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CASE REPORT

Overcoming the Challenge: Successful Bridge to Allogeneic Transplantation in KAT6A::CREBBP-Positive AML with Hemophagocytosis

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ABSTRACT

Background: **Acute myeloid leukemia (AML) with the t(8;16)(p11.2;p13.3) translocation, leading to the lysine acetyltransferase 6A (KAT6A)::CREB-binding protein (CREBBP) fusion, is a rare and distinct subtype with unique clinical and biological features.**
Methods: **We conducted a detailed clinical and molecular analysis of a patient with de novo KAT6A::CREBBP-positive AML, focusing on the diagnostic implications of the hallmark blast-mediated hemophagocytic phenomenon.**
Results: **The patient presented with characteristic clinical features and responded to intensive chemotherapy followed by hematopoietic stem cell transplantation (HSCT). Molecular monitoring revealed minimal residual disease (MRD) dynamics that correlated with treatment response.**
Conclusions: **Our findings underscore the importance of early diagnosis and tailored management in KAT6A::CREBBP-positive AML. Ongoing MRD monitoring is essential for guiding treatment and predicting outcomes in this high-risk leukemia subtype.**
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KEYWORDS

acute myeloid leukemia, KAT6A::CREBBP fusion, allogeneic hematopoietic stem cell transplantation, minimal residual disease

INTRODUCTION

Acute myeloid leukemia (AML) harboring the t(8;16)(p11;p13) translocation constitutes an exceptionally rare (< 0.5% of AML cases) yet clinically aggressive subtype, exhibiting a strong female predominance and frequent association with therapy-related AML (t-AML) [1,2]. This high-risk entity is characterized by monocytic differentiation and a propensity for devastating complications, including extramedullary infiltration and disseminated intravascular coagulation (DIC), culminat-

ing in dismal clinical outcomes [1]. The molecular hallmark involves fusion of the KAT6A (MYST3) gene at 8p11 with CREBBP at 16p13 [3]. KAT6A encodes a MYST-family histone acetyltransferase, while CREBBP functions as a transcriptional coactivator regulating chromatin remodeling through CREB-mediated pathways [4,5]. This chimeric oncoprotein drives leukemogenesis via aberrant epigenetic modulation. Clinically, KAT6A::CREBBP-rearranged AML frequently manifests with pathognomonic erythrophagocytosis by leukemic blasts - a diagnostically critical feature particularly evident in monocytoid variants [6]. The co-occurrence of hemophagocytosis and monoblastic morphology should prompt immediate cytogenetic investigation for t(8;16). Despite recent advances, this malignancy remains profoundly understudied, with fewer than 100 documented cases worldwide. Substantial knowledge gaps persist regarding optimal therapeutic approaches and long-term survival data, underscoring the imperative for collaborative multicenter studies.

CASE PRESENTATION

A 31-year-old woman presented with a one-week history of persistent fever (axillary temperature 38.5 - 39.8°C) and generalized myalgia. Initial laboratory evaluation revealed pancytopenia: leukopenia (WBC 1.33 x 10^9/L), anemia (Hb 74 g/L; RBC 2.62 x 10^{12}/L), and thrombocytopenia (102 x 10^9/L), with a markedly reduced hematocrit (22.7%). Coagulation studies showed normal activated partial thromboplastin time (APTT 21.7 second) but elevated D-dimer (4.56 mg/L FEU), raising concern for consumptive coagulopathy. Bone marrow aspiration demonstrated hypercellularity with 83.5% blast infiltration. Morphological assessment identified characteristic erythrophagocytosis and granulocyte phagocytosis by leukemic blasts (Figure 1A, B), consistent with acute monocytic leukemia. Cytochemical staining revealed dual positivity: peroxidase (POX, Figure 1C) and α-naphthyl butyrate esterase (α-NBE, NaF-inhibitable; Figure 1D), confirming monocytic lineage differentiation. Flow cytometric immunophenotyping detected an aberrant immature monocytic population (28.30% of nucleated cells) expressing CD33, CD64, and CD4 (bright), with partial CD13 and HLA-DR. The absence of CD14 maturation marker further supported the diagnosis of acute monocytic leukemia (FAB-M5).

Hematologic tumor myeloid mutation gene testing revealed the presence of a KAT6A(E17)-CREBBP(E2) fusion gene. Cytogenetic analysis revealed a karyotype of 46,XX,t(8;16)(p11;13)[17]/46,XX[3] (Figure 2A). The treatment regimen comprised chemotherapy with cytarabine, idarubicin hydrochloride, and vinaclat, supplemented by hydration, alkalinization, and gastric protection measures. Following stabilization, the patient was discharged from the hospital and continued to undergo observation and treatment. During the discharge period, the patient underwent six bone marrow aspirations, which demonstrated a persistent and recurrent increase in the proportion of primitive and naïve monocytes. Notably, there was no evidence of erythrophagocytosis by these cells. Furthermore, flow cytometry-based minimal residual disease (MRD) analysis indicated that the patient had not achieved remission (Figure 2B). For further treatment, the patient underwent a modified Bu/Cy + VP16 + ATLG chemotherapy regimen as conditioning for hematopoietic stem cell transplantation (HSCT). The peripheral hematopoietic stem cell transplantation was successfully performed, and the patient received symptomatic treatments, including anti-infective therapy, circulatory support, hepatogastrointestinal protection, and antiemetics, during the transplantation process. During the treatment, the patient developed leukopenia, thrombocytopenia, and severe anemia due to chemotherapy-induced bone marrow suppression. He received granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO) therapy to improve his hematopoiesis, along with several transfusions of irradiated platelets and leukoreduced red blood cells to support his condition. At present, the patient's condition has achieved relative stability.

DISCUSSION

This study presents a patient who was admitted for persistent fever and generalized pain. Bone marrow cytology and flow cytometry analysis led to an initial diagnosis of acute monoblastic leukemia. Subsequent molecular genetic testing revealed the presence of a KAT6A-CREBBP fusion gene and a t(8;16)(p11;13) chromosomal translocation. Based on these comprehensive diagnostic findings, the patient was definitively diagnosed with acute myeloid leukemia (AML) associated with the t(8;16)(p11;13)/KAT6A::CREBBP fusion. Despite initial chemotherapy, the patient's response was suboptimal, and minimal residual disease (MRD) analysis indicated that the disease was not in remission, highlighting the therapeutic challenges of this condition. The patient experienced severe bone marrow suppression during treatment, which was effectively managed with anti-infective therapy, circulatory support, and blood transfusions to control related complications. Subsequently, the patient underwent hematopoietic stem cell transplantation (HSCT) and received comprehensive supportive care during the transplant process. This case underscores the prognostic factors and treatment advances in AML with the t(8;16)(p11;13)/KAT6A::CREBBP fusion, emphasizing the importance of patient age, specific molecular genetic features, and treatment regimens in influencing prognosis. Additionally, this case has significant implications for clinical practice, reminding clinicians to consider a multifaceted approach in the diagnosis, treatment, and follow-up of patients with this disease.

The bone marrow morphology in this case is distinctive,

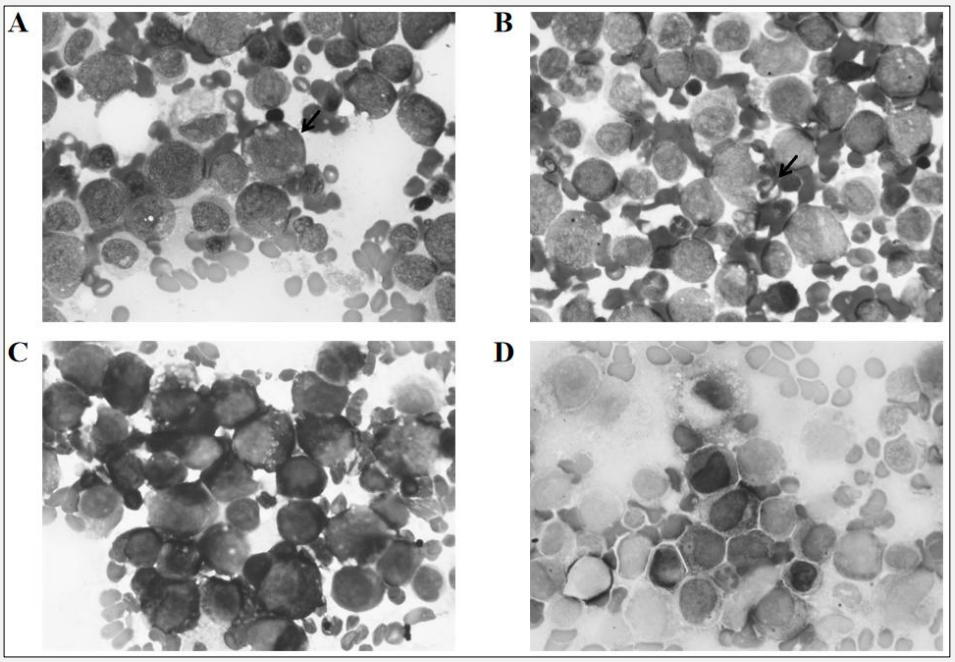


Figure 1. Bone marrow smear findings.

A: Erythrophagocytosis by leukemic blasts (arrows; Wright-Giemsa stain, x 1,000 magnification). B: Neutrophil phagocytosis by primitive monocytoid cells (arrows; Wright-Giemsa stain, x 1,000). C: Strong cytoplasmic positivity for myeloperoxidase (MPO) staining (x 1,000). D: α-naphthyl butyrate esterase (α-NBE) staining showing NaF-inhibitable activity (x 1,000), confirming monocytic differentiation.

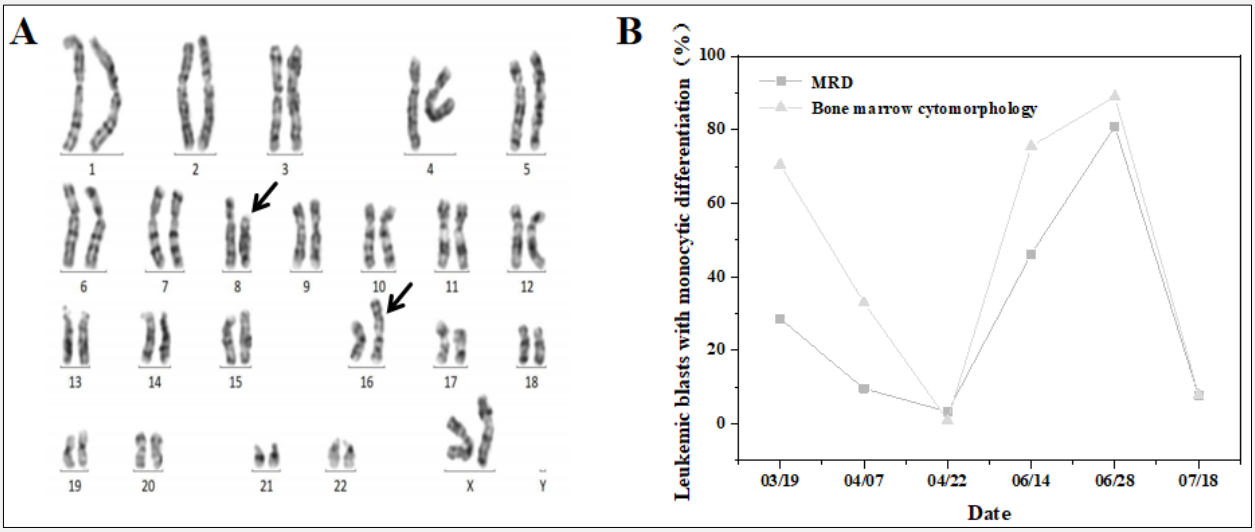


Figure 2. Cytogenetic and treatment response analysis.

A: Karyotype analysis demonstrating reciprocal translocation between chromosomes 8 and 16 [t(8;16)(p11;p13)] (G-banding, x 1,000). B: Longitudinal monitoring of blast percentage through bone marrow morphology and minimal residual disease (MRD) assessment by multiparameter flow cytometry during chemotherapy.

characterized by the phagocytosis of erythrocytes and neutrophils by primitive and immature monocytes, which holds multifaceted significance. Diagnostically, this phenomenon suggests the presence of a t(8;16)(p11;p13) chromosomal translocation or a KAT6A-CREBBP fusion gene [6], and it serves as a hallmark cytogenetic feature of this AML subtype, providing crucial clues for diagnosis. It prompts physicians to conduct targeted cytogenetic and molecular biological tests to differentiate this subtype from other AML subtypes, with accurate diagnosis being essential for the development of personalized treatment plans. This phenomenon also reveals the abnormal phagocytic activity of acute monoblastic leukemia cells, which is closely related to the patient's severe anemia and may indicate a poor prognosis, suggesting that a more aggressive approach to treatment, including potential targeted therapies against monocyte phagocytic function, may be necessary. From a pathophysiological perspective, the monocyte-like primitive cells indicate that this AML subtype has characteristics of monocyte differentiation, reflecting the abnormality of leukemia cells during the differentiation process, which may be related to the transcriptional regulatory disorder caused by the fusion of KAT6A and CREBBP genes. The erythrocyte phagocytosis phenomenon may be related to the abnormal expression of receptors on the surface of leukemia cells and the disorder of cellular signaling pathways [2,7]. Further research on this phenomenon will help to deepen our understanding of the pathophysiological mechanisms of the disease and provide a basis for the development of new therapeutic targets. Therefore, a thorough understanding of the molecular mechanisms underlying this phenomenon is of great significance for improving the treatment outcomes of patients with acute monoblastic leukemia.

Acute myeloid leukemia (AML) with t(8;16) is characterized by distinct cytological, cytogenetic, molecular, and prognostic features, representing a specific AML subtype. Although its incidence is low, it is more prevalent in therapy-related AML (t-AML) and carries a poor prognosis. The present study reports a primary case of AML with t(8;16)(p11;13)/KAT6A::CREBBP fusion, which is exceedingly rare. This abnormality is associated with unique clinical features, including hemophagocytic syndrome, disseminated intravascular coagulation (DIC), and cutaneous leukemia, presenting significant challenges in diagnosis and treatment. The KAT6A and CREBBP genes play critical roles in embryogenesis, cellular differentiation, apoptosis, and proliferation. Their fusion is believed to induce leukemia through aberrant chromatin remodeling. While the functional transcriptional output of the fusion gene remains unclear, its role in leukemogenesis is widely acknowledged.

Acute myeloid leukemia (AML) characterized by the t(8;16)(p11;13)/KAT6A::CREBBP fusion exhibits an extremely poor prognosis, with a median overall survival (OS) of less than 10 months post-diagnosis [8]. This adverse prognosis is linked to the aberrant cellular proliferation and differentiation driven by the fusion gene, as well as to potential treatment-related complications such as infections, hemorrhages, and cardiac events. While standard AML induction and consolidation therapies are effective in some patients, the recurrence rate remains notably high [9]. Consequently, a multifaceted treatment approach, encompassing chemotherapy, targeted therapy, and allogeneic stem cell transplantation (SCT), is essential for AML patients with the t(8;16)(p11;13)/KAT6A::CREBBP fusion to enhance survival rates and quality of life. In the present case, the patient's disease remains stable following HSCT, underscoring the effectiveness of this treatment modality for this individual. Notably, the patient underwent regular minimal residual disease (MRD) monitoring both pre- and post-transplantation. MRD monitoring is instrumental in providing precise prognostic assessments and risk stratification, thereby offering critical insights for the formulation of consolidation treatment regimens and facilitating early warning of recurrence risks, enabling timely adjustments to therapeutic strategies. Ongoing MRD surveillance post-transplantation is also vital for the early detection of relapse indicators, thereby allowing for prompt intervention.

CONCLUSION

This case report and subsequent investigations demonstrate that advancements in detection technologies will significantly enhance the precision and efficiency of bone marrow morphological characterization and minimal residual disease (MRD) monitoring. Such improvements are expected to facilitate earlier prediction of disease relapse, thereby optimizing therapeutic strategies and improving overall survival rates.

Furthermore, our study highlights the critical need to investigate the molecular mechanisms underlying the rare AML subtype characterized by t(8;16)(p11.2;p13.3) chromosomal translocation and KAT6A::CREBBP gene fusion. Elucidation of its distinct pathogenic pathways may not only advance our understanding of leukemogenesis but also provide a theoretical foundation for developing targeted therapies. The integration of precise diagnostics, molecularly-guided treatment approaches, and personalized medicine protocols holds substantial promise for improving clinical outcomes and alleviating the disease burden in this rare AML variant.

Declaration of Generative AI in Scientific Writing:
During the preparation of this work, the authors did not use any generative AI or AI-assisted technologies.

Declaration of Interest:
The authors have no conflicts of interest relevant to this article to disclose.

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