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PLAG1-Driven Lipoblastomatosis: Diagnostic Insights from a Case Report and Literature Review

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ABSTRACT

Lipoblastomatosis is a rare benign adipocytic tumour of infancy and early childhood, characterized by rapid growth. Diagnosis is challenging, owing to tumour heterogeneity and overlap with other pediatric soft-tissue neoplasms. PLAG1 rearrangement is the defining molecular hallmark, with an expanding list of fusion partners.

We report a case of a 1-year-old child with a firm, nonmobile mass in the right thigh, which on CECT was deep-seated and heterogeneously enhanced. Gross evaluation of the excision specimen demonstrated an ill-circumscribed soft tissue mass. Histopathologically, the tumour showed myxoid nodules with primitive mesenchymal spindle-cell areas, and peripheral adipose tissue containing scattered lipoblasts, features suggestive of lipoblastomatosis. The IHC study showed S100 and CD34 positivity in adipocytes, and desmin and myogenin positivity in spindle-cell components. Molecular testing by NGS revealed a COL1A2::PLAG1 gene fusion, thus further establishing the diagnosis. Differentials such as myxoid liposarcoma, fibrous hamartoma of infancy, and infantile fibrosarcoma also harbour distinct genetic drivers, including EWSR1::DDIT3, EGFR exon 20 alterations, and ETV6::NTRK3, respectively.

This case highlights the diagnostic workup of soft-tissue tumours and underscores the importance of integrating histopathology, IHC, and molecular testing. Identification of PLAG1 rearrangement is crucial for confirming the diagnosis. With the growing number of molecularly defined soft-tissue tumours of diagnostic and prognostic significance, incorporating molecular analysis is essential in the evaluation of soft-tissue lesions.

Keywords: Soft tissue tumour, Paediatric soft tissue tumour, Lipoblastoma, PLAG1 rearrangement, Molecular genetics

INTRODUCTION

Lipoblastomatosis is a rare benign mesenchymal tumour that arises from embryonal adipose tissue characterised by rapid growth of painless masses (1). It is typically seen in infants and early childhood, with 75 - 90% of cases occurring within the first three years of age. These tumours commonly present in the extremities, trunk, head and neck; however, they are also reported in unusual locations (2). Lipoblastoma and lipoblastomatosis represent distinct entities based on their anatomical location, plane of occurrence, and circumscription (3).

The characteristic histopathological features include a nodular, lobulated architecture with intersecting fibrovascular septa and a spectrum of fat-cell maturation, including primitive mesenchymal cells, lipoblasts, and mature adipocytes, within a myxoid background. Lipomas are benign adipocytic tumours and, although rare in the paediatric age group, should be considered an important differential diagnosis. They are well-circumscribed, encapsulated, and pale yellow, with a homogeneous appearance. Histologically, they are composed of lobules of mature adipose tissue with intervening thin fibrous septa.

A panel of immunohistochemical (IHC) markers, consisting of S100, CD34, and desmin, highlighting various components of the tumour, is essential for diagnosis. However, a definite diagnosis may be challenging at times, owing to tumour heterogeneity, particularly in core needle biopsies. In such scenarios, other paediatric mesenchymal tumours such as lipoma, fibrous hamartoma of infancy, primitive myxoid mesenchymal tumour of infancy, and infantile fibrosarcoma constitute key differentials. Despite the use of an appropriate IHC panel, there remains a risk of misdiagnosis due to clinical and histological overlap and the non-specific immunoprofile of these tumours (4).

PLAG1 (pleomorphic adenoma gene 1) rearrangements, resulting from diverse structural chromosomal alterations involving the 8q11 > q13 (8q12) region, represent the key genetic hallmark of lipoblastoma. With advances in next-

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generation sequencing (NGS), common fusion partners such as *CHCHD7* and *COL3A1* have been identified, while rare and novel fusion partners are increasingly being reported (1). Identification of these molecular genetic alterations is crucial in establishing the definitive diagnosis, particularly in challenging cases, to avoid misdiagnosis and guide treatment decisions.

We report a complex case of lipoblastomatosis in the thigh of a young child, demonstrating a characteristic *COL1A2::PLAG1* fusion identified by NGS-based RNA sequencing.

CASE REPORT

A 1-year-old female child was presented to the surgical oncology outpatient department with a history of gradually progressive swelling in the right thigh for 3 months. On examination, a firm, non-mobile mass measuring 7 x 6 cm was noted. There was a history of prior consultation and biopsy at an outside centre. Subsequently, contrast-enhanced computed tomography (CECT) (Figure 1) revealed a heterogeneously enhancing lesion measuring 5.7 x 4 cm, abutting and infiltrating the muscle and displacing the femoral vessels. FDG-PET showed no distant metastasis.

Pathology

The biopsy slides from the outside centre were reviewed, and showed a spindle cell neoplasm with morphology suggestive of fibroblastic/myofibroblastic differentiation, without obvious malignant features; IHC was inconclusive. Subsequently, tissue blocks were sent for an expert soft tissue pathology opinion, which also revealed similar immunomorphology without a definitive diagnosis. In view of the increasing tumour size, the child then underwent wide local excision of the lesion.

Gross evaluation showed an ill-circumscribed, nodular, irregular mass measuring 6.5 x 5.3 cm with adherent soft tissue. The cut surface was solid and nodular, with predominant pale white, firm fibrous areas separating the myxoid nodules and yellow areas in the periphery (Figure 2).

Microscopic evaluation revealed a heterogeneous tumour with lobulated architecture, myxoid nodules, areas of fibrous proliferation, and peripheral adipocytic components. The myxoid areas consisted of plexiform vascular networks and primitive stellate mesenchymal cells (Figure 3). There were wide areas of spindled cells in a fibrous stroma. The periphery of the tumour showed lobules and sheets of adipocytes, including occasional multivacuolated and small signet ring cell lipoblasts (Figure 4). These features represent a spectrum of adipocytic maturation. No areas of marked atypia, necrosis, or increased mitotic activity were noted. The tumour cells were focally seen abutting the inked/cauterised resection margin.

An additional IHC panel was performed in keeping with the earlier marker study. The adipocytic components were immunoreactive for S100 and CD34, whereas the spindle cells showed immunopositivity for desmin and myogenin (focal) (Figure 5). CD34 also highlighted the blood vessels. These tumour cells were negative for ALK, PanTRK, beta-catenin, and MDM2.

With the characteristic histomorphological spectrum of adipocytes at various stages of maturation and corresponding immunoprofile, in conjunction with the clinical and ra-

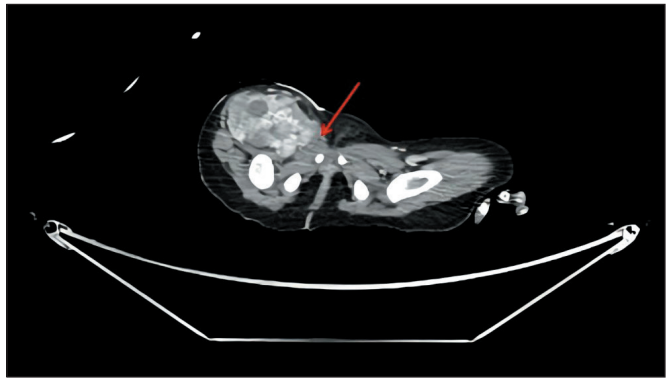


Figure 1: CECT: Heterogeneously enhancing deep seated lesion (5.7 x 4 cm) in right thigh. The lesion is seen abutting and displacing the femoral vessels anterior. (Red arrow show suspicious infiltrative areas)

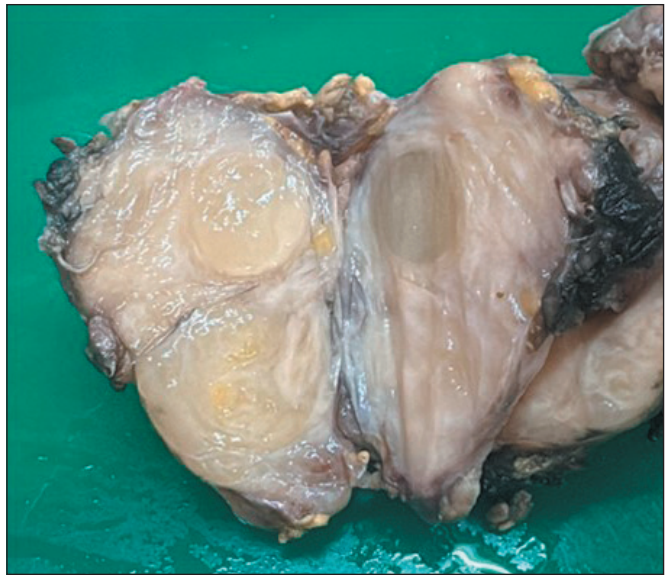


Figure 2: Gross: Ill-circumscribed mass with myxoid nodules, pale white - yellow areas in the periphery

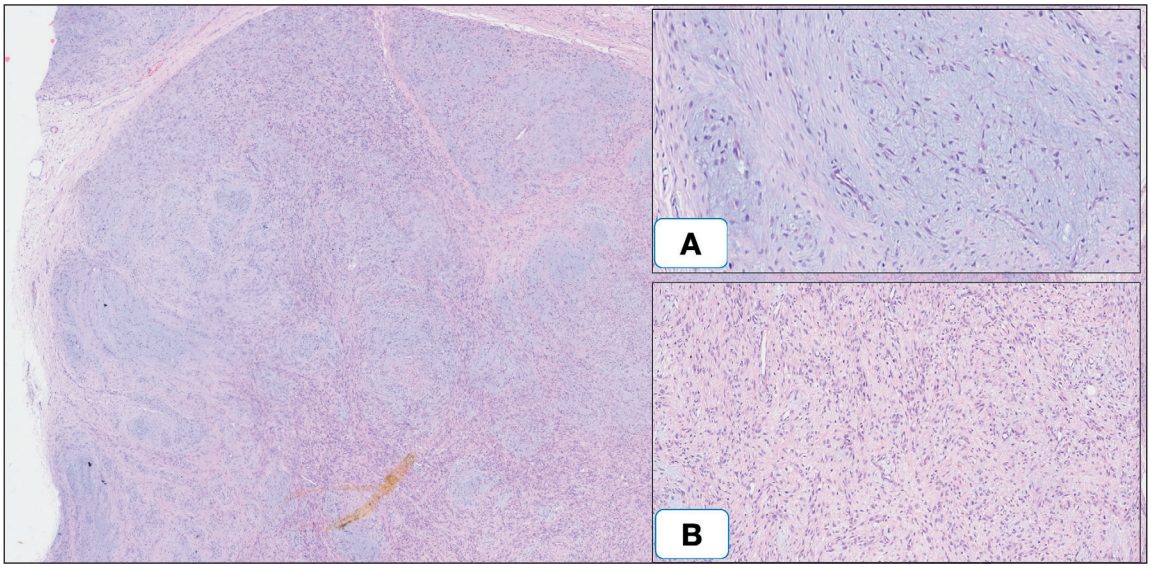


Figure 3: H&E (4X): Myxoid nodules in fibrous areas. **A(20X):** plexiform vascular network; primitive stellate - mesenchymal cells. **B(20X):** Spindled mesenchymal cells

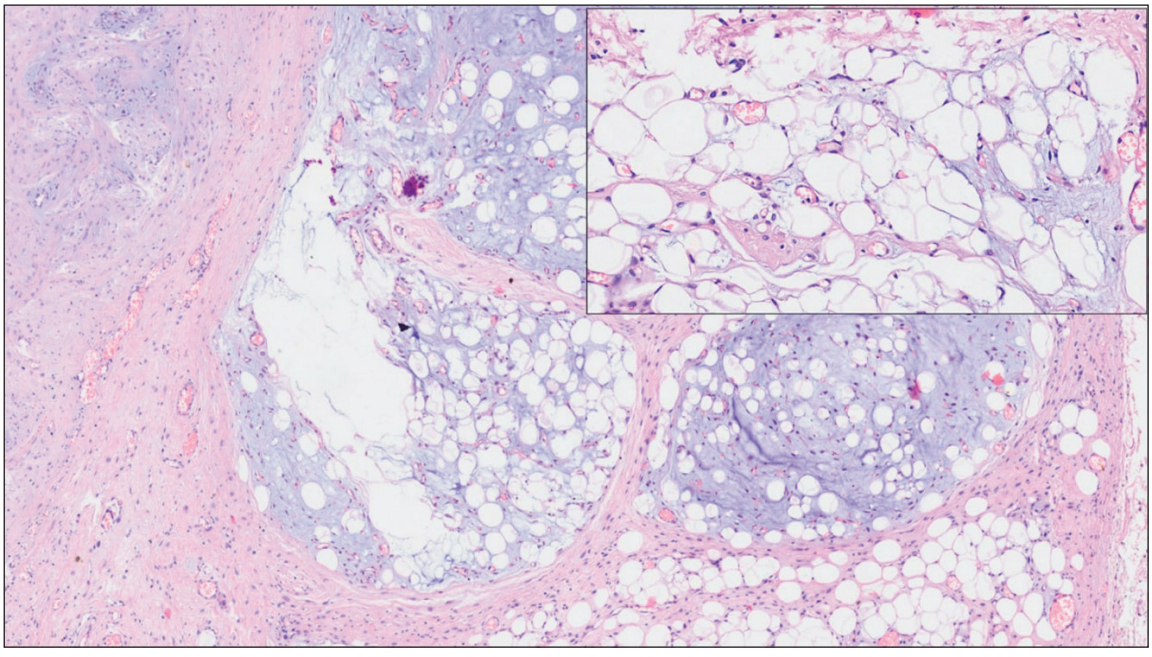


Figure 4: H&E (4X): Lobules & sheets of adipocytes, spectrum of adipocytic maturation with myxoid areas. Inset (40X) showing multivacuolated or small signet ring cell lipoblasts.

diological findings of an ill-defined, deep-seated tumour, a final diagnosis of lipoblastomatosis was rendered.

Subsequently, to establish the underlying molecular alteration, the tissue sample was sent for sequencing analysis.

Molecular Analysis

Molecular analysis was performed on the NGS platform (Illumina, Inc., San Diego, California) with a laboratory-developed multi-gene panel covering 108 key genes, including SNVs, indels, and gene fusions. Nucleic acid was extracted from the FFPE tissue block (tumour cellularity ~65%), followed by library preparation using a custom hybrid capture kit. The QC-passed libraries were sequenced to a minimum depth of 250x on the sequencing platform. The variants were annotated using an in-house pipeline, and genomic alterations were prioritised, classified, and reported in accordance with AMP/ASCO/CAP guidelines.

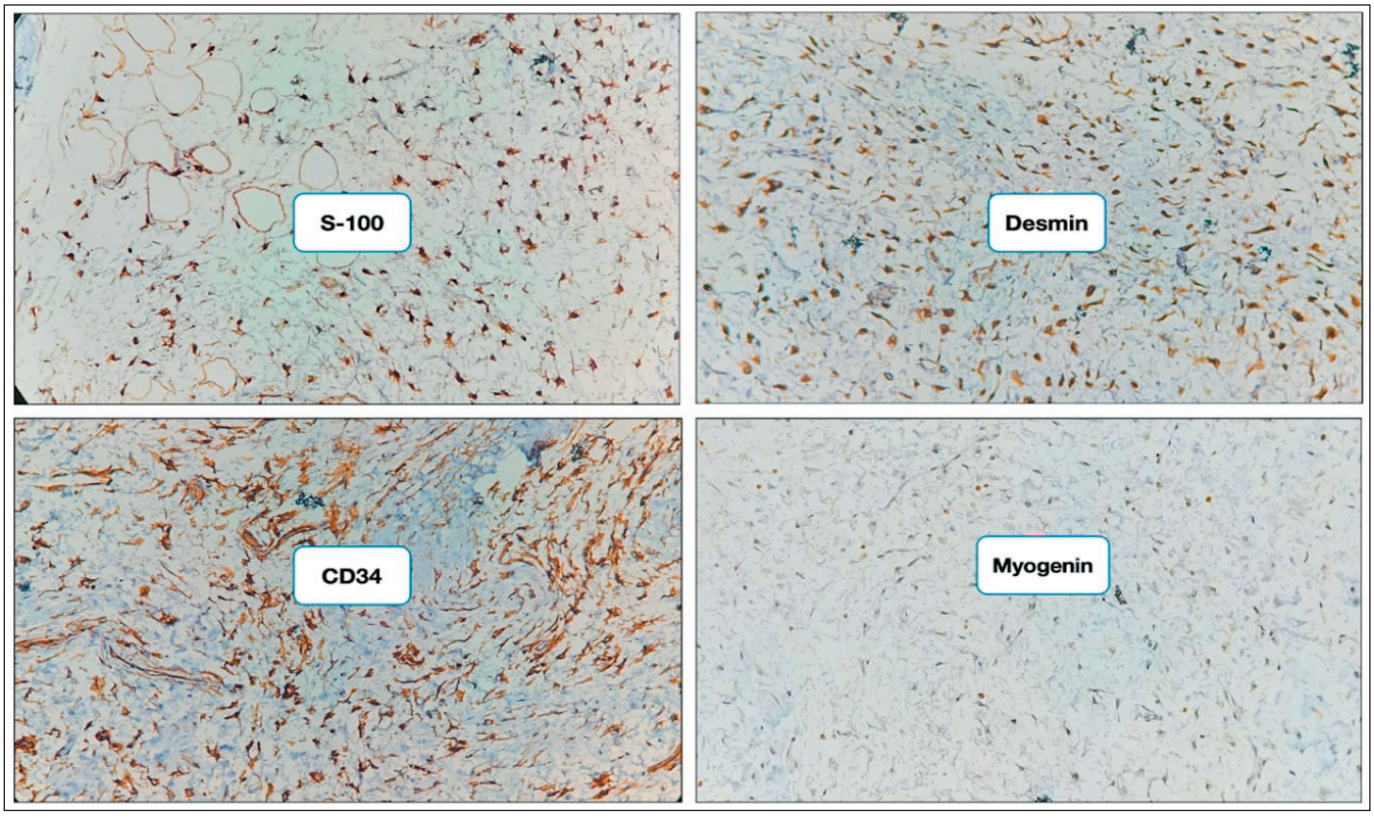


Figure 5: IHC (20X): S100 highlighting the adipocytic component; CD34 showing immunoreactivity for adipocytes and vascular channels; Desmin staining the primitive mesenchymal cells.

Sequencing analysis revealed a pathogenic variant of *COL1A2::PLAG1* fusion with a read depth of 28x. This represents a tier II pathogenic variant of diagnostic significance, with no specific therapeutic implications. No co-occurring mutations were detected. The child remains asymptomatic with no evidence of loco-regional recurrence at 12-month follow-up.

DISCUSSION

Rapid advances in molecular genetics have refined the classification of soft tissue tumours, leading to the identification of a variety of molecular alterations, thereby enabling the emergence of well-defined and certain entities (5). Immunohistochemistry, although it is a widely used diagnostic tool, provides limited insights into the underlying genetic alterations. The diagnosis of soft tissue tumours remains challenging, owing to rarity, numerous subtypes, and significant histological overlap, particularly in needle biopsies (6). This necessitates the need for integrating diagnostic tools like molecular genetics and IHC with that of conventional histopathology for a definite diagnosis. Paediatric soft tissue tumours are particularly complex, encompassing lesions ranging from malformations and benign tumours to intermediate tumours and aggressive malignancies (7). This highlights the need for a thoughtful approach to soft tissue lesions for accurate categorisation.

Lipoblastoma is a rare benign soft-tissue tumour of infancy and early childhood. Zhang et al., in their review of 36 cases, report that 78% of cases occurred within 3 years of age, similar to our case, in which the child presented at 1 year of age. Lipoblastomatosis, in contrast, is multicentric, more aggressive, and locally infiltrative with poorly defined borders (8). These tumours are typically painless and commonly occur in the trunk and extremities; however, unusual sites such as the chest wall, mediastinum, retroperitoneum, and mesentery have been reported (9). They are usually less than 5 cm in size, but larger lesions up to 25 cm have been reported in the literature (10). In our case, the lesion measured 5.7 cm and was located in the thigh in a deep soft tissue plane abutting the vessels, making the surgical planes difficult.

Histomorphologically, these tumours exhibit lobulated myxoid nodules with intervening fibrovascular areas and a spectrum of adipocyte cell maturation, ranging from primitive stellate or spindled mesenchymal cells to multivacu-

olated, small signet-ring cell lipoblasts. The resection specimens show typical zonation, with immature myxoid cells at the periphery and mature adipocytes at the centre. Other variations such as chondroid metaplasia, extramedullary haematopoiesis and multinucleated/floret cells are rarely noted (11). The diagnosis may be relatively straightforward in an appropriate clinical context. However, a definitive diagnosis by needle biopsy is challenging owing to the tumour's heterogeneous architectural and cellular patterns.

The differential diagnoses when myxoid-predominant areas are encountered include paediatric myxoid liposarcoma and lipoma. Paediatric myxoid liposarcoma is rare in this age group, whereas most of the lipoblastomas are seen in children less than 3 years of age (2). Lipoma, although rare in children, lacks lipoblasts or primitive mesenchymal cells. The list of possible differentials is broad when a spindle cell (primitive mesenchyme)-predominant area is encountered, including infantile fibrosarcoma, fibrous hamartoma of infancy, inflammatory myofibroblastic tumours (usually seen in the abdomen or chest), and, rarely, primitive myxoid mesenchymal tumour of infancy and ectomesenchymoma.

Although histologically similar, lipoblastoma differs from lipoblastomatosis in its growth pattern. Lipoblastoma is a well-circumscribed, encapsulated tumour, whereas lipoblastomatosis is diffuse, non-encapsulated, and infiltrating, with a higher risk of local recurrence.

Immunohistochemistry plays a pivotal role in narrowing the differential diagnosis; hence, judicious selection of an appropriate panel and careful interpretation of results are crucial. The typical IHC findings in lipoblastoma are as described in our case. We did not have access to PLAG1 by IHC, which is positive in ~80% of cases and shows intense diffuse nuclear staining in adipocytes and spindle cells (12). PLAG1 expression is a reliable surrogate for *PLAG1* rearrangements, and Warren et al. reported a sensitivity of 94% for PLAG1 IHC as compared to FISH / molecular techniques in lipoblastomas (12).

Molecular genetics is crucial for the diagnosis and classification of soft tissue tumours by identifying specific molecular genetic alterations (13). Thus, it facilitates the distinction between types of soft tissue tumours and makes a definite diagnosis possible when histological overlap exists.

The *PLAG1* gene, located on chr8, encodes a zinc finger protein with 2 putative nuclear localization signals, which functions as a transcription factor and regulates cell growth and proliferation. *PLAG1* alterations are associated with various cancers and can impact gene expression, including the growth-promoting gene *IGF2* (14). *PLAG1* rearrangements involving the chromosomal region 8q12 represent the defining genetic hallmark of lipoblastoma. These rearrangements typically arise from diverse structural chromosomal events, such as minor inversions, insertions or circular chromosomes that lead to promoter swapping and subsequent *PLAG1* over-expression.

In lipoblastoma, the most frequently reported *PLAG1* fusion partners are *CHCHD7::PLAG1* and *COL3A1::PLAG1*, both of which drive aberrant *PLAG1* transcription. Currently, with the increasing use of NGS, a spectrum of fusion partners has been documented, including *HAS2, RAD51B, TCEA1, RAB2A, CTDSP2,* and *ACTA2*. In our case, we detected a *COL1A2::PLAG1* fusion, accounting for 25% of all *PLAG1* fusions in lipoblastoma and representing a tier II pathogenic variant.

Beyond lipoblastoma, *PLAG1* rearrangements are implicated in a wide variety of tumours, including pleomorphic adenoma, uterine tumours resembling ovarian sex cord tumours (UTROSCT), and myofibroblastoma of the breast, and are rarely implicated in hepatoblastoma. This underscores the broad relevance and necessitates its documentation (15).

Among paediatric soft-tissue tumours, *PLAG1* alterations serve as a valuable diagnostic marker, especially when there is significant immunohistochemical overlap. The key differentials, such as myxoid liposarcoma, fibrous hamartoma of infancy, and infantile fibrosarcoma, also harbour distinct genetic drivers, including *EWSR1::DDIT3*, *EGFR* exon20 alterations, and *ETV6::NTRK3*, respectively. Thus, identification of specific genetic alterations reinforces the diagnosis and helps avoid overtreatment, particularly in paediatric patients (16).

Although FISH is a reliable tool for detecting gene rearrangements, NGS offers broader advantages, such as characterization of fusion partners, identification of cryptic rearrangements, and detection of rare or novel genetic alterations. With declining sequencing costs and increasing accessibility, NGS is poised to become the preferred diagnostic tool, enriching our understanding of tumour biology and refining diagnostic accuracy in soft-tissue pathology.

CONCLUSION

Lipoblastoma/lipoblastomatosis is a benign paediatric soft-tissue tumour with significant tumour heterogeneity and histological overlap. Our case emphasises the importance of a multidisciplinary diagnostic approach incorporating morphology, immunohistochemistry, and molecular ge-

netics. The identification of the *COL1A2::PLAG1* fusion confirmed the diagnosis and enabled appropriate treatment selection. With the expanding spectrum of molecularly defined soft-tissue tumours and their established diagnostic and prognostic significance, molecular analysis has become essential for evaluating soft-tissue lesions. With sequencing platforms becoming more accessible, comprehensive genomics profiling is poised to play a central role in identifying actionable alterations thus exploring novel targeted therapeutic options.

Conflict of Interest
The authors declared that they have no conflict of interest.

Authorship Contributions
Concept: **MK,** Design: **MK,** Data collection and/or processing: **LAP,** Analysis and/or interpretation: **MM, RS,** Literature search: **MK, LAP,** Writing: **MK,** Approval: **MM.**

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