KMT2A amplification: rare cytogenetic abnormality in a case of pediatric acute lymphoblastic leukemia

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ABSTRACT

Background: Rearrangements or translocations involving the *KMT2A* gene (lysine methyltransferase 2A gene) are well-recognized genetic abnormalities in acute lymphoblastic leukemia (ALL) across both adult and pediatric populations, and their presence is typically associated with adverse prognosis and high-risk disease. In contrast, *KMT2A* gene amplification is an exceedingly rare abnormality in ALL, with only a few reported cases to date, predominantly in adults. Owing to its extreme rarity, the prognostic significance of *KMT2A* amplification in pediatric ALL remains unclear, although available reports in adult cases suggest an association with poor outcome.

Case Presentation: This is a case of *KMT2A* amplification in a 4-year-old child diagnosed with B-cell ALL who presented with standard-risk disease features and achieved complete remission following induction chemotherapy, maintaining remission at 12 months post-diagnosis. Interestingly, limited data from previously reported pediatric cases also suggest that *KMT2A* amplification may not adversely influence clinical outcomes in this age group. To the best of our knowledge, this represents the first reported case of pediatric ALL with KMT2A amplification from India.

Conclusion: This case highlights a rare cytogenetic abnormality - *KMT2A* amplification - in pediatric ALL. Although this abnormality has been associated with poor prognosis in adult ALL, our observation suggests that it may not necessarily confer an adverse outcome in pediatric patients. Further studies and accumulation of additional pediatric cases are required to better understand the clinical and prognostic implications of this rare genetic abnormality.

Keywords: Pediatric ALL, *KMT2A* amplification, rare gene amplification, ALL cytogenetics, acute leukemia, case report.

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Background

Molecular investigations have dramatically advanced risk stratification in pediatric acute lymphoblastic leukemia (ALL) by facilitating more precise disease subclassification and identification of genetic alterations with prognostic significance. Genomic profiling techniques, such as next-generation sequencing (NGS), have revealed a diverse array of molecular subtypes within pediatric ALL, which have prognostic implications and guide the clinical management and treatment [1]. Novel genetic subtypes have recently been identified in approximately 30% of B-ALL cases while lacking established chromosomal abnormalities, yet their prognostic significance is still largely uncertain [2]. One such gene that is gaining recent attention is the *KMT2A* (lysine methyltransferase 2A gene) gene (previously known as MLL (mixed lineage leukemia gene). *KMT2A* encodes the histone lysine-specific N-methyltransferase 2A, located on chromosome 11q23. This gene is a frequent target for recurrent chromosomal translocations associated with acute myeloid leukemia (AML), ALL, and mixed phenotype (biphenotypic) leukemia [3]. However, *KMT2A* amplification is rare and occurs in only 1% of AML and even less frequently in ALL in the adult as well as pediatric population [4]. On review of the available literature on *KMT2A* amplification in ALL and AML, it was considered a high-risk genetic abnormality with dismal clinical outcome in adults. However, due to paucity of the literature available on *KMT2A* amplification, its natural course, prognostic and therapeutic implications in pediatric ALL are yet to be established. To the best of our knowledge, we report the first documented case of pediatric ALL with *KMT2A* amplification in India.

Case Presentation

A 4-year-old male presented to the emergency department in October 2024 with a history of fever and pancytopenia (HB-5.2 gm/dl, WBC-368/cumm, Platelets-11800/cumm, blast-20% in peripheral blood smear). Clinically, he was pale, lethargic, and had high grade fever with palpable cervical lymphadenopathy without organomegaly. Bone marrow examination revealed 70% blasts, which were positive for CD19, CD10, dim CD20, CD38, dim CD34, and cytoplasmic CD79a on multi-colored flow cytometry. Based on these findings, a diagnosis of Precursor-B ALL (standard risk) was established. On evaluation, the sanctuary sites (testes and CNS-CNS1) were uninvolved. Initial fluorescent in situ hybridization (FISH) analysis (with LSI dual color break apart probe - MetaSystems) for common high-risk ALL mutations (*BCR::ABL1* fusion, *ETV6::RUNX1* fusion, *KMT2A* rearrangement, and *TCF3::PBX1* fusion) and cytogenetic evaluation were inconclusive due to technical reasons or sample inadequacy. He was started on the BFM 2002 protocol induction phase (06/11/2024) along with other supportive care and antibiotics for *Pseudomonas* blood infection. He clinically improved and recovered well from the infection. His day 8 steroid response was good. Bone marrow aspiration was repeated on Day 15 of induction therapy, which showed 5% blast in the bone marrow study, though the results of the repeat ALL FISH panel this time revealed 25% of cells with extra fusion signals of the *KMT2A* gene, suggesting multiple copies of the *KMT2A* gene, hence amplification (details of reports mentioned in Figure 1).

End of induction phase A (day 33) disease assessment showed bone marrow in morphologic remission (2% blasts), and minimal residual disease (MRD) by flow cytometry was negative (<0.01). In view of the documented *KMT2A* amplification, serial fluorescence in situ hybridization (FISH) studies were repeated following each phase of chemotherapy, along with disease re-evaluation. Patient received induction phase-B from 24/12/2024 to 25/01/2025. Post-induction phase B, bone marrow evaluation indicated continued morphological remission with 1% to 2% blasts on light microscopy. MRD by flow cytometry was negative, and the repeat FISH showed no evidence of *KMT2A* amplification. The patient was initiated on the consolidation chemotherapy. During the third week of consolidation therapy, the patient developed left-sided unilateral painless tonsillar hypertrophy. This was evaluated with an excisional biopsy (tonsillectomy), along with bone marrow aspiration and biopsy, and a diagnostic lumbar puncture to rule out disease relapse. Histopathological examination of the excised tonsil and immunohistochemistry (IHC) findings were suggestive of reactive changes with chronic inflammation. Bone marrow and cerebrospinal fluid studies showed no evidence of disease relapse. The consolidation protocol was subsequently continued for a total duration of 8 weeks, followed by the re-induction phase of chemotherapy. The patient tolerated the subsequent phases of chemotherapy well and is currently undergoing the maintenance phase of treatment.

Discussion

The *KMT2A* gene is present on chromosome 11q23 and encodes a protein that is a histone methyltransferase, which assembles in protein complexes that regulate gene transcription via chromatin remodeling [5]. Upregulated expression of *KMT2A* is considered the main driving event in myeloid neoplasms, also rarely in B-ALL and B-cell lymphomas.

Abnormalities of *KMT2A* occur in the form of

(1) Rearrangements involving multiple partner genes, which is extensively researched and well documented in the literature, with both their prevalence and clinical impact extensively characterized. Translocations of the *KMT2A* gene are observed in approximately 80% of infant ALL cases, 5% of AML cases, and up to 85% of secondary AML cases arising in patients previously treated with topoisomerase II inhibitors worldwide [5]. Despite intensive chemotherapy, these patients consistently demonstrate poor clinical outcomes.

(2) Amplifications either as extrachromosomal double minutes or intrachromosomal partial tandem duplications. Owing to the rarity of this abnormality, only a limited number of case reports and small series have been published in the literature. Consequently, the exact prevalence and

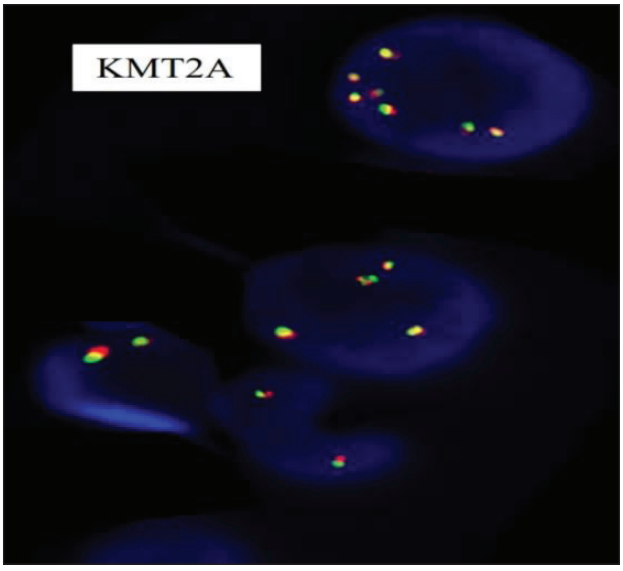

Figure 1. *Fish Analysis by LSI MLL dual colour break apart probe - Metasystem (200 interphase counted)- multiple copies of KMT2A gene (fused yellow signals) in each cell.*
nuc ish (KMT2A x 2) - 150 (75%)
nuc ish (KMT2A x 3) - 06 (03%)
nuc ish (KMT2A x 4) - 28 (04%)
nuc ish (KMT2A x 5) - 06 (03%)
nuc ish (KMT2A x 7) - 10 (05%)

prognostic significance of *KMT2A* amplification remain uncertain [6]. Through an extensive review of the literature, we identified several case reports describing *KMT2A* amplification in de novo adult cases of ALL and AML. Most of these reports describe an aggressive disease course with poor outcomes, including refractory disease, early relapse, and early mortality following diagnosis [7-11]. An 86-year-old woman reported by Espinet et al. with intrachromosomal amplification of the *KMT2A* gene died shortly after diagnosis [9]. Similarly, a *de novo* adult ALL case with *KMT2A* amplification described by Catherine Wren et al. demonstrated an aggressive clinical presentation with death occurring shortly after diagnosis [12]. The UKCCG study [7] reported a case series of KMT2A gene amplification comprising 12 cases (11 adult AML and 1 pediatric ALL), in which all adult AML cases were associated with poor clinical outcomes.

In contrast, the available pediatric literature is extremely limited. To the best of our knowledge, only three case reports describing this genetic abnormality in pediatric ALL have been published, and interestingly, these cases have documented comparatively more favorable outcomes than those reported in adults [6,7,12].

Here, we report a case of a 4-year-old boy diagnosed with Pre-B ALL harboring *KMT2A* gene amplification, identified during the induction phase of chemotherapy. At diagnosis, he did not exhibit any high-risk clinical features, such as elevated white blood cell count, extramedullary disease, or poor prednisolone response. He was initiated on treatment according to the BFM 2002 protocol and tolerated the intensive phases of chemotherapy well. Disease re-evaluation following each phase of intensive therapy confirmed complete remission with negative MRD. The patient is currently in the maintenance phase of treatment, 12 months post-diagnosis. Contrary to expectations, this patient exhibited a clinical course consistent with standard-risk Pre-B ALL, despite the presence of *KMT2A* amplification as a cytogenetic abnormality. Interestingly, three previously reported pediatric B-ALL cases in the literature demonstrated similar findings (refer to Table 1 for details), showing no apparent impact of KMT2A amplification on disease behavior or treatment outcome. This case further contributes to the limited literature on KMT2A amplification in pediatric ALL and suggests that its clinical significance in this age group may differ from that reported in adults, highlighting the need for larger studies to better understand its prognostic implications.

Conclusion

To conclude, *KMT2A* amplification represents an extremely rare genetic abnormality in ALL, particularly in pediatric cases, and its true incidence has not yet been

Table 1. *Summary of de novo pediatric ALL with KMT2A amplification: literature review.*

YEAR OF PUBLICATION	AGE OF PATIENT (YEARS)	SEX	DIAGNOSIS BY FLOW CYTOMETRY	FISH	CYTOGENETICS	TREATMENT	REMISSION POST-INDUCTION	OUTCOME	REFERENCE
2025	4	M	B-ALL (CD10 positive)	Multiple copies of the *KMT2A* gene in a defined region	NA	ALL-IC-BFM-2002	Achieved	In remission post 14 months of diagnosis in the maintenance phase	This case
2012	12	M	B-LBL	Gain of intact *MLL* locus on 11q, with a total of 3 copies of the *MLL* gene	Segmental inverted duplication of the 11q region	COG A5971	Achieved	In remission post 9 months of diagnosis in the maintenance phase	[12]
2012	4	F	T-ALL	4-6 copies of the *MLL* gene	Intrachromosomal Amplification	ALL-IC-BFM	Achieved	In remission post 25 months of diagnosis	[6]
2000	7	M	B-ALL (CD10 positive)	Multiple copies of *MLL* in a very defined region	NA	NA	NA	In remission post 21 months of diagnosis	[7]

M: male, F: Female, B-ALL: B-cell Acute Lymphoblastic Leukemia, T-ALL: T-cell Acute Lymphoblastic Leukemia, B-LBL: B-type Lymphoblastic Lymphoma, IC-BFM: Intercontinental Berlin-Frankfurt-Münster Study Group, COG: Children's Oncology Group, *MLL*: Mixed Lineage Leukemia, NA: Not Applicable, KMT2A: Lysine Methyltransferase 2A.

well documented in the literature. Based on our review, it seems that *KMT2A* amplification does not appear to have a significant clinical impact on treatment outcome in pediatric ALL. In contrast, it has been reported as an adverse prognostic factor in adult acute leukemias, denoting early relapse or refractory disease. However, due to the rarity of this alteration, longer follow-up periods and larger studies are warranted to better elucidate the prognostic significance and potential role of *KMT2A* amplification in risk stratification of pediatric ALL.

What's new?

We report a rare case of KMT2A amplification in a 4-year-old child with B-cell ALL who presented with standard-risk features and achieved complete remission after induction chemotherapy, remaining disease-free at 12 months. Unlike adult cases where KMT2A amplification is linked to poor prognosis, this pediatric case demonstrated a favorable clinical outcome. This case highlights the rare occurrence of KMT2A amplification in pediatric ALL and adds to the limited pediatric literature on this rare abnormality. It also Suggests that KMT2A amplification may not always predict poor prognosis in children, unlike in adults.

List of Abbreviations

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
B-LBL	B-type Lymphoblastic Lymphoma
KMT2A	lysine methyl transferase 2A
MLL	Mixed Lineage Leukemia Gene
MRD	Minimal Residual Disease

Consent for publications

Written informed consent for publication of the clinical details and clinical images was obtained from the parents.

Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this case report.

Data availability

Data are available upon request.

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None.

Ethical approval

Ethical approval is not required at our institution for anonymous case reports.

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Summary of the case

1	Patient (Gender, Age)	4 years, Male
2	Final diagnosis	Pre B ALL (high risk in view of KMT2A amplification)
3	Symptoms	Fever, cervical lymphadenopathy
4	Medications	Chemotherapy as per BFM 2002
5	Clinical procedure	Bone marrow aspiration and biopsy, intrathecal chemotherapy, tonsillar biopsy
6	Specialty	Pediatric hematology