Tenofovir Disoproxil Fumarate as a Possible Agent of Drug-Induced Anemia in a Liver Transplant Patient

Karaciğer Nakilli Bir Hastada İlaç İlişkili Aneminin Muhtemel Sebebi Olarak Tenofovir Disoproksil Fumarat

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ABSTRACT

Tenofovir disoproxil fumarate is an antiviral agent with high potency and low side effect profile. It is also used for the prevention of recurrence in patients undergoing liver transplantation due to liver cirrhosis secondary to hepatitis B. In this article, we report a patient with liver transplantation who had been treated with adefovir for hepatitis B prophylaxis and whose treatment was changed to tenofovir disoproxil fumarate, and was then thought to develop drug-induced hemolytic anemia.

Keywords: Tenofovir disoproxil fumarate, Anemia, Chronic hepatitis B, Liver transplantation

ÖZ

Tenofovir disoproxil fumarat kronik hepatit B tedavisinde kullanılan etki gücü yüksek yan etki potansiyeli düşük bir antiviral ajandır. Hepatit B'ye bağlı karaciğer sirozu nedeniyle karaciğer nakli yapılan hastalarda nakil sonrası rekürrensin önlenmesi amacıyla da kullanılmaktadır. Bu yazıda hepatit B proflaksisi için adefovir kullanmaktayken tedavisi tenofovir disoproksil fumarata değiştirilen ve sonrasında ilaç ilişkili hemolitik anemi geliştiği düşünülen karaciğer nakilli bir hasta bildirilmiştir.

Anahtar Sözcükler: Tenofovir disoproksil fumarat, Anemi, Kronik hepatit B, Karaciğer nakli

INTRODUCTION

Liver cirrhosis secondary to chronic hepatitis B infection is one of the most common indications for liver transplantation. Antiviral treatment is recommended in the post-transplant period to avoid recurrence of hepatitis B infection (1). Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are potent antiviral drugs used for prevention of recurrent hepatitis B infection in liver transplant patients. We will report a liver transplant patient with probable drug-induced hemolytic anemia after adefovir therapy was changed to TDF therapy for hepatitis B prophylaxis.

CASE PRESENTATION

An otherwise healthy 49-year-old female liver transplant patient was admitted to the liver transplantation outpatient clinic for routine follow-up. She had undergone liver transplantation surgery in 2009, due to cirrhosis secondary to chronic hepatitis B infection. She did not have any major post-transplantation complication, and her history revealed intermittent iron-preparation use for iron deficiency anemia in the post-transplant period. Her physical examination was normal, with no specific pathological findings. Her medications were tacrolimus and adefovir dipivoxil. Laboratory test results were as follows: ALT: 14 U/L, AST: 21 U/L, GGT: 11 U/L, ALP: 65 U/L, total bilirubin: 0.61 mg/dl, direct bilirubin: 0.21 mg/dl, hemoglobin 10 g/dL, MCV: 101 fL, WBC: 5.650/mm^3,

platelets: 182.000/mm³, vitamin b12: 531 pg/ml, serum iron 64.6 (50-170), total iron binding capacity: 338 ug/dL (250-425) ferritin: 17.8 ng/mL (13-150), and tacrolimus level: 6.1 ng/ml. The patient had a history of intolerance to oral iron preparations, and intravenous iron replacement was planned. Hepatitis B prophylaxis was changed from adefovir to TDF for more potent antiviral effect and fewer possible side effects of long-term antiviral usage.

Two months after this routine follow-up meeting, the patient presented to the emergency department with palpitations, dyspnea, and exhaustion. Systemic review was negative for hematuria, hypermenorrhea, hematemesis, hematochesia, or melena. She did not have fever and the physical examination was normal except for paleness, breathlessness, and sinus tachycardia. Laboratory tests were performed and results revealed a severe anemia with a hemoglobin level of 5 g/dl. Other test results were as follows: MCV: 110 fL, WBC: 5.130/ mm³, Thrombocytes: 156.000/mm³, ALT: 19 U/L, AST: 26 U/L, GGT: 6 U/L, ALP: 54 U/L, total bilirubin: 1.66 mg/dl, direct bilirubin: 0.21 mg/dl, LDH: 202 U/L, and tacrolimus level 4.5 ng/ml (5-20). The patient was hospitalized for further evaluation and treatment. Additional laboratory tests were performed and provided the following results: Serum iron: 99 (50-170), total iron binding capacity: 270 (250-425), ferritin: 426 (13-150), folic acid: 10.7 (5.3-24), vitamin B12: 471 (211-911), LDH: 202 (120-246), Haptoglobin: 29.8 (30-200), reticulocyte count: 9.04% (0.5-1.51), corrected reticulocyte count: 5%, indirect and direct Coombs tests: both negative, total bilirubin: 2.82 mg/dl, and indirect bilirubin: 1.8 mg/dl. Toxoplasmosis IgM, CMV IgM, Parvovirus IgM, and EBV VCA IgM were negative. Upper and lower gastrointestinal endoscopy were performed and neither revealed any potential source for blood loss. The patient was consulted with the Haemotology department. The blood smear was polychromatic but there were no spherocytes or schistocytes. Bone marrow aspiration and biopsy were performed and a normocellular bone marrow with hyperplasia in the megakaryocytic lineage was reported. TDF treatment was changed to ETV, as TDF was the only agent that was changed in the previous outpatient evaluation. The patient was discharged after intermittent erythrocyte transfusion, with a hemoglobin level of 8.9 g/dl on the day of discharge. After weekly follow-up at the outpatient clinic, the hemoglobin level rose to 13.5 g/dl within 45 days, without further treatment or blood transfusion.

DISCUSSION

TDF and ETV are antiviral drugs with good potency and the drugs of choice for post-transplant prophylaxis in patients with chronic hepatitis B who have undergone liver transplantation (1, 2). TDF has been shown to be more effective than adefovir in the treatment of chronic hepatitis B infection (3). Adefovir treatment was changed to TDF in our patient to achieve higher antiviral potency.

In a recent study evaluating the adverse effects of oral antiviral hepatitis B drugs, TDF treatment was associated with visual impairment, nausea, asthenia, gait disturbance, weight loss, depression, muscular weakness, muscular pain, and psoriasis but anemia was not reported within the potential adverse effects (4). There are no reports in the literature showing a connection between TDF and drug-induced anemia. A study on patients with HIV infection using zidovudine, TDF, and stavudine was performed by Parkes-Ratanshi et al. Zidovudine treatment was associated with anemia but TDF and stavudine were reported to be safe in terms of drug-induced anemia (5).

In the current case, the anemia was thought to be caused by potential drug-induced hemolysis due to TDF. Normocellular bone marrow and increased reticulocyte counts are supportive to exclude drug-induced bone marrow suppression. Despite the lack of blood smear findings specific to hemolysis, the elevations of indirect bilirubin levels, increased reticulocyte count, and low haptoglobin levels are suggestive of a hemolytic process. Spontaneous rise of serum hemoglobin levels to a normal range after cessation of TDF is also a positive finding for drug-induced anemia.

In conclusion, anemia should be kept in mind in patients on TDF therapy. A study has shown that tenofovir trough concentrations are correlated with renal dysfunction (6). This method might be valuable in situations where a tenofovir-induced adverse drug effect is suspected.

Ethics Committee Approval: Since this study is a case report, ethics committee approval was not obtained.

Informed Consent: Informed constent was obtained from the patient.

Author Contributions: The authors contributed equally to the follow-up of the case, the literature review and the writing of the article.

Conflict of Interest: There is no conflict of interest between authors.

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