Case Report

JAK2 V617F Mutation and t(8;21) Positive Acute Myeloid Leukemia After Renal Transplantation

Böbrek Nakli Sonrası JAK2 V617F Mutasyonu ve t(8;21) Pozitif Akut Miyeloid Lösemi

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ABSTRACT

There is an increased risk of malignancy after solid organ transplantation. Acute myeloid leukemia is one of these malignancies. The translocation (8;21) is one of the most frequent karyotypic abnormalities in acute myeloid leukemia. The JAK2 V617F mutation is rarely seen in cases of de novo acute myeloid leukemia. There is no case with translocation (8;21) and JAK2 V617F mutation-positive acute myeloid leukemia after kidney transplantation in the literature. We report a 43 years old female patient who had a kidney transplant from her brother 10 years ago applied to our clinic with the complaint of fatigue. The JAK2 V617 mutation and translocation t(8;21) positive acute myeloid leukemia was detected in this patient. The patient received 3+7 remission induction treatments. After chemotherapy, translocation (8,21) and JAK2 V617F mutation were negative. Acute myeloid leukemia cases developing after kidney transplantation should be evaluated in terms of JAK2V617F mutation positivity.

Keywords: JAK2 V617F mutation, translocation (8;21), renal transplantation

ÖZET

Solid organ transplantasyonundan sonra malignite riski artar. Akut miyeloid lösemi bu malignitelerden biridir. Translokasyon (8;21), akut miyeloid lösemide en sık görülen karyotipik anormalliklerden biridir. JAK2 V617F mutasyonu, de novo akut miyeloid lösemi vakalarında nadiren görülür. Literatürde böbrek nakli sonrası translokasyon (8;21) ve JAK2 V617F mutasyon pozitif akut miyeloid lösemi gelişen bir olgu yoktur. 10 yıl önce kardeşinden böbrek nakli olan 43 yaşında halsizlik şikayeti ile kliniğimize başvuran kadın hastayı sunduk. Bu hastada JAK2 V617 mutasyonu ve translokasyon t(8;21) pozitif akut miyeloid lösemi tespit edildi. Hasta 3+7 remisyon indüksiyon tedavisi aldı. Kemoterapi sonrası translokasyon (8,21) ve JAK2 V617F mutasyonu negatifti. Böbrek nakli sonrası gelişen akut miyeloid lösemi olguları JAK2V617F mutasyon pozitifliği açısından değerlendirilmelidir.

Anahtar kelimeler: JAK2 V617F mutasyonu, translokasyon (8;21), böbrek nakli

Introduction

Acute myeloid leukemia (AML) constitutes approximately 80% of acute leukemia seen in the adult age group. Myelodysplastic syndrome, chronic myeloproliferative diseases, Down and Bloom syndrome, radiation exposure, smoking, benzene exposure, and chemotherapeutic agents are risk factors for the development of AML. Approximately 5-10% of de novo AML cases have t(8;21), and this mutation is associated with a more favorable prognosis. The Janus kinase 2 (JAK2) gene has cytoplasmic tyrosine kinase activity and is located on the

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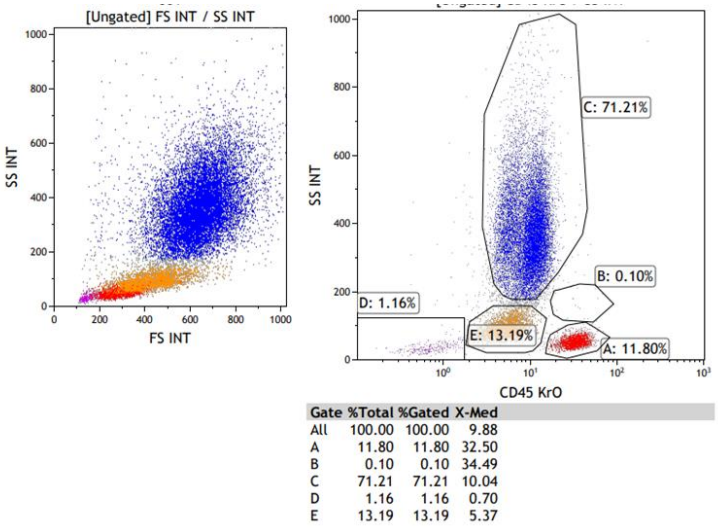

Figure 1. Flow cytometric (CD45) examination of bone marrow aspiration.

short arm of the 9th chromosome. JAK2 V617F mutation may also be positive in cases with AML developing secondary to chronic myeloproliferative disease or de novo AML. Its incidence in de novo AML cases is approximately 1% [1]. The JAK2 V617F mutation is detected in 3.5% of t(8;21) positive AML cases.

Overall survival in patients with chronic renal failure undergoing kidney transplantation is better than in patients undergoing chronic hemodialysis [2]. In particular, immuno-suppressive agents such as Tacrolimus and Mycophenolate Mofetil contribute to the improvement of the prognosis in these patients. It is thought that these agents increase the risk of cancer by disrupting the immune reaction against oncogenetic viruses and increasing cytokine levels [3]. AML accounts for approximately 43% of leukemias that develop after solid organ transplantation [4]. We present our case who developed t(8;21) and JAK2 V617 mutation-positive de novo AML after kidney transplantation, as she is the first case in the literature.

Case Report

A 43-year-old female patient was admitted to our hospital with the complaint of fatigue for 15 days. This complaint did not affect his daily work and increased with effort. The patient had chronic renal failure for 11 years and had a kidney transplant from her brother 10 years ago. She was using Mycophenolate Mofetil tablet (tb) 2x500 mg/day, Tacrolimus tb morning:1.5 mg evening:1 mg and Deltacortil tb 1x2.5mg/day.

During the physical examination of the patient, she was conscious, cooperative, oriented, and arterial blood pressure: 120/70 mmHg, heart rate: 80/minute, and body temperature: 36.5 °C. There were no abnormal findings were found except for the incision scar of the renal transplantation procedure. In the laboratory tests, hemoglobin: 7.1 g/dL, hematocrit: 23.3%, leukocyte: 27240/µL, platelet: 54000 /µL, lactate dehydrogenase (LDH): 439 U/L, kidney and liver function tests were normal. There was no abnormal finding in the complete urinalysis. Since blastic cells were seen in the peripheral smear of the patient, bone marrow aspiration was performed. Blast cell with extensive cytoplasm and prominent nucleolus (13%) was detected in bone marrow aspiration smear (Figure 1). Flow cytometric evaluation of bone marrow aspiration sample revealed cluster differentiation (CD) 13: 71%, CD 33:

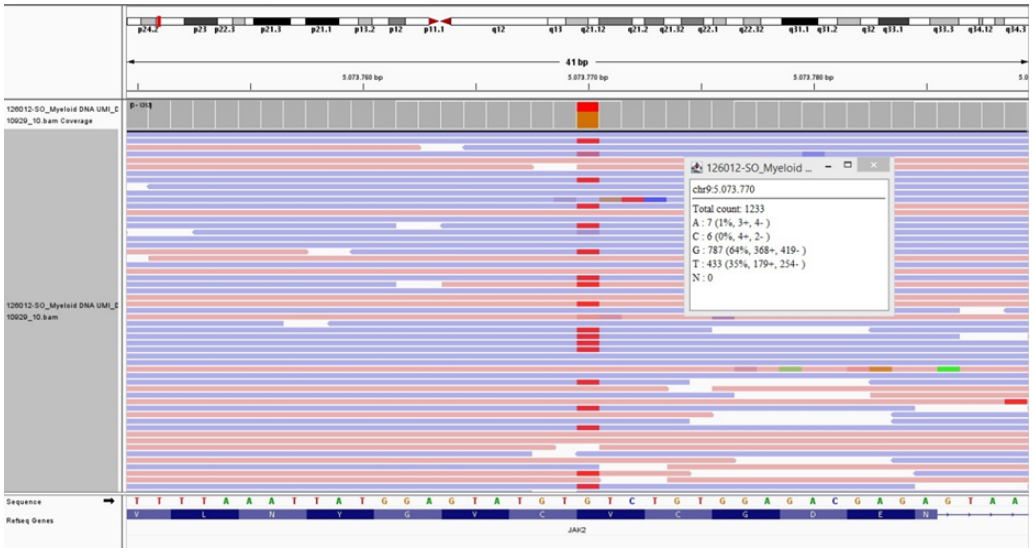

Figure 2. The visualization of JAK2 V617F mutation on IGV software

No.	C	Name	Type	Ct	Ct Comment	Given Conc (Cop	Calc Conc (Copie	% Var
1		our patient	Unknown	23,74			84.167	
3		NTC	NTC					
5		F2	Standard	34,30		100	105	4,8%
7		F4	Standard	23,77		100.000	82.784	17,2%
8		F5	Standard	19,61		1.000.000	1.152.233	15,2%

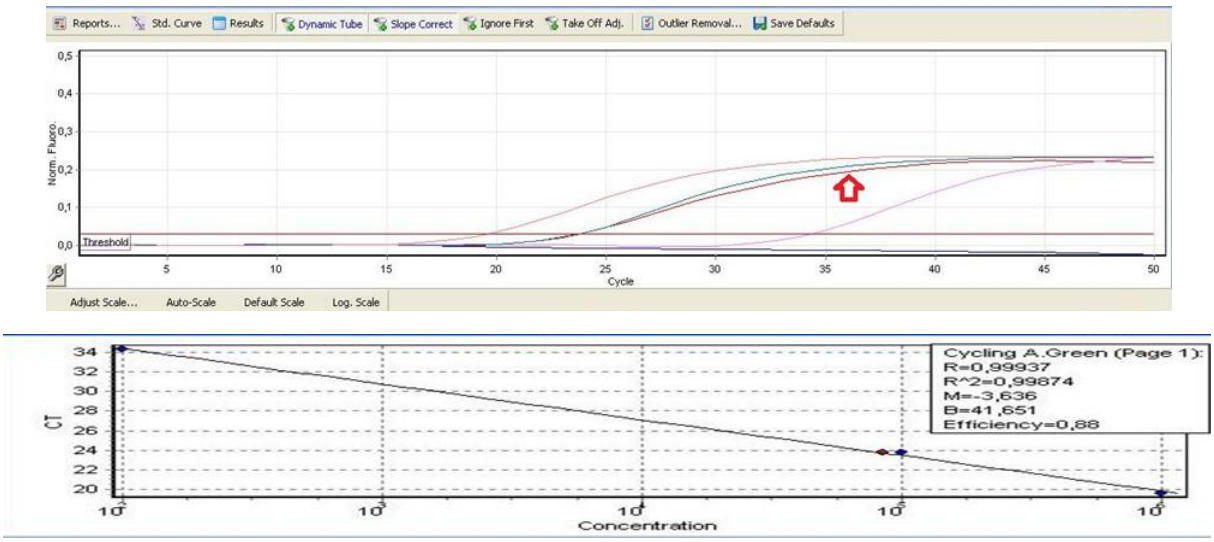

Figure 3. Amplification plots of t(8;21) on qPCR.

28%, myeloperoxidase: 78%, CD 19: 83% positive in the blast gate. The karyotype analysis was normal. JAK2 V617F mutation was detected by the next-generation sequencing method and t(8;21) was positive (5.37%) by the Polymerase Chain Reaction method (Figure 2 and 3, respectively). The blood tacrolimus level was 5.34 ng/ml. Mycophenolate Mofetil and Deltacortil treatment, which the patient was using due to a history of renal transplantation, was discontinued after consultation with the nephrology clinic. Tacrolimus treatment had been arranged according to the blood level of the drug. The patient received 3+7 remission induction treatments (Cytosine Arabinoside 100 mgx2/m^2/day and Doxorubicin 45mg/m^2/day). Tacrolimus treatment was

discontinued when the patient developed neutropenia. The patient's creatinine value was always within the normal range during follow-up. The patient's hemogram parameters and LDH value returned to normal range in the follow-up.

Discussion

Hall et al. reported that the incidence of cancer in solid organ transplant recipients increased between 2000 and 2008 compared to the incidence of cancer between 1987-1999 [5]. The increase in cancer incidence may be related to the prolongation of the life span of transplant patients and the immunosuppressive therapy. Our patient was receiving Tacrolimus, Mycophenolate Mofetil, and Dexamethasone as immunosuppressive therapy. Rashidi et al. reported that 72% of patients who developed AML after solid organ transplantation were male and their median age was 50 years [6]. Our case was female and her age was compatible with the literature.

Rashidi et al reported 51 patients who developed AML after solid organ transplantation[6]. Twenty-three of these patients were kidney transplant recipients, 20 were liver transplant recipients, six were heart transplant recipients, and two were lung transplant recipients. The median time between organ transplant and development of AML was 3.8 years, and more than 70% of cases developed AML within the first 5 years after transplant. The median time between kidney transplant and development of AML was 4.7 years, and more than 70% of these cases developed AML within the first 5 years after kidney transplant. In our case, AML did not develop in the first 5 years after kidney transplantation.

Cardarelli et al. reported a 33-year-old man who developed AML 9 years after kidney transplantation. In this patient, page kidney developed after 3-7 remission induction treatments [7]. Our patient did not develop any renal complications after 3-7 remission induction treatments. Scherrer et al. determined a case with t(9;11) positive AML after kidney transplantation [8]. In our case, t(8;21) was positive.

JAK2 V617 mutation has an important role in the diagnosis of chronic myeloproliferative diseases. But some studies reported that this mutation may be present in de novo AML cases. Steensma et al. analyzed 162 AML patients and found JAK2 V617F mutations in 13 patients [9]. Three of these patients had de novo AML. Döhner et al. examined 61 patients with AML who were positive for t(8;21) and found a JAK2 V617F mutation in 4 (6%) patients [10]. The positivity of JAK2 V617F mutation has negative effects on prognosis in AML cases with t(8,21) and t(16,16) or inv 16 [1]. In our case, only remission induction therapy was given and the hemogram value returned to normal. In conclusion, we present our case who presented with the complaint of fatigue and developed AML after kidney transplantation.

There was no other patient with a diagnosis of de novo AML that included both t(8;21) and JAK2V617F mutations after kidney transplantation in the literature. More comprehensive studies on this subject will provide us with more detailed information about the malignancies developing in solid organ transplant patients in the future.

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