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Case Report

A Challenging Case of High-Risk Pediatric AML with Novel ZNF348/SF11 Fusion and Mixed Phenotypic Features: Navigating Genomic Complexity, Resistant Infections, and MRD-Driven Therapy toward Remission

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ABSTACT

Acute Myeloid Leukemia (AML) with mixed phenotypic features represents a rare and high-risk subset of childhood leukemia. This case highlights a pediatric patient harboring a novel ZNF348/SF11 fusion and NRAS mutation, emphasizing the diagnostic complexity, therapeutic resistance, and role of Minimal Residual Disease (MRD)-guided treatment in achieving remission. A 5-year-old male presented with fever, vomiting, petechiae, hepatosplenomegaly, and pancytopenia. Diagnostic evaluation included peripheral smear, bone marrow cytology, flow cytometry, and molecular profiling. The patient was treated with sequential chemotherapy regimens-ADE induction, FLA-B salvage, and MRD-adapted therapy using Venetoclax and Blinatumomab-along with aggressive infection control for carbapenem-resistant organisms. Initial ADE induction achieved morphologic remission but persistent MRD (19.25%). Following FLA-B and subsequent FLA-B + Venetoclax therapy, MRD declined to 0.6%. The combination of Blinatumomab and Venetoclax was initiated to achieve MRD negativity prior to allogeneic Hematopoietic Stem Cell Transplantation (HSCT). The course was complicated by multidrug-resistant infections, successfully managed through targeted antibiotic therapy and multidisciplinary care. This case underscores the clinical and genomic complexity of mixed-phenotypic AML with novel gene fusion. Persistent MRD after standard therapy necessitated precision-guided salvage regimens integrating Venetoclax and Blinatumomab. Early MRD monitoring, infection control, and timely transplant planning are critical for improving outcomes in such high-risk pediatric AML cases.

Keywords: Pediatric AML, Mixed Phenotypic Acute Leukemia, ZNF348/SF11 Fusion, NRAS Mutation, MRD, Venetoclax, Blinatumomab, Carbapenem-Resistant Infection, Allogeneic Stem Cell Transplantation.

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INTRODUCTION

Acute Myeloid Leukemia (AML) is a heterogeneous hematologic malignancy characterized by clonal proliferation of myeloid precursors with impaired differentiation (Döhner *et al*., 2015). Although AML is predominantly seen in adults, pediatric AML accounts for approximately 15-20% of all childhood leukemias (Creutzig *et al*., 2013). Among these, a small subset of patients exhibit Mixed Phenotypic Acute Leukemia (MPAL), defined by the co-expression of markers from more than one hematopoietic lineage. This mixed immunophenotype often complicates both diagnosis and treatment, resulting in poorer prognosis compared to lineage-specific leukemias (Matutes *et al*., 2011; Weinberg and Arber, 2010).

MPAL frequently harbors complex cytogenetic abnormalities and recurrent mutations such as NRAS, KRAS, and FLT3, which contribute to therapeutic resistance (Papaemmanuil *et al*., 2016). The identification of novel fusions and mutations through advanced genomic testing has improved risk stratification and precision therapy. However, certain genetic rearrangements remain exceedingly rare, with limited literature to guide management.

We report a high-risk pediatric AML case harboring a novel ZNF348/SF11 fusion with concurrent NRAS mutation, accompanied by aberrant B-lineage marker expression (CD19, CD22, and cCD79a). The case illustrates the diagnostic complexity, genomic uniqueness, and the challenges of achieving MRD-negative remission amidst recurrent, multidrug-resistant infections. Through sequential salvage therapies and MRD-adapted treatment using Venetoclax and Blinatumomab,

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remission was pursued to enable early allogeneic hematopoietic stem-cell transplantation (Locatelli *et al*., 2017).

CASE PRESENTATION

A 5-year-old male presented with persistent fever, pallor, generalized weakness, and gingival hypertrophy for 2 weeks. There was no significant past medical history. Physical examination revealed pallor, hepatosplenomegaly, and multiple petechial spots over the extremities. The patient did not develop gingival hyperplasia.

Initial investigations revealed hemoglobin of 6.5 g/dL, WBC count of 78 × 10^9/L, and platelet count of 24 × 10^9/L. Peripheral smear showed 70% blasts, and bone marrow aspiration demonstrated hypercellularity with 80% blasts expressing CD13, CD33, MPO, CD34, and aberrant CD19, CD22, and cCD79a, consistent with acute myeloid leukemia with aberrant B-lineage antigen expression (MPAL-like) (Weinberg and Arber, 2010).

Cytogenetic analysis identified a novel ZNF348/SF11 fusion and NRAS mutation on exon 2. FLT3, NPM1, and CEBPA mutations were negative. Investigation includes pancytopenia, with Hb-8.5g/dL,180 cells/µL (profound neutropenia), and platelet count 30,000 cells/µL and 73% blast cell in smear test

Treatment course

The patient received ADE induction chemotherapy (cytarabine, daunorubicin, etoposide) as per pediatric AML protocol (Creutzig *et al*., 2013). Post-induction, MRD remained positive (19.25%), suggesting suboptimal response. The patient then underwent FLA-B reinduction (fludarabine, cytarabine, G-CSF, and idarubicin), which reduced MRD.

Due to high-risk features (novel fusion, NRAS mutation, and persistent MRD), Venetoclax and Blinatumomab were introduced sequentially as MRD-directed therapy, aiming to achieve deep remission before allogeneic stem cell transplantation (Locatelli *et al*., 2017). After FLA-B reinduction MRD stiill persisted, following FLA-B with venetoclax, MRD reduced to 0.6%.

Throughout treatment, the patient developed multidrug-resistant *Klebsiella pneumoniae* sepsis, fungemia, and severe pancytopenia-complications frequently seen in intensively treated pediatric AML cases (Walsh *et al*., 2008). Broad-spectrum antimicrobials, antifungals, and supportive care were administered as per infectious disease guidelines.

Despite complications, MRD negativity was achieved after Blinatumomab consolidation. He was stabilized and referred for matched sibling donor allogeneic stem cell transplantation, which remains the only curative option for high-risk pediatric AML (Döhner *et al*., 2015).

DISCUSSION

Acute Myeloid Leukemia (AML) represents a genetically and clinically heterogeneous malignancy, and its prognosis in children depends on cytogenetic and molecular abnormalities (Döhner *et al*., 2015). The coexistence of myeloid and lymphoid markers in the same blast population, as observed in this case, fulfills the criteria for Mixed Phenotypic Acute Leukemia (MPAL). MPALs are rare and generally associated with unfavorable outcomes due to diagnostic ambiguity and therapeutic resistance (Matutes *et al*., 2011; Weinberg and Arber, 2010).

The discovery of a novel ZNF348/SF11 fusion along with an NRAS mutation suggests a complex molecular interplay influencing leukemogenesis. Mutations in the RAS pathway (NRAS, KRAS) have been shown to promote proliferation and reduce apoptosis, contributing to chemotherapy resistance (Papaemmanuil *et al*., 2016). This explains the patient's suboptimal response to standard induction and the persistence of Measurable Residual Disease (MRD).

MRD assessment is now a central component of pediatric AML management, guiding post-induction therapy and predicting relapse (Creutzig *et al*., 2013). Persistent MRD (>0.1%) after induction, as seen in this case, identifies patients at high relapse risk who may benefit from intensified or targeted therapy.

The FLA-B regimen is often chosen as salvage therapy in refractory AML due to its synergistic cytotoxicity on dividing blasts. Addition of Venetoclax, a BCL-2 inhibitor, helps overcome apoptotic resistance, while Blinatumomab, a bispecific T-cell engager, targets CD19-positive leukemic cells. Their sequential use has shown encouraging results in MRD-positive or relapsed AML and MPAL (Locatelli *et al*., 2017).

However, the case also highlights a major challenge-infectious complications during intensive therapy. Pediatric AML patients often experience bacterial and fungal infections due to profound neutropenia and mucosal damage. Mortality from resistant Gram-negative and fungal pathogens remains significant despite prophylaxis (Walsh *et al*., 2008). Early recognition, aggressive antimicrobial therapy, and multidisciplinary supportive care are essential to improve survival.

In this case, despite multiple infections, MRD negativity was achieved before transplantation, emphasizing the effectiveness of MRD-adapted sequential therapy and comprehensive supportive management. Blinatumomab in combination with venetoclax reduced MRD to 0.03% approaching near negativity.

CONCLUSION

This case demonstrates the complexity of pediatric AML with mixed phenotype expression and novel genetic fusion. It underscores the importance of integrated genomic profiling, MRD-guided therapy, and infection control in achieving

remission. The successful use of Venetoclax and Blinatumomab sequentially before allogeneic HSCT highlights their potential role in high-risk AML subsets with poor initial response. Continuous monitoring and individualized treatment remain crucial for optimizing long-term outcomes in such challenging cases.

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ABBREVIATIONS

AML: Acute Myeloid Leukemia; **MPAL:** Mixed Phenotypic Acute Leukemia; **MRD:** Minimal Residual Disease; **HSCT:** Hematopoietic Stem Cell Transplantation; **ADE:** Cytarabine + Daunorubicin + Etoposide; **FLA-B:** Fludarabine + Cytarabine + Mitoxantrone; **NGS:** Next-Generation Sequencing; **CARBA-R:** Carbapenem-Resistant; **HRCT:** High-Resolution Computed Tomography; **G-CSF:** Granulocyte Colony Stimulating Factor; **BiTE:** Bispecific T Cell Engager.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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