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A Case of Hepatitis B Reactivation with Acute Flare Three Months After Tenofovir Prophylaxis Withdrawal in a Allogenic Hematopoietic Stem Cell Transplantation Patient

Bir Allojenik Hematopoietik Kök Hücre Nakli Hastasında, Tenofovir Profilaksisinin Bırakılmasından Üç Ay Sonra Akut Alevlenme ile Hepatit B Reaktivasyon Olgusu

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ABSTRACT

Hepatitis B virus (HBV) infection is a major health problem worldwide. HBV reactivation is associated with high mortality rates in hematopoietic stem cell transplantation (HSCT) and, prophylactic antiviral treatment is suggested to prevent this phenomenon. However, the duration of antiviral treatment in HSCT patients is not fully defined and the time of immune recovery is considered the best parameter for a drug to be safely interrupted. We aimed to present a case of hepatitis B reactivation after cessation of one-year prophylactic tenofovir treatment in a anti-hepatitis B core immunoglobulin G-positive patient who received allogenic HSCT treatment for chronic lymphocytic leukemia.
Keywords: Hepatitis B reactivation, tenofovir, hematopoietic stem cell transplantation

ÖZ

Hepatit B virüs (HBV) enfeksiyonu dünya çapında önemli bir sağlık sorunudur. Hematopoietik kök hücre transplantasyonunda (HSCT) HBV reaktivasyonu yüksek mortalite oranları ile ilişkilidir ve bu durumun önlenmesi için profilaktik antiviral tedavi önerilmektedir. Bununla birlikte, HSCT hastalarında verilecek antiviral tedavinin süresi tam olarak tanımlanmamıştır ve antiviral tedavinin sonlandırılmasında bağışıklık kazanım zamanı en güvenilir parametre olarak kabul edilmektedir. Biz burada, kronik lenfositik lösemi tanısıyla allojenik HSCT tedavisi uygulanan anti-hepatit B core immünoglobulin G pozitif bir hastada transplant sonrası verilen bir yıl profilaktik tenofovir tedavisinin kesilmesi sonrasında ortaya çıkan bir hepatit B reaktivasyonu olgusunu sunmayı amaçladık.
Anahtar Kelimeler: Hepatit B reaktivasyonu, tenofovir, hematopoietik kök hücre transplantasyonu

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Introduction

The natural course of hepatitis B virus (HBV) infection is determined through the interaction between viral replication and the host immune response. HBV reactivation is defined as elevation of the viral DNA level or alteration of the hepatitis B surface antigen (HBsAg) seroconversion status. In HBsAg carriers, it is characterised by either increase in HBV DNA level by >1 log (10 fold) or HBV DNA turning positive. Other than this, in HBsAg- and antibody to hepatitis B core antigen (anti-HBc)+ patients, reverse seroconversion of HBsAg from negative to positive is defined as reactivation (reappearance of HBsAg with or without increased liver enzymes) (1,2). Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are considered high risk for HBV reactivation (3), with a mortality rate of up to 40%. Third-generation antiviral drugs (entecavir or tenofovir) are recommended for patients with HBsAg or anti-HBc immunoglobulin (Ig) G-positive haematologic patients regardless of

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HBV DNA levels (4,5). Antiviral therapy initiated simultaneously with or prior to immunosuppressive therapy can reduce the risk of HBV reactivation. Many studies have evaluated the efficacy of prophylactic therapy (6,7); however, the duration of antiviral treatment in HSCT patients is not fully defined. We aimed to present a case of hepatitis B reactivation after cessation of one-year prophylactic tenofovir treatment in an anti-HBc IgG-positive patient who received allogenic HSCT treatment for chronic lymphocytic leukemia.

Case

A 64-year-old male patient was admitted to our clinic with the complaints of fatigue, nausea, vomiting, and jaundice. His complaints began 3 days ago and gradually increased. Anti-HBc IgG positivity was detected 16 months ago with the screening tests performed before the immunosuppressive treatment. The patient was treated with 2 cycles of rituximab and then allogenic HSCT was performed for chronic lymphocytic leukemia. He was administered cyclosporin 5 mg/kg for six months after HSCT, then the dose was reduced and stopped at the end of the one-year treatment. During the rituximab period, he was administered prophylactic tenofovir 245 mg/day and for one year following HSCT treatment. Tenofovir treatment was stopped three months ago (one year after HSCT). He did not have any chronic diseases and there was no any liver disease in his family history. On physical examination, his sclera and the skin were icteric. His laboratory findings were as follows: alanine aminotransferase (ALT): 1365 U/L, aspartate aminotransferase (AST): 1066 U/L, alkaline phosphatase (ALP): 276 U/L, gamma-glutamyl transferase (GGT): 108 U/L, total biluribin: 18.44 mg/dL, direct biluribin: 9.46 mg/dL, international normalized ratio (INR): 1.40, albumin: 4.1 g/dL, white blood cell count: 5.690/uL, hemoglobin level: 15 g/dL, and platelet count: 67.000/uL. Alpha feto-protein level was not measured. The kidney function tests and electrolyte levels were normal. HBsAg, anti-HBc IgM, anti-HBc IgG, and anti- hepatitis B e (HBe) were found to be positive whereas HBe antigen (HBeAg) and delta antigen were found negative. HBV DNA level was 486.336.116 IU/mL. Other serological markers of viral infection (such as Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A, C, and E viruses) were all negative. Abdominal ultrasonography showed normal liver.

When the patient's tests performed prior to tenofovir withdrawal were investigated, it was seen that anti-HBc IgG was positive and HBsAg was negative. Liver function tests were normal when he received chemotherapy and one year post-HSCT. The treatment of tenofovir 245 mg was started again with the diagnosis of hepatitis B reactivation. After 2 months of tenofovir treatment his laboratory findings were found to be: ALT: 48 U/L, AST: 76 U/L, ALP: 230 U/L, GGT: 305 U/L, total bilirubin: 4.19 mg/dL, direct bilirubin: 1.60 mg/dL, INR: 1.12, albumin: 3.2 g/dL, and HBV DNA 17.932 IU/mL (Table 1).

Informed consent for publication was obtained from the patient.

Table 1. Laboratory findings

	Before HSCT	Before tenofovir cessation	3 months after tenofovir cessation, acute HBV flare	After 2 months of tenofovir treatment
ALT U/L	26	30	1365	48
AST U/L	30	18	1066	76
Total biluribin mg/dL	0.45	0.86	18.44	4.19
INR	1	0.98	1.40	1.21
HBsAg	-	-	+	+
Anti-HBc IgG	+	+	+	+
Anti-HBs	-	-	-	-
HBe Ag	-	-	-	-
Anti-HBe	+	+	+	+
Anti-HBc IgM	-		+	
HBV DNA IU/mL	-	-	486.336.116	17.932

HSCT: Hematopoietic stem cell transplantation, HBV: Hepatitis B virus, ALT: Alanine aminotransaminase, AST: Aspartate aminotransferase, INR: International normalized ratio, HBsAg: Hepatitis B surface antigen, HBc: Hepatitis B core antigen, IgG: Immunoglobulin G, HBs: Hepatitis B surface, HBe: Hepatitis B e, IgM: Immunoglobulin M

Discussion

Patients with malignancy, autoimmune diseases or HSCT with serologic evidence of HBV infection (HBsAg or anti-HBc IgG-positive) are at risk for HBV reactivation if they receive immunosuppressive therapy. Reactivation of HBV infection in the setting of chemotherapy and immunosuppression is associated with significant morbidity and mortality (8).

Hepatitis B reactivation appears to correlate with the level of immunosuppressive potency of the chemotherapy administered as well as with the use of concomitant steroids (9). The rate of HBV reactivation has been reported to be as high as 70% among HBsAg-positive individuals receiving HSCT or anti CD20 treatment (2). The risk of HBV reactivation depends on many factors including the virological and serological status of the infected patient, immunosuppressive potency of the therapy received, underlying disease, male sex, younger age, HBsAg, HBeAg and/or HBV DNA positivity at the baseline (10). HBsAg-positive patients are more likely to experience HBV reactivation than HBsAg-negative and anti-HBc-positive patients (11). Although the risk is lower, isolated anti-Hbc-positive patients still carry a definite risk of reactivation (12). However, there is limited evidence that the presence of anti-HBs is protective against HBV reactivation. An earlier study on 29 lymphoma patients reported no HBV reactivation in any of the patients (0/10) whose anti-HBs titer was higher than 100 IU/mL and low anti-HBs titer was independently associated with HBV reactivation (13). In patients receiving HSCT, anti-HBs titer of the donor was associated with a reduction in HBV reactivation risk. These findings have not yet been confirmed (14). Severe hepatitis can develop in up to 30-50 percent of patients with HBV reactivation (2,15), therefore, antiviral therapy should be initiated in these patients.

According to the American Gastroenterological Association guidelines, high-risk patients should be treated with prophylactic antiviral therapy prior to or concurrently with the immunosuppressive treatment. Moderate-risk patients can be

treated with antiviral prophylaxis or monitored closely (16). Antiviral prophylaxis is not recommended for low-risk patients and there are no recommendations about monitoring in untreated patients. The European Association for the Study of the Liver (EASL) recommends antiviral prophylaxis for HBsAg-positive patients and for HBsAg-negative/anti-HBc-positive patients receiving rituximab, bone marrow or stem cell transplantation (17). Regarding HBsAg-positive patients, most treatment guidelines such as the American Association for the Study of Liver Diseases (initiation of antivirals at the onset of immunosupression), and the Asian Pacific Association for the Study of the Liver guidelines (initiation of antivirals one week prior to chemotherapy) recommend prophylactic treatment (18,19).

Seto et al. (20) published a prospective study investigating the course of 62 HBsAg-negative, anti-HBc-positive HSCT recipients. The 2-year cumulative HBV DNA detectability rate was 40.8%, occurring at a median of 44 weeks, and entecavir successfully suppressed HBV DNA to undetectable levels, with no cases developing biochemical hepatitis.

Entecavir or tenofovir can be used in the treatment of HBV reactivation (21). The success rate of early antiviral therapy is high in patients with acute flare (22). The EASL recommends ALT and HBV DNA testing every 1-3 months during monitoring and treatment upon any evidence of HBV reactivation (23).

Patients with positive HBV serologic markers receiving immunosuppressive therapy or HSCT are at high risk for reactivation. As seen in our case, 12 months of prophylaxis treatment may not be sufficient for patients undergoing allogeneic HSCT. Current guidelines recommend that the duration of prophylaxis after HSCT and high-risk immunosuppressive therapy should be 12-18 months (24). However, the risk of HBV reactivation in HSCT can persist for several years after transplantation due to the long delays in the immune reconstitution.

Ethics

Informed Consent: Informed consent for publication was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.T., A.T.E., M.A., Design: B.T., F.G.A., Data Collection or Processing: B.T., A.T.E., F.G.A., M.A., A.Ş.K., Analysis or Interpretation: B.T., A.T.E., A.Ş.K., Literature Search: B.T., A.T.E., F.G.A., Writing: Bilal Toka, A.T.E., F.G.A., M.A., A.Ş.K.

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