Section: Internal Medicine

Case Report

UNUSUAL IMMUNOPHENOTYPIC AND CYTOGENETIC FEATURES OF ACUTE MYELOID LEUKEMIA IN A 9-YEAR-OLD CHILD: A CASE REPORT

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Received *: 24/08/2025*
Received in revised form *: 07/10/2025*
Accepted *: 28/10/2025*

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DOI: 10.70034/ijmedph.2025.4.124

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (4); 690-694

ABSTRACT

Background: Acute myeloid leukemia (AML) in children is an uncommon hematologic malignancy characterized by the proliferation of immature myeloid precursors in the bone marrow. Pediatric AML differs from its adult counterpart in genetic profile, biology, and clinical outcomes. Unusual immunophenotypic and cytogenetic patterns may complicate diagnosis and prognostication. This case report highlights a rare presentation of AML in a 9-year-old child exhibiting aberrant immunophenotypic features and an uncommon cytogenetic translocation, emphasizing the importance of integrated diagnostic evaluation and MRD-guided management.

Case Presentation: A 9-year-old boy presented with swollen and bleeding gums, fever, and bilateral cervical lymphadenopathy. Physical examination revealed gingival hypertrophy and firm cervical lymph nodes without hepatosplenomegaly. Laboratory findings showed anemia (Hb 10.1 g/dL), leukocytosis (23,720 cells/µL), and thrombocytopenia (3.5 × 10^3/µL). Peripheral smear indicated increased neutrophils, lymphocytes, and monocytes. Bone marrow aspiration revealed hypercellularity with 75.7% myeloblasts. Flow cytometric immunophenotyping demonstrated dim CD45, bright CD33, CD117, HLA-DR positivity, and aberrant CD4 expression, confirming myeloid lineage. Cytogenetic analysis revealed a t(9;11)(p21;q23) translocation involving the KMT2A (MLL) gene in 8 of 20 metaphases. The diagnosis of AML with KMT2A-MLLT3 rearrangement was established.

Management and Outcome: The patient was treated using a pediatric AML induction regimen comprising cytarabine, daunorubicin, and etoposide, followed by supportive care. Post-induction bone marrow evaluation demonstrated morphological remission with minimal residual disease (MRD) <0.1%. The child remained in complete hematologic and molecular remission at six-month follow-up. Conclusion: This case underscores the clinical and diagnostic importance of comprehensive immunophenotypic and cytogenetic evaluation in pediatric AML. The presence of aberrant CD4 expression and t(9;11) translocation, though atypical, did not preclude a favorable outcome. Early diagnosis, individualized therapy, and MRD-based monitoring were pivotal in achieving remission. Documentation of such rare variants contributes to refining diagnostic criteria and improving risk stratification in pediatric AML.

Keywords: Pediatric Acute Myeloid Leukemia, KMT2A (MLL) Rearrangement, Aberrant CD4 Expression.

INTRODUCTION

Acute myeloid leukemia (AML) represents a heterogeneous group of clonal hematopoietic stem-cell malignancies characterized by the proliferation and accumulation of immature myeloid precursor cells in the bone marrow and peripheral blood. It accounts for approximately 15-20% of all pediatric leukemias and is the second most common childhood leukemia after acute lymphoblastic leukemia (ALL). Although AML in children shares morphological similarities with adult forms, it differs substantially in its cytogenetic, molecular, and immunophenotypic profiles, therapeutic responses, and long-term outcomes. Pediatric AML often arises de novo, without prior myelodysplasia or exposure to cytotoxic agents, and is influenced by unique genetic aberrations that determine both prognosis and therapeutic strategy.[1]

The identification of specific immunophenotypic markers and chromosomal abnormalities has significantly refined AML classification under the current World Health Organization (WHO) framework. Immunophenotyping by flow cytometry enables distinction between AML subtypes, while cytogenetic analysis aids in identifying chromosomal translocations and gene rearrangements with diagnostic and prognostic implications. Common cytogenetic abnormalities in pediatric AML include t(8;21) (q22;q22), inv(16) (p13q22), and t(15;17) (q22;q21), each associated with distinct clinical behaviors. However, a subset of pediatric AML cases presents with rare or atypical cytogenetic and immunophenotypic features that may complicate diagnosis and prognostic assessment.[2]

Among the unusual cytogenetic findings, t(9;11)(p21;q23) involving the KMT2A (MLL) gene is particularly significant, as it confers intermediate to adverse prognosis depending on accompanying molecular lesions. The KMT2A rearrangement is observed more frequently in infants and young children, accounting for 15-20% of pediatric AML cases. Immunophenotypically, AML blasts with KMT2A rearrangements often show monoblastic or myelomonocytic differentiation with aberrant antigen expression such as CD4, CD56, or lymphoid markers. These aberrations underline the biological complexity of pediatric AML and necessitate comprehensive diagnostic evaluation for optimal therapeutic planning.[3]

Despite advances in multi-agent chemotherapy and hematopoietic stem-cell transplantation, pediatric AML remains challenging, with overall survival rates of approximately 60-70% in developed nations. Prognostic evaluation in children is multifactorial, incorporating cytogenetic and molecular findings, treatment response, and minimal residual disease (MRD) monitoring. MRD assessment by multiparametric flow cytometry or polymerase chain reaction (PCR) serves as a sensitive measure of subclinical disease burden and a strong predictor of relapse and survival. Attaining MRD negativity post-induction correlates with improved long-term remission.[4]

The rarity of atypical immunophenotypic patterns such as aberrant CD4 expression and dim CD45 intensity, coupled with uncommon cytogenetic rearrangements like t(9;11), poses diagnostic dilemmas. Such presentations blur the morphological boundaries between AML subtypes and occasionally mimic mixed phenotype acute leukemia (MPAL). Therefore, documentation and analysis of such rare variants are essential to broaden clinical understanding and to aid in establishing robust diagnostic and prognostic frameworks.[5]

The present case report describes a 9-year-old male child diagnosed with acute myeloid leukemia displaying unusual immunophenotypic and cytogenetic characteristics-namely, CD45 dim expression, aberrant CD4 positivity, and a t(9;11) translocation observed in eight of twenty metaphases. This case underscores the importance of an integrated diagnostic approach encompassing morphology, flow cytometry, cytogenetics, and MRD assessment to ensure accurate diagnosis, effective risk stratification, and favorable therapeutic outcomes in pediatric AML.

CASE DESCRIPTION

A 9-year-old boy presented to the pediatric outpatient department at Konasemma Institute of Medical Sciences, accompanied by his father, with complaints of swollen and bleeding gums for 12 days, intermittent fever for 10 days, and bilateral neck swelling for one week. There was no history of weight loss, night sweats, bone pain, or prior similar episodes. The patient had been treated by a local dentist with oral penicillin, paracetamol syrup, and benzydamine mouthwash without improvement.

Medical, Developmental, and Family History

The child was born at term after an uneventful antenatal and perinatal period. Growth and developmental milestones were appropriate for age. Immunizations were complete as per the National Immunization Schedule. There was no family history of hematologic disorders or consanguinity. The socioeconomic status, as per the modified Kuppuswamy classification, placed the family in the lower-middle class category.

Physical Examination

On examination, the child appeared pale but alert and cooperative. Anthropometric assessment revealed a height of 143 cm (75th-90th percentile), weight of 26 kg (10th-25th percentile), and a BMI of 12.7 kg/m², indicating undernutrition. The most striking features were gingival hypertrophy with bleeding gums and bilateral cervical lymphadenopathy. The lymph nodes were firm, mildly tender, non-fluctuant, and ranged from 1 × 0.5 cm to 4 × 3.5 cm. No hepatosplenomegaly was noted. Cardiovascular and respiratory system examinations were normal, with

no murmurs or adventitious sounds. Abdominal examination revealed a soft, non-tender abdomen with audible bowel sounds. Neurological examination was unremarkable, with no focal deficits.

Laboratory Investigations

Complete blood count (CBC) demonstrated hemoglobin 10.1 g/dL, total leukocyte count 23,720 cells/µL, and platelets 3.5 × 10^3/µL, consistent with thrombocytopenia and leukocytosis. Peripheral smear revealed normocytic, normochromic red cells with increased neutrophils, lymphocytes, and monocytes, suggestive of a reactive process. Fine-needle aspiration cytology (FNAC) of cervical lymph nodes revealed reactive lymphadenopathy.

Given persistent leukocytosis and gum hypertrophy, bone marrow aspiration and flow cytometric immunophenotyping were performed. Bone marrow smears were hypercellular with a predominance of myeloblasts exhibiting high nuclear-to-cytoplasmic ratio, fine chromatin, and conspicuous nucleoli. Flow cytometry demonstrated 75.7% blasts with dim CD45 expression. The blasts were bright for CD33, moderate to bright for HLA-DR and CD117, and expressed CD64, CD38, and dim CD13, CD99, and CD36 (subset). Cytoplasmic myeloperoxidase (MPO) positivity confirmed myeloid lineage. Aberrant CD4 expression was observed, a finding atypical for conventional myeloid blasts. Other lymphoid and progenitor markers were negative, effectively excluding mixed-phenotype acute leukemia (MPAL).

Cytogenetic analysis of 20 metaphases showed a translocation between chromosomes 9 and 11 (t(9;11)(p21;q23)) in 8 metaphases, while the remaining 12 displayed a normal karyotype. This rearrangement implicated KMT2A (MLL) gene involvement, consistent with an intermediate-risk subgroup. Abdominal ultrasonography revealed normal solid organs with no hepatosplenomegaly or lymphadenopathy elsewhere.

Diagnosis

Integrating morphological, immunophenotypic, and cytogenetic findings, a diagnosis of acute myeloid leukemia with t(9;11)(p21;q23); KMT2A rearrangement was established.

Treatment and Clinical Course

The patient was initiated on an intensive pediatric AML induction regimen (cytarabine, daunorubicin, and etoposide-ADE protocol) according to standard risk-adapted protocols. Supportive therapy included prophylactic antimicrobials, antifungal coverage, transfusion support, and rigorous infection control. During induction, transient febrile neutropenia and mucositis were managed conservatively.

Post-induction bone marrow examination showed morphological remission. Flow-cytometric minimal residual disease (MRD) assessment revealed MRD levels <0.1% of CD45-positive white blood cells, confirming MRD negativity. The patient subsequently proceeded to consolidation therapy and was maintained under close hematologic follow-up.

Outcome and Follow-Up

At six-month follow-up, the patient remained in complete hematologic and molecular remission. There was no recurrence of lymphadenopathy or mucosal bleeding, and growth parameters had improved modestly. The favorable therapeutic response despite the presence of atypical immunophenotypic and cytogenetic features underscores the importance of personalized pediatric AML management and early MRD monitoring to optimize prognosis.

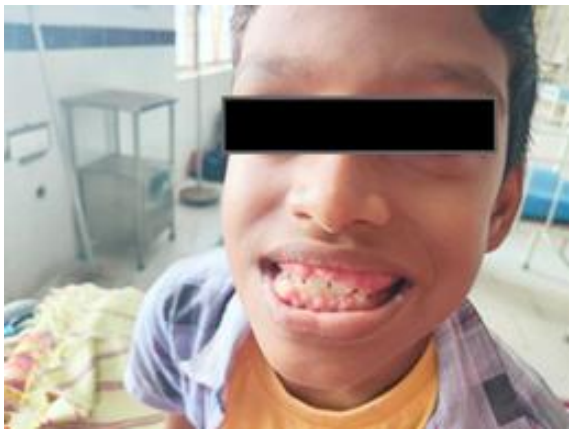

Figure 1: Gingival hypertrophy and bleeding at presentation.

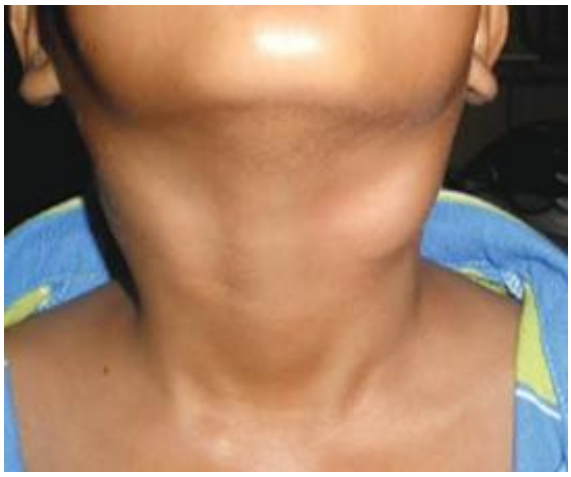

Figure 2: Bone marrow smear showing blasts with high N/C ratio and fine chromatin (Leishman stain, ×1000).

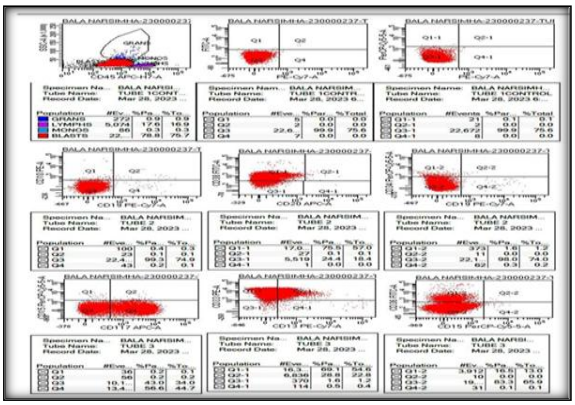

Figure 3: Flow cytometric dot plot showing dim CD45 and aberrant CD4 positivity in myeloblast population.

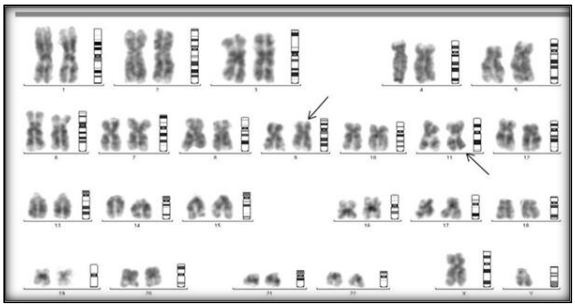

Figure 4: Karyogram depicting t(9;11)(p21;q23) translocation in 8/20 analyzed metaphases.

DISCUSSION

Acute myeloid leukemia (AML) in children represents a biologically heterogeneous and clinically challenging malignancy, constituting approximately 15-20% of pediatric leukemias. The present case of a 9-year-old child diagnosed with AML exhibiting atypical immunophenotypic and cytogenetic characteristics-namely CD45 dim expression, aberrant CD4 positivity, and t(9;11)(p21;q23) translocation-adds valuable insight to the existing literature on pediatric AML variants. The rarity and clinical implications of such features warrant detailed exploration, as they bear diagnostic, prognostic, and therapeutic significance.

1. Clinical and Morphological Correlation

The initial presentation with gingival hypertrophy, bleeding gums, fever, and cervical lymphadenopathy was consistent with the classical manifestations of acute monoblastic or myelomonocytic leukemia subtypes (FAB M4/M5). Gingival infiltration is particularly characteristic of monocytic AML due to the propensity of monoblasts to infiltrate extramedullary tissues such as gums and skin. The absence of hepatosplenomegaly in this case was notable, as organomegaly is commonly reported in t(9;11)-positive AML; however, the lack of such findings may reflect early disease detection or a less aggressive extramedullary phenotype. The cytopenias-specifically thrombocytopenia with leukocytosis-supported marrow infiltration by malignant myeloblasts, aligning with classical hematologic patterns of AML.

2. Diagnostic Challenges and Immunophenotypic Significance

Flow cytometry revealed 75.7% blasts with dim CD45 expression and bright CD33, CD117, and HLA-DR positivity, indicating myeloid lineage. The most striking finding was aberrant CD4 positivity, typically a T-cell-associated marker. Aberrant expression of lymphoid antigens in myeloid leukemias, although reported, remains uncommon and diagnostically challenging. Such cross-lineage antigen expression may mimic mixed phenotype acute leukemia (MPAL), necessitating careful interpretation alongside cytochemical myeloperoxidase (MPO) staining and cytogenetics.

CD4 expression in AML has been associated with monocytic differentiation and may signify lineage infidelity linked to KMT2A (MLL) rearrangements. A study by Chisholm KM et al. (2023)[6] demonstrated that CD4+ AML cases often harbor t(9;11) translocations and display monocytoid morphology, consistent with the current case. Moreover, the dim CD45 expression pattern observed in flow cytometry aligns with an immature blast phenotype and may correlate with aggressive disease biology. However, the subsequent minimal residual disease (MRD) negativity post-induction indicates effective therapeutic response despite these atypical markers.

3. Cytogenetic Findings and Molecular Insights

The identification of t(9;11)(p21;q23) translocation is of considerable clinical relevance. This translocation involves rearrangement of the KMT2A (MLL) gene at chromosome 11q23, producing fusion proteins that dysregulate hematopoietic transcription and block differentiation. KMT2A rearrangements occur in approximately 15-20% of pediatric AML cases and are frequently observed in infants, though less commonly in children older than 5 years. The presence of this rearrangement in a 9-year-old underscores its rarity and expands the age spectrum associated with this cytogenetic abnormality.

Clinically, KMT2A rearrangements confer intermediate to poor prognosis, depending on the fusion partner gene and co-existing molecular aberrations. The t(9;11)(p21;q23) translocation typically fuses KMT2A with MLLT3 (AF9), generating a chimeric transcriptional activator that enhances expression of HOXA cluster genes and MEIS1, driving leukemogenesis. According to Gajendra S et al (2023),[7] (2013), t(9;11)-positive AML demonstrates a distinctive immunophenotype with CD15+, CD64+, and CD4+ expression-features mirrored in the present case-highlighting the diagnostic consistency of this cytogenetic entity.

Interestingly, cytogenetic heterogeneity was observed in the form of mosaicism, with 8 of 20 metaphases showing the translocation and the remainder being normal. This partial clonality may reflect disease evolution, subclonal heterogeneity, or therapy-induced cytogenetic instability. The presence of both normal and abnormal karyotypes raises questions regarding clonal dominance and its prognostic implications, warranting long-term molecular monitoring.

4. Differential Diagnosis and Exclusion of Other Entities

The overlapping immunophenotypic features between AML with t(9;11) and mixed phenotype acute leukemia (MPAL) necessitated a rigorous differential diagnosis. The strong MPO positivity, along with absence of cytoplasmic or surface CD3, CD19, and CD79a, ruled out biphenotypic leukemia. Furthermore, lack of Auer rods or promyelocyte morphology excluded acute promyelocytic leukemia (APL). The diagnosis was consolidated by integrating flow cytometry and cytogenetic evidence, reinforcing the importance of multimodal diagnostic confirmation. Ohki K et al. (2020).[8]

5. Treatment Response and MRD Dynamics

The patient achieved MRD negativity (<0.1%) following induction chemotherapy under a pediatric AML protocol incorporating cytarabine, daunorubicin, and etoposide (ADE regimen). MRD monitoring has emerged as the cornerstone of post-therapy evaluation, offering superior sensitivity over morphological remission in predicting relapse. The attainment of MRD negativity in this case signifies an excellent therapeutic response and improved long-term prognosis, even in the context of intermediate-risk cytogenetics. Pessoa FM et al (2023),[9] emphasized that early MRD clearance strongly correlates with higher event-free survival in pediatric AML, supporting the positive outlook for this child.

6. Comparison with Existing Literature

Previous studies have reported that t(9;11) AML often presents with monocytic differentiation, extramedullary infiltration, and a variable prognosis. et al,[10] classified t(9;11) AML as an intermediate-risk cytogenetic group, yet outcomes vary depending on age and additional mutations. In contrast, the present case, despite harboring this translocation, demonstrated a favorable response, suggesting that early diagnosis, adherence to standardized chemotherapy, and MRD-based management may mitigate the traditionally adverse implications of KMT2A rearrangements. Rezaei MS et al. (2020).[11] Aberrant CD4 expression in AML has been reported sporadically in pediatric cohorts. Suratman RS et al,[12] (2023) described that CD4 expression in myeloid leukemias may reflect altered transcriptional regulation mediated by KMT2A fusions, potentially conferring altered homing behavior of leukemic blasts. While historically linked to poorer prognosis, recent treatment protocols and MRD-guided therapy have improved survival outcomes even in such biologically complex subtypes. Thus, the current case supports evolving evidence that atypical immunophenotypes do not invariably predict inferior outcomes when modern risk-adapted therapy is applied. Varotto E et al (2022).[13]

CONCLUSION

This case of a 9-year-old boy with acute myeloid leukemia exhibiting unusual immunophenotypic (CD45 dim, aberrant CD4 positivity) and cytogenetic (t(9;11)(p21;q23)) features underscores the heterogeneity of pediatric AML and the importance of comprehensive diagnostic evaluation. Despite the presence of an intermediate-risk cytogenetic lesion and atypical antigen expression, the patient achieved complete remission and MRD negativity following standard induction chemotherapy, highlighting that tailored therapy and vigilant monitoring can overcome unfavorable biological markers.

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