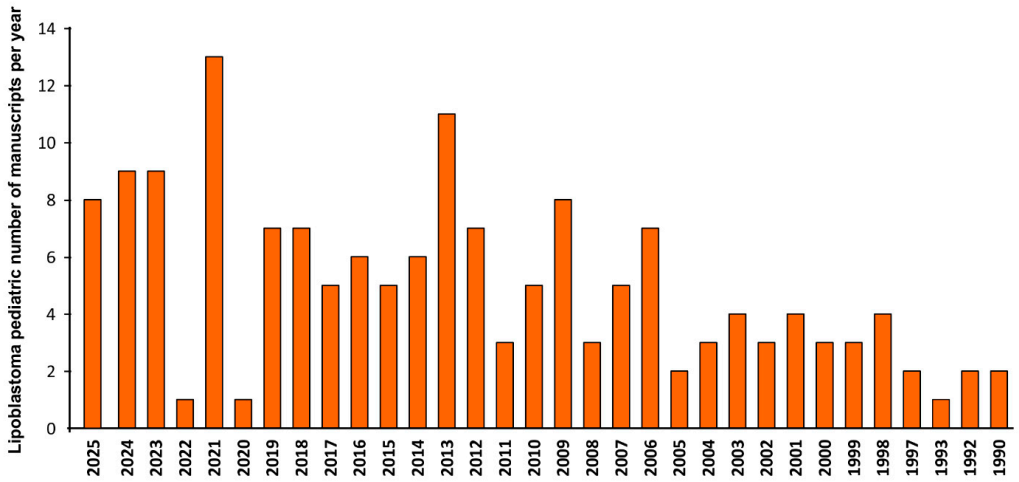

Figure 4. Lipoblastoma pediatric number of manuscripts by year.

Furthermore, we reviewed the literature investigating fusion genes in lipoblastoma. In the period from 1990 to 2025, only 2 cases were published on PubMed, which supports the relevance of this topic.

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When we added "tumor driver *CHCHD7-PLAG1* lipoblastoma" to the PubMed literature search, we found a total of one paper. Given that gene fusions or chromosomal rearrangements play an important role in tumorigenesis, this highlights the importance of our research.

4. Materials and Methods

4.1. Patient and Tumor Tissue Sample

Our patient was an 18-month-old female with no past medical, family or hereditary history relevant to the case, with a painless solid tumefaction (size of a grape) in the middle third of the right leg above the margo anterior tibiae.

Patient Consent. The parents gave written consent for the publication of this case report. At our institution, the publication of case reports is exempt from requiring approval by our Institutional Review Board.

4.2. Histopathological and Immunohistochemical Analyses

For histopathological analysis, the samples were fixed in 10% phosphate-buffered formalin, sectioned at 5 μm and stained with hematoxylin and eosin (H&E) stain (Sigma–Aldrich, USA) for light microscopic examination. Immunohistochemistry was performed on deparaffinized, rehydrated sections obtained from a representative formalin- fixed, paraffin-embedded block using antibody-specific epitope retrieval techniques with the Dako Envision (Dako, Carpinteria, CA, USA) automated system for detection of the following primary antigens: vimentin, desmin, CD34, Myogenin, MyoD1, Rb, LCA, SOX10, alpha SMA, caldesmin, CD56, NSE, S100, and Ki67 according to the manufacturers' instructions and standard protocols.

4.3. Fluorescence In Situ Hybridization

Interphase fluorescence in situ hybridization (FISH) for FOXO1 rearrangement was performed on FFPE tumor tissues using a locus specific dual-color break-apart FOXO1 (13q14.11) probe set according to the manufacturers' instructions and standard protocols.

4.4. Next-Generation Sequencing and RNA-Sequencing

Tumor panel TUM01 was used in somatic molecular genetic analysis of a tumor tissue sample in order to evaluate somatic variants of potential clinical relevance. RNA fusions panel analysis (STR) was employed to identify gene fusions. The isolation of DNA and RNA from tumor in FFPE as well as normal DNA from normal tissue (EDTA blood) was performed. The tumor material was assessed by a pathology specialist. *NGS-laboratory DNA:* Protein-coding regions, as well as flanking intronic regions and additional disease-relevant non-coding regions, were enriched using in-solution hybridization technology, and were sequenced using the Illumina NovaSeq 6000/NovaSeq X Plus system. *NGS-laboratory RNA:* RNA from tumor tissue was sequenced. Fusion transcripts were enriched using in-solution hybridization technology. For fusion transcripts with known breakpoints, breakpoint spanning probes were used. For genes with unknown breakpoints or a large number of possible fusion partners, the coding sequence was used for enrichment. Sequencing was performed on Illumina NovaSeq 6000/NovaSeq X Plus systems, while Illumina bcl2fastq2 was used to demultiplex sequencing reads.

5. Conclusion

Recognition of this rare tumour is important because lipoblastomas are easily misdiagnosed and excision before proper investigation may result in incomplete resection and recurrence. Careful integration of clinical presentation, histopathological, immunohistochemical analysis, and cytogenetic/molecular changes facilitates the diagnosis of this rare, potentially under-recognized entity in infants. Targeted RNA-sequencing technology to demonstrate fusion transcripts affecting *PLAG1* must be employed as a diagnostic tool for accurate diagnosis of lipoblastoma.

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Institutional Review Board Statement: At our institution, the publication of case reports is exempt from requiring approval by our Institutional Review Board.

Informed Consent Statement: The parents gave written consent for the publication of this case report.

Conflicts of Interest: The authors declare that there is no conflict of interest.

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