Clonal Evolution of Acute Myeloid Leukemia with *CEBPA* Double Mutations after Long-Term Remission: Case Report and a Literature Review

Uzun Süreli Remisyon sonrası *CEBPA* Çift Mutasyonu ile Akut Myeloid Löseminin Klonal Evolüsyonu: Olgu Sunumu ve Bir Literatür Derlemesi

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To the Editor,

Mutations in the *CEBPA* gene occur in 7%-15% of all acute myeloid leukemia (AML) patients [1,2]. However, we found that the frequency of such mutation may be high in Chinese AML patients [3,4]. Although AML with *CEBPA* double mutations *(CEBPA^{dm})* indicates a favorable outcome, recent data show that more than 50% of patients finally relapsed when consolidated with chemotherapy alone [5]. Clonal evolution (CE) is an important factor for relapse [6]. However, studies discussing CE in AML patients with *CEBPA^{dm}* are limited [7,8]. Here, we report CE in two patients with *CEBPA^{dm}* determined by sensitive next-generation sequencing (NGS).

Two female AML patients were diagnosed in our hospital in January 2012 and September 2013. Standard '3+7' induction chemotherapy was administered. Both of them achieved CR after induction therapy. Patient 1 received consolidation therapy with one course of DA (daunorubicin + cytarabine), four courses of high-dose cytarabine (HD-Ara-C), and one course of DA. Patient 2 received consolidation therapy with three courses of HD-Ara-C and two courses of immunotherapy. After long-term remissions (63 and 40 months), they both relapsed. Cytogenetic and fusion gene analyses indicated no difference from diagnosis. NGS analysis indicated altered mutations sites of the *CEBPA* gene in Patient 2 (Figure 1). New co-occurring mutations emerged at relapse: *SETD2* mutation in Patient 1 and *WT1* mutation in Patient 2 (Table 1). After relapse, Patient 1 achieved CR with a DA regimen and Patient 2 refused treatment.

The first report for CE in patients with *CEBPA^{dm}* included two patients [7]. In the first patient, the amino-terminal frame-shift mutation was duplicated and found on both alleles at relapse. In the second patient, the amino-terminal frame-shift

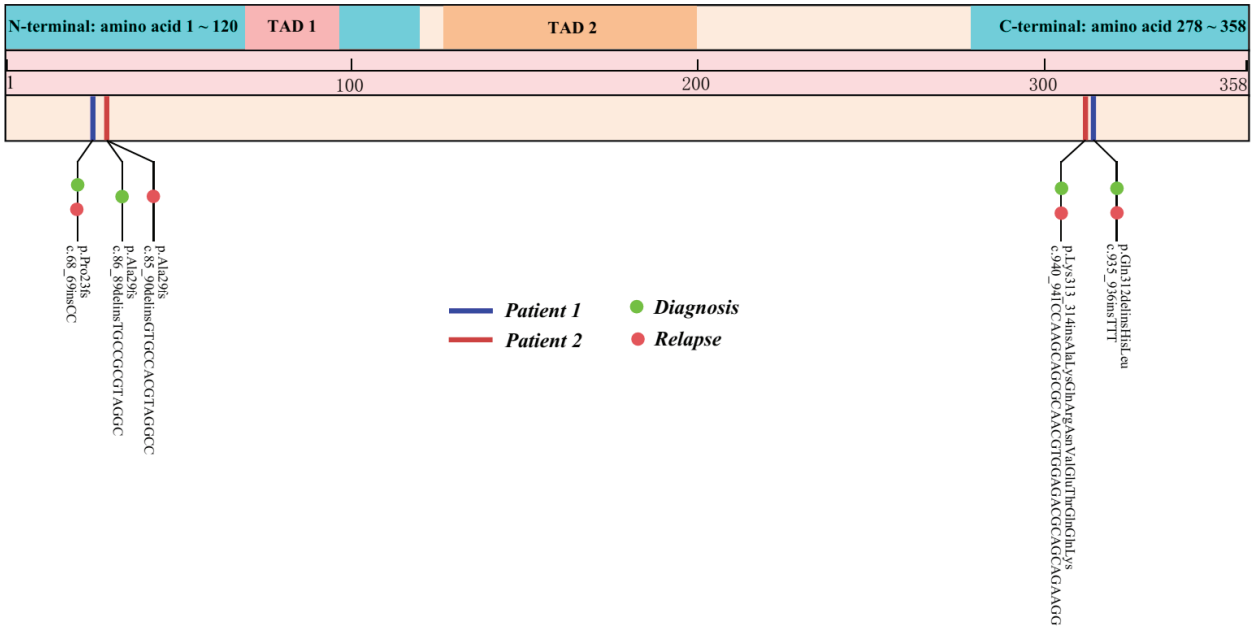

Figure 1. *CEBPA* gene mutations of these two patients at diagnosis and relapse.

Table 1. *CEBPA* and co-occurring mutations at diagnosis and relapse.

	Diagnosis		Relapse		
	Patient 1	Patient 2	Patient 1	Patient 2	
CEBPA mutations					
Nucleotide change	68_69insCC	86_89delinsTGCCGCGTAGGC	68_69insCC	85_90delinsGTGCCACGTAGGCC	
	940_941insCCA AGCAGCGCAA CGTGGAGACG CAGCAGAAGG	935_936insTTT	940_941insCCA AGCAGCGCAA CGTGGAGACG CAGCAGAAGG	935_936insTTT	-
Amino acid change	Pro23fs	Ala29fs	P23fs	Ala29fs	-
	Lys313_Val314insAla LysGlnArgAsnValGlu ThrGlnGlnLys	Gln312delinsHisLeu	Lys313_Val314insAla LysGlnArgAsnValGlu ThrGlnGlnLys	Gln312delinsHisLeu	-
Co-occurring mutations	No	*GATA2*	*SETD2*	*GATA2*	*WT1*
Nucleotide change	-	949A>C	4715C>A	949A>C	1142dupC
	-	953C>T	-	953C>T	
Amino acid change	-	Asn317His	Ser1572X	Asn317His	Ser381fs
	-	Ala318Val	-	Ala318Val	

mutation and a mutation in the fork region were found either alone or combined on the same allele, suggesting a subclone formation [7]. Another study reported CE in 22 patients; two of them lost mutations and none acquired new mutation at relapse [8]. Twenty patients harboring *CEBPA* mutations relapsed with identical mutation patterns; three of them had a second relapse that also exhibited the same patterns as their initial diagnosis and first relapse [8]. Two patients had concomitant *FLT3*-ITD mutations at diagnosis and one was lost at relapse. Two patients acquired *FLT3*-TKD mutations at relapse. N-RAS mutations were detected in three patients at diagnosis and two of them retained the identical mutation at relapse [8]. In this case report, we found mutation site alteration in the *CEBPA* gene and two newly emerged co-occurring mutations.

CE of patients with $CEBPA^{dm}$ can be summarized as follows: 1) allele alteration of *CEBPA* gene: acquire or lose mutation site in allele; 2) mutation site alteration in *CEBPA* gene: acquire or lose mutation site in *CEBPA* gene other than allele; 3) co-occurring mutation alteration: acquire or lose co-occurring mutation. One issue that needs to be resolved is the relationship between time and CE after CR. In this case report, these two patients relapsed after long-term remissions, and new co-occurring mutations emerged in both of them. Hence, whether late relapse is associated with new co-occurring mutations is unknown.

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Keywords: Acute myeloid leukemia, *CEBPA* mutations, Next-generation sequencing, Clonal evolution, Relapse

Anahtar Sözcükler: Akut myeloid lösemi, *CEBPA* mutasyonu, Yeni nesil dizileme, Klonal evolüsyon, Relaps

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Progressive Hepatic Cirrhosis Early After Allogeneic Hematopoietic Stem Cell Transplantation in a Patient with Chronic Hepatitis C Infection

Kronik Hepatit C Enfeksiyonu Olan Hastada Allojenik Kök Hücre Nakli Sonrası Erken Dönemde Progresif Karaciğer Sirozu

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To the Editor,

Hepatitis C virus (HCV)-infected allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients have a higher incidence of liver cirrhosis over long-term follow-up compared to recipients without HCV infection [1,2]. However, liver dysfunction related to HCV is usually mild in the first 3 months after allo-HSCT [3]. We present the progressive hepatic cirrhosis soon after allo-HSCT in an HCV-infected recipient. The clinical and histopathological features were very similar to fibrosing cholestatic hepatitis (FCH) caused by HCV reactivation.

A 50-year-old woman with myelodysplastic syndrome with excess blasts-1 was admitted to undergo allo-HSCT. The patient had a history of hepatitis C positivity (genotype 2a) for more than 20 years. Liver enzyme levels at admission were slightly elevated (aspartate aminotransferase 57 U/L, alanine aminotransferase 61 U/L, alkaline phosphatase 434 U/L, cholinesterase 115 U/L, total bilirubin (T-Bil) 1.2 mg/dL, and hepatitis C viral load $2.5x10^4$ IU/mL). The serological tests for hepatitis B virus (HBV) and polymerase chain reaction for HBV-DNA were negative. Computed tomography (CT) demonstrated hepatosplenomegaly. Abdominal ultrasonography (US) showed coarse hepatic echostructure over the entire liver with a dull edge, smooth surface, and straight hepatic vein without ascites or any signs of portal hypertension. Liver biopsy was not performed because of thrombocytopenia.

Just before transplantation, no risk factors except for the mild hepatic dysfunction and age were found, the hematopoietic cell transplantation-comorbidity index (HCT-CI) was 1, and the age-adjusted HCT-CI score was 2 [4,5]. Meanwhile, bone marrow examination revealed active disease with 6.7% myeloblasts. Considering the situation, the patient underwent peripheral blood stem cell transplantation from her human leukocyte antigen-identical sibling after myeloablative conditioning with cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy). Considering drug-induced liver dysfunction, we avoided the use of busulfan. Cyclosporine and short-term methotrexate were used for graft-versus-host disease (GVHD) prophylaxis. After neutrophil engraftment, T-Bil was elevated up to 8.3 mg/dL and hepatitis C viral load was noted to have increased to $4.0x10^6$ IU/mL on day 36 after allo-HSCT. Methylprednisolone was started at 1 mg/kg/day on day 36 for acute GVHD, with gradual improvement in liver test results. We performed deliberate observation of the patient with weekly US and monthly CT