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CASE REPORT

A Rare Case of Juvenile Myelomonocytic Leukemia (JMML) with t(3;5)(q25;q34)/NPM::MLF1 Fusion Gene in a Pediatric Patient

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SUMMARY

Background: **Juvenile myelomonocytic leukemia (JMML) is a rare and aggressive pediatric hematologic malignancy characterized by clonal proliferation of myelomonocytic cells. It predominantly affects young children and presents significant diagnostic challenges due to overlapping features with other myeloid disorders. Here, we report the case of a 2-year-old male patient with unique genetic findings involving the NPM::MLF1 fusion gene and NRAS mutation.**

Methods: **A comprehensive diagnostic evaluation was conducted, including physical examination, complete blood count, bone marrow aspiration, flow cytometry, cytogenetic analysis, and molecular testing for fusion genes. Imaging studies, including abdominal ultrasound, were also performed. Therapeutic interventions included hydroxyurea for leukocytosis and supportive transfusions. Family members declined chemotherapy and hematopoietic stem cell transplantation.**

Results: **The patient presented with leukocytosis, anemia, thrombocytopenia, splenomegaly, and abnormal bone marrow findings consistent with JMML. Genetic testing revealed a rare t(3;5)(q25;q34) involving the NPM::MLF1 fusion gene and an NRAS mutation. Supportive treatment was provided, but the family declined definitive chemotherapy and hematopoietic stem cell transplantation.**

Conclusions: **This case represents a rare presentation of JMML with t(3;5)(q25;q34) involving the NPM::MLF1 fusion gene, a finding uncommon in pediatric myeloid malignancies. The presence of this genetic abnormality presents significant diagnostic and therapeutic challenges, emphasizing the need for comprehensive genetic profiling in JMML. The rarity of the NPM::MLF1 fusion complicates the establishment of a standard treatment protocol, underscoring the necessity for individualized treatment approaches and further research.**

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KEYWORDS

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INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is a rare, aggressive hematopoietic malignancy that primarily affects infants and young children [1]. It is characterized by the excessive proliferation of monocytic and granulocytic cells. The pathogenesis of JMML involves dysregulation of the RAS-signaling pathway, which is crucial for myeloid hematopoietic cell proliferation [2].

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Mutations in genes such as PTPN11, NRAS, KRAS, and NF1 are common in JMML and lead to abnormal activation of the RAS pathway, driving leukemic cell growth [3]. Additionally, CBL mutations are observed in some patients, typically presenting as germline mutations with subsequent loss of heterozygosity [4].

Patients typically present with leukocytosis, monocytosis, organomegaly (especially splenomegaly), anemia, and thrombocytopenia, with bone marrow examinations revealing hypercellularity and myelomonocytic proliferation. Diagnosing JMML can be challenging due to symptom overlap with other pediatric conditions. According to the 2017 WHO criteria [5], diagnosis requires splenomegaly and a molecular abnormality or clonal chromosomal changes, with hyperphosphorylation of STAT5 as a minor criterion [6].

Although blastic transformation is rare, JMML is an aggressive and often fatal disorder if left untreated. Poor prognostic factors include a low platelet count, age above 2 years at diagnosis, and elevated hemoglobin F (Hb F) levels [7]. JMML is a disease with a poor prognosis, and most patients require hematopoietic stem cell transplantation (HSCT) for potential cure, with success rates ranging from 50% to 60%. Disease relapse remains the primary cause of treatment failure.

We report a rare case of juvenile myelomonocytic leukemia with a karyotype of 46,XY and the translocation t(3;5)(q25;q34), leading to the NPM1::MLF1 fusion gene, which contributes to disease aggression and highlights JMML's genetic complexity. This rare case enhances clinicians' understanding and awareness of such conditions.

CASE PRESENTATION

A 2-year-old male patient was admitted to the pediatric department of our hospital 10 days ago due to "fever accompanied by abnormal blood cells." Physical examination revealed: temperature 37.0℃, pulse 93 beats/minute, respiration 20 breaths/minute, blood pressure 98/50 mmHg, alert mental status, pallor with anemic facies, no jaundice in skin or mucosa, presence of petechiae and ecchymosis, mild pharyngeal congestion, no tonsillar enlargement, coarse breath sounds in both lungs without apparent dry or wet rales, regular heart rhythm, soft and flat abdomen, liver not palpable below the costal margin, and spleen palpable 2 cm below the costal margin. Laboratory findings included: white blood cells (WBC) 36.96 x 10^9/L; neutrophils 20.43 x 10^9/L; monocytes 9.36 x 10^9/L; hemoglobin 75 g/L; platelets 62 x 10^9/L. Abdominal ultrasound showed: 1) slightly enlarged liver and spleen; 2) no obvious abnormalities in the gallbladder or pancreas; 3) normal portal vein diameter and hepatopetal flow velocity. Bone marrow aspiration revealed decreased granulocyte system ratio, with a few binucleated granulocytes, pseudo-Pelger anomaly, and hypersegmentation. Lymphocytes accounted for 14.75%, monocytes for 59%, significantly elevated, with 18.25% immature monocytes, predominantly mature monocyte proliferation (Figure 1A and B). Bone marrow findings suggested myeloproliferative neoplasm. Flow cytometric analysis of the bone marrow showed 18.94% myeloid-origin blasts. Both BCR-ABL fusion gene P210 and P190 were negative. Fusion gene analysis showed NPM/MLF positivity (Figure 1C). Juvenile myelomonocytic leukemia (JMML)-related gene mutation analysis revealed an NRAS missense mutation. Chromosome karyotype analysis showed 46, XY, t(3;5)(q25;q34). Peripheral blood morphology showed blasts and Auer rods. Lactate dehydrogenase was elevated at 618.00 U/L. Liver and kidney function tests, electrolytes, cardiac enzyme profile, and coagulation parameters were within normal limits. The patient was treated with hydroxyurea to reduce WBC count and supportive transfusions. Family opted against combination chemotherapy and bone marrow transplantation, and chose discharge against medical advice. The risks associated with discharge were explained, and the family declined hematopoietic stem cell transplantation.

DISCUSSION

This case represents an unusual presentation of juvenile myelomonocytic leukemia (JMML), defined by splenomegaly, leukocytosis, monocytosis, anemia, thrombocytopenia, and the presence of the t(3;5)(q25;q34) chromosomal translocation leading to the NPM1::MLF1 fusion gene. The t(3;5) translocation is rare in JMML and is more commonly associated with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). To our knowledge, this is a rare JMML case reported with this specific translocation.

A notable aspect of this case is the identification of the t(3;5)(q25;q34)/NPM::MLF1 fusion gene, known to contribute to dysregulation in cellular proliferation and differentiation [2]. This genetic anomaly has been primarily reported in AML and MDS, where it is often associated with distinct clinical and morphological features. The presence of this fusion gene in JMML suggests a possible link to more aggressive disease behavior and highlights the genetic complexity of JMML [8]. Tumors containing NPM1 fusion genes are rare and more commonly found in younger males. The blast cell counts in these patients may present features akin to myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML). According to the WHO 2016 revision classification, the majority of AML cases with t(3;5)(q25;q34) are categorized as AML with myelodysplastic-related changes [9]. However, the latest WHO Fifth Edition (blasts ≥ 20%) and the International Consensus Classification (ICC; blasts ≥ 10%) now categorize these cases as AML with recurrent genetic abnormalities.

In this case, while the blast cell count did not meet the thresholds for either classification, the formation of the NPM1 fusion gene is considered to have biological significance akin to that of NPM1 mutations, underscoring

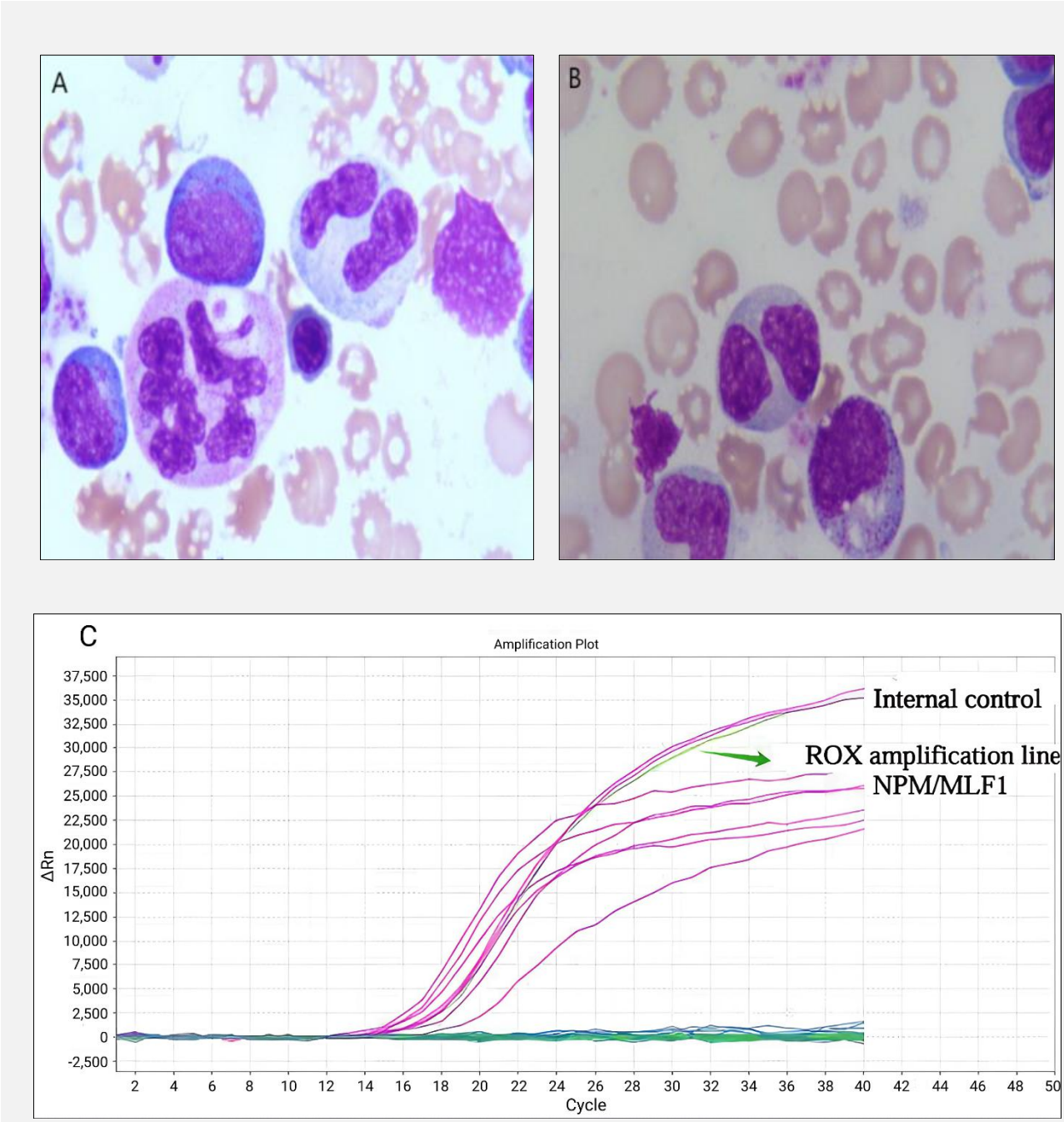

Figure 1.The bone marrow morphology showed a proportion of mature monocytes at 32.5%, with approximately 23% of blasts/immature monocytes (A). The granulocytic system was reduced, with the presence of binuclear granulocytes, pseudo-Pelger-Huët anomaly, and hypersegmentation (B). Fusion gene analysis showed NPM/MLF1 fusion gene positive (C).

the diagnostic challenges associated with such rare cases. Notably, JMML and its related myeloproliferative tumors often present atypically in clinical settings, leading to misdiagnosis or treatment delays.

The emergence of this rare case emphasizes the importance of comprehensive genetic analysis and thorough pathological evaluation in pediatric leukemia management to ensure accurate diagnosis and appropriate treatment strategies [7]. Clinicians should maintain a high index of suspicion for patients harboring NPM1 fusion genes, as they may require treatment approaches that differ from traditional AML or MDS regimens [10].

This rare case not only provides valuable clinical insights into the diagnosis and management of JMML but also highlights the complexities present in pediatric leukemia care. Further research should focus on elucidating the molecular mechanisms of JMML and their relationship with clinical outcomes to pave the way for personalized treatment strategies in the future.

Declaration of Interest:
The authors declare that there are no conflicts of interest.

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