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Case Report
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Successful Outcome of Allogeneic Stem Cell Transplant in a Patient with FLT3-ITD and CBL Mutations in Refractory/ Relapsed AML Accompanied by Pulmonary Cavity: A Case Report

*Li Z[1#], Pan Y[2#], Chen J[1], Li X[1] and Chen P[2]**

[1]*Hematopoietic Stem Cell Transplantation Center, The Tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University, China*

[2]*The Tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University or The First School of Clinical Medicine, Southern Medical University, China*

[#]*These authors have contributed equally to this work*

Abstract

Background: The Fms-Like Tyrosine kinase 3 (FLT3) gene is frequently mutated in adult Acute Myeloid Leukemia (AML), with a detection rate of approximately 30%. Patients harboring both FLT3-ITD and Casitas B-lineage Lymphoma proto-oncogene (CBL) frequently encounter relapse or refractoriness, posing a significant challenge in treatment as conventional drugs have limited efficacy in clinical practice.

Case Report: We present a rare and complex case of successful transplantation of refractory/ relapsed AML with FLT3-ITD and CBL double mutations in a young female patient. Chemotherapy was initially administered to treat AMI; however, she developed persistent agranulocytosis, recurrent hyperthermia, and a severe lung infection, subsequently progressing into a serious pulmonary cavity. After receiving active anti-infective treatment and targeted drug therapy, there was slight improvement in the patient's condition. The donor screening and matching for stem cell transplantation were conducted once the patient's condition had stabilized, leading to a successful allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT). Fortunately, the patient exhibited recovery of hematopoietic function and showed improvement after the transplant.

Conclusion: In conclusion, for patients with refractory/relapsed AML harboring FLT3-ITD mutations combined with CBL mutations, timely initiation of remission induction therapy followed by prompt and proactive HSCT can significantly improve patient outcomes.

Keywords: Acute myeloid leukemia; Fms-like tyrosine kinase 3; Casitas B-lineage lymphoma proto-oncogene; Hematopoietic stem cell transplantation; Targeted therapy

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Correspondence:
Peier Chen, The Tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University or The First School of Clinical Medicine, Southern Medical University, Dongguan 523018, China,

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Abbreviations

FLT3: Fms-Like Tyrosine kinase 3; AML: Acute Myeloid Leukemia; CBL: Casitas B-lineage Lymphoma proto-oncogene; allo-HSCT: allogeneic Hematopoietic Stem Cell Transplantation; JMD: Juxtamembrane Domain; CMML: Chronic Myelomonocytic Leukemia; JMML: Juvenile Myelomonocytic Leukemia; HSCT: Hematopoietic Stem Cell Transplantation; NR: Non-Remission Status; NSG: Next-Generation Sequencing; MRD: Minimal Residual Disease; GVHD: Graft Versus Host Disease; CR: Complete Remission; GVL: Graft-Versus-Leukemia; R/R AML: Relapsed or Refractory Acute Myeloid Leukemia

Background

FLT3, a crucial receptor tyrosine kinase involved in cellular signaling pathways, is one of the most commonly mutated genes in Acute Myeloid Leukemia (AML), with a detection rate of around 30% in adult AML patients [1]. The majority of FLT3 mutations are mainly seen as FLT3-Internal Tandem Duplications (FLT3-ITD) in the Juxtamembrane Domain (JMD). Patients with FLT3-ITD AML often show characteristics like high white blood cell count and a tendency for recurring or treatment-resistant disease, which are classified as medium-risk and indicate an unfavorable

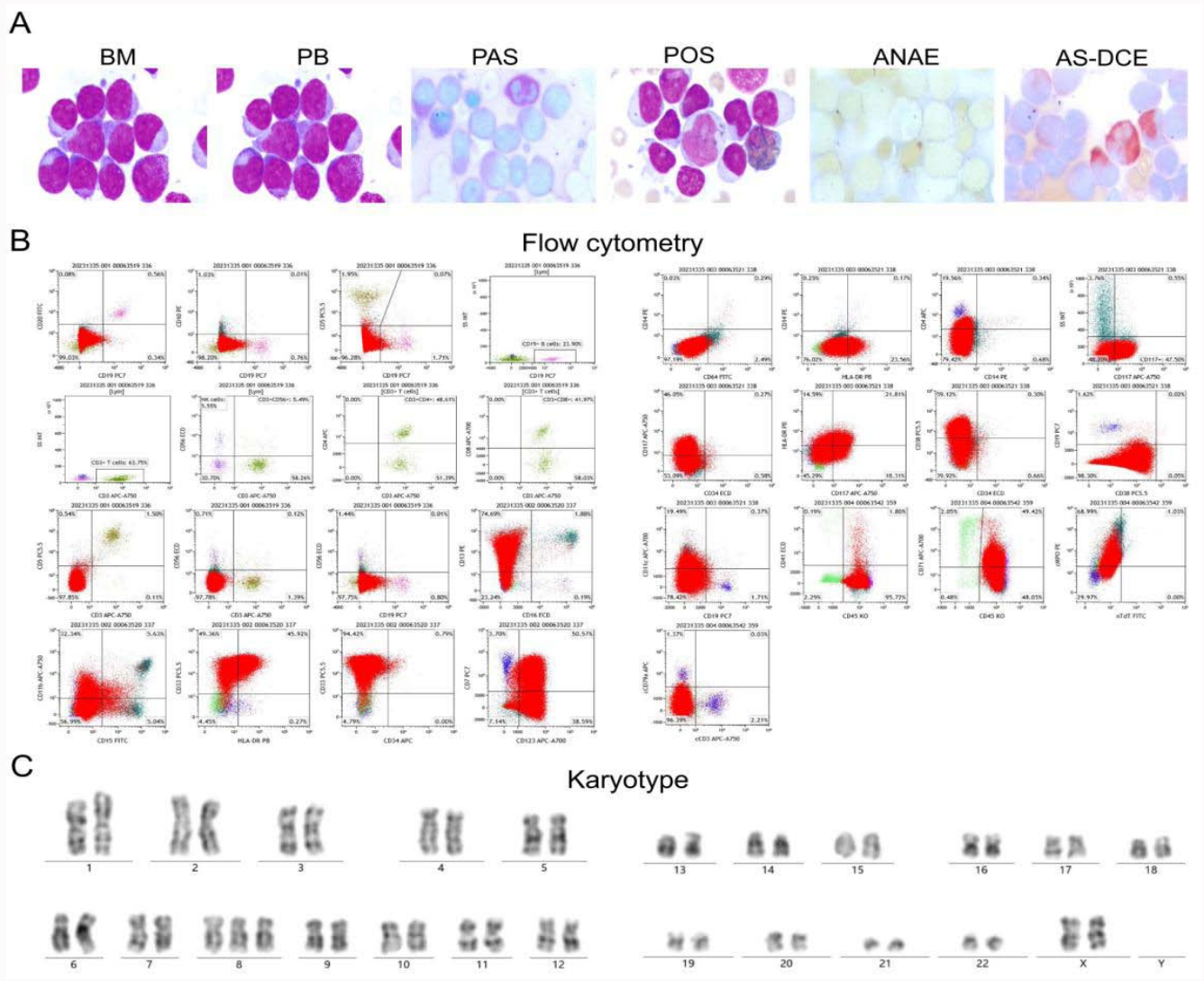


Figure 1: (A) The bone marrow cell morphology examination of the patient upon admission to the hospital. (B) The Flow Cytometry (FCM) test report of the patient's bone marrow. (C) The result of the patient's Karyotype.

prognosis [2].

The Casitas B-lineage Lymphoma proto-oncogene (CBL) is a crucial regulator of signal transduction, playing a pivotal role in the regulation of cell growth and differentiation. Mutations in the CBL gene have been identified in various cancers, including AML. Previous clinical studies have shown that individuals with CBL mutation in Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML) tend to exhibit shorter overall survival rates [3-5]. However, the comprehensive clinical implications of FLT3-ITD and CBL double mutations in AML are still unclear.

The main challenge in treating relapsed/refractory AML patients in clinical practice is the ineffectiveness of conventional drugs [6]. Hence, expedited Hematopoietic Stem Cell Transplantation (HSCT) is recommended whenever a compatible donor is accessible [7]. Here, we report a successful allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) case of refractory/relapsed AML with FLT3-ITD and CBL double mutations accompanied by pulmonary cavity.

Case Presentation

The 34-year-old female patient was admitted with a one-week history of dizziness and abnormal blood pattern. It was observed that 90% of the cells in the blood sample were immature. The bone marrow biopsy further revealed a significant presence of leukocytes, with 66.2% identified as myeloblasts, thereby confirming the diagnosis of Acute Myeloid Leukemia (AML) subtype M2. Flow cytometry analysis showed that 89.53% of the cells were of myeloid origin. The cytogenetics analysis indicated abnormal karyotypes (47, XX, +8[13]/46, XX [7]) (Figure 1). Molecular studies further demonstrated mutations in FMS-related tyrosine kinase 3 Internal Tandem Duplication (FLT3-ITD) and the E3 ubiquitin ligase (CBL) (Supplementary Image 1 and Table 1). Based on the above inspection results, the patient underwent a timed sequential induction using a '3+7' regimen, along with Sorafenib and symptomatic treatment, commencing on April 21st, 2023 [8,9]. Regrettably, the patient was determined to be in a Non-Remission Status (NR) based on the results of a bone marrow reexamination and flow cytometry analysis.

The patient subsequently initiated reinduction chemotherapy

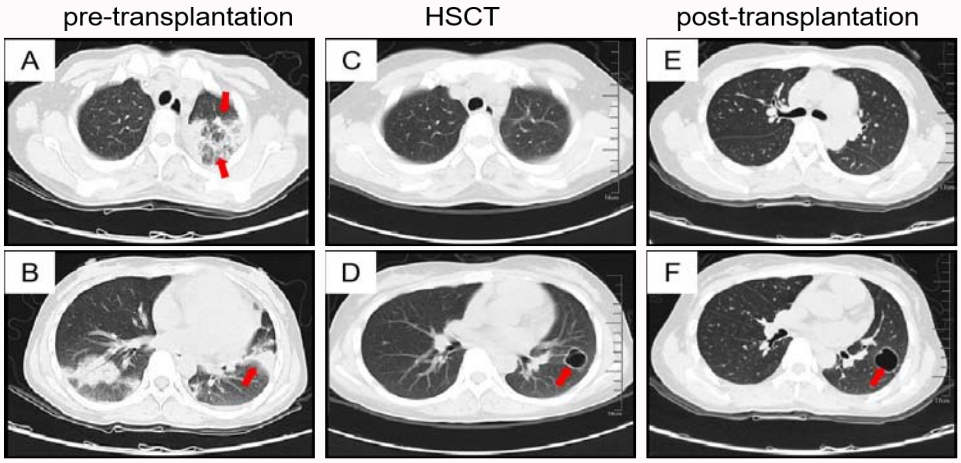


Figure 2: Computed Tomography (CT) scanned before and post-treatment and during transplantation. CT images obtained prior to transplantation (A-B), when the patient received an allo-HSCT (C-D), and post-transplantation (E-F).

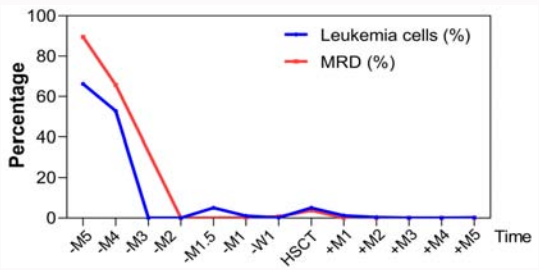


Figure 3: The percentages of leukemia cells in bone marrow and Minimal Residual Disease (MRD) by flow cytometry at different time points. M: Month; W: Week.

with Gilteritinib in combination with HVA (Harringtonin, Venclexta, and Azacitidine) on May 30th, 2023. However, the patient experienced persistent agranulocytosis and recurrent hyperthermia. Blood culture and Next-Generation Sequencing (NGS) analysis revealed the presence of *Stenotrophomonas maltophilia*. Additionally, a chest Computed Tomography (CT) scan showed multiple infectious lesions in both lungs, including partial consolidation of the left lung (Figure 2A, 2B). Therefore, targeted therapy with Gilteritinib at a dosage of 120 mg/d was recommended [10]. A bone marrow reexamination 3 weeks later showed active hyperplasia with 1% granulocytes and 0.23% MRD. Additionally, a follow-up chest CT showed more significant absorption of infectious lesions in both lungs compared to previous scans. In view of the patient's improving condition, azacytidine was administered in combination with Gilteritinib maintenance chemotherapy on August 7th, 2023 [11,12].

A bone marrow reexamination 5 days later revealed a new increase of 5% in granulocytes and 3.7% in MRD as detected by flow

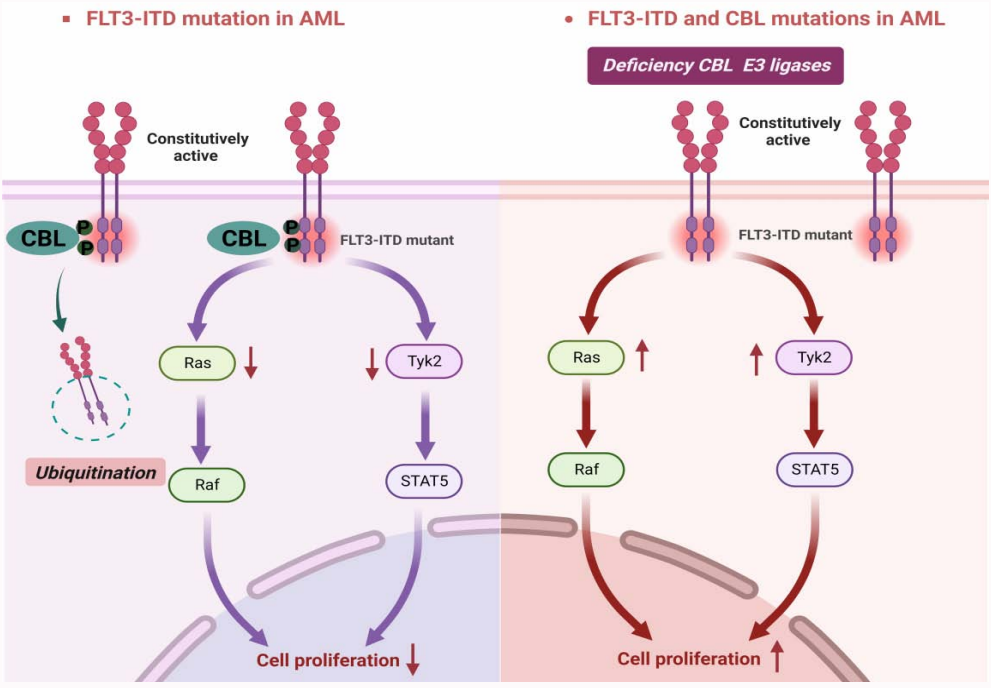


Figure 4: The possible mechanism diagram illustrating the impact of FLT-ITD mutation and CBL gene mutation on AML disease.

Table 1: List of variation sites.

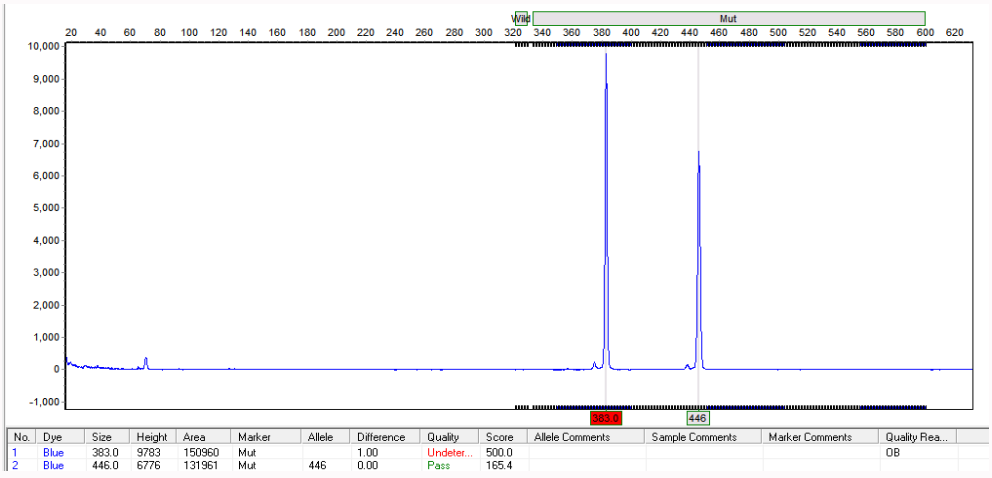
Gene	Variation point	Frequency of mutation
FLT3	ITD	**≥ 0.5**
CBL	c.1255T>C; p.Cys419Arg	**2.40%**

cytometry. A repeat CT scan showed further resolution of infectious lesions in both lungs, with absorption of infected lesions resulting in a cavity formation in the left lung (Figure 2C, 2D). The doctors recognized it was a favorable time for allo-HSCT, and her brother's HLA matching showed a 10/10 compatibility [7]. Therefore, with the patient and her family's informed consent, an allogeneic hematopoietic stem cell transplantation was initiated on September 6th, 2023. We carefully administered anti-rejection medications before and after the transplant. One week later, her brother's peripheral blood stem cells (247 ml) were transfused back to the patient. No other serious adverse reactions were observed during the transplantation. Hematologic evaluation at 9 days post-allo-HSCT showed full engraftment of granulocytes and platelets. Several months have passed now and the patient's MRD remains negative. Blood tests indicate normal levels for all three blood cell lines (Figure 3), and bone marrow chimerism is observed to be 99.56% (Supplementary Table 1, 2). Importantly, there has been no recurrence of the disease despite the presence of lung cavity impairment after transplantation (Figure 2E, 2F).

Discussions and Conclusion

In this particular case, the patient presented with primary Acute Myeloid Leukemia (AML) featuring FLT3-ITD and CBL mutations (Supplementary Image 2), accompanied by a leukocyte count exceeding 100 × 10^9/L, categorizing it as hyperleukocytic acute leukemia. The treatment was initially started with a combination of targeted drug Sorafenib and the IA regimen for induction chemotherapy and leukocyte reduction [8,9]. Despite these efforts, the patient failed to respond to induction therapy, prompting reintroduction of chemotherapy with the second-generation targeted drug Gilteritinib in conjunction with the HVA regimen [13,14]. Currently, both first and second-generation FLT3 inhibitors have been developed specifically for AML patients with FLT3 mutations [1,9,10,15]. Despite advancements in novel FLT3 inhibitors, drug resistance remains a formidable challenge due to multiple mutation sites within FLT3, complicating the clinical treatment [1,16]. The protein CBL is expressed in both lymphocytes and myeloid cells, making it a potential target. By inhibiting the enzyme activity of E3 ubiquitin ligase CBL, which reduces degradation of FLT3 protein, it disrupts the process of CBL-mediated ubiquitination of FLT3 [17]. The inefficient degradation of FLT3 leads to abnormal activation of its downstream signaling pathway, driving the malignant proliferation of leukemia cells [6,18,19] (Figure 4). The patient, however, experienced severe bone marrow suppression and a secondary lung infection, resulting in rapid disease progression and subsequent septic shock, suggesting that the efficacy of second-generation FLT3 inhibitors in managing patients with double mutations may be limited.

The risk of relapse may increase if allo-HSCT is delayed for additional consolidation therapy, considering it offers the highest chance of survival for FLT3-ITD AML patients. Therefore, despite the potential risk of recurrent lung infections and worsening hemoptysis, we recommend promptly initiating allo-HSCT for the patient upon the onset of lung cavity absorption. To efficiently reduce the recurrence rate of high-risk AML after allo-HSCT, we implemented a



Supplementary Image 1: The allelic ratio of FLT3-ITD.

Supplementary Image 2: The mutation sites of the FLT3 and CBL genes.

Table 2: The chimeric status analysis report of the patient in four months.

Detection Result				
STR site	Allele Site			Site state
	Patient before transplantation	donor	Patient after transplantation	
THO1	9	7	9/7	MC
D21S11	28/30	32.2/33.2	32.2/33.2	
D2S1338	21/25	17/21	17/21/25	MC
Penta E	14	14/18	14/18	
D5S818	13	13	13	
D13S317	8/13	11/13	8/11/13	MC
D7S820	10/13	10/13	10/13	
D16S539	11	11	11	
CSF1PO	12	10/12	10/12	
Amel	X	X/Y	X/Y	
VWA	14/18	14/18	14/18	
D8S1179	11/13	11/14	11/14	
TPOX	8/11	8/11	8/11	
FGA	21/22	21/23	21/23	
D6S1043	12/18	14/18	14/18	
D12S391	18/21	19/22	19/22	
D10S1248	13/15	13/15	13/15	
Penta D	10/14	9/10	9/10/14	MC

Detection conclusion: After transplantation, the donor cells accounted for 99.56% of the patients, showing complete chimerism.
Note: Complete chimerism (CC): Donor Chimerism (DC) ≥ 95%; Mixed Chimerism (MC): 5% ≤ DC<95%; Microchimeric state, DC <5%

pretreatment combining G-CSF with low-dose Decitabine to enhance effectiveness. Furthermore, Decitabine can modulate donor stem cells, activate cytotoxic CD8+ T cells, and dissolve tumor cells to enhance the Graft-Versus-Leukemia (GVL) effect. Additionally, we carefully administered anti-rejection drugs before and after the transplant, and continued targeted maintenance therapy with Gilteritinib post-procedure. The patient is currently five months post-allo-HSCT, with consistently negative MRD.

In conclusion, for patients with refractory/relapsed AML harboring FLT3-ITD mutations combination with CBL mutations, timely initiation of remission induction therapy followed by prompt and proactive HSCT can significantly improve patient outcomes. By actively managing associated complications and seizing the critical window of relative disease stability, clinicians have a pivotal opportunity to offer patients the chance for HSCT. This juncture represents one of the crucial focal points that clinical physicians should attentively monitor and remain vigilant about.

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