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Hepatitis B Virus Belated Reverse Sero-conversion After Hematopoietic Stem Cell Transplantation or Rituximab Chemotherapy

Geç Dönem Hematopoietik Kök Hücre Transplantasyonu ve Rituksimab Kemoterapisi Sonrasında Hepatit B Virüsü Ters Serokonversiyonu

Tuncer TEMEL[1], Nur OĞUZ[2], Şafak Meriç ÖZGENEL[1], Hava ÜSKÜDAR TEKE[3], Eren GÜNDÜZ[3], Ayşegül ÖZAKYOL[1]

[1] Division of Gatroenterology, Department of Internal Medicine, Faculty of Medicine, University of Eskisehir Osmangazi, Eskisehir, Turkey

[2] Department of Internal Medicine, Faculty of Medicine, University of Eskisehir Osmangazi, Eskisehir, Turkey

[3] Division of Hematology, Department of Internal Medicine, Faculty of Medicine, University of Eskisehir Osmangazi, Eskisehir, Turkey

SUMMARY

Recovery and immunity to hepatitis B virus (HBV) are marked by antibody to hepatitis B core antigen (anti-HBc) with or without antibody to hepatitis B surface antigen (anti-HBs) in the absence of hepatitis B surface antigen (HBsAg). In the profoundly immune compromised individual, HBV may reactivate even in the presence of serologic evidence of resolved infection. The loss of anti-HBs followed by reactivation with development of HBsAg is known as reverse sero-conversion. A 62-year-old female patient with the diagnosis of IgG type of multiple myeloma had received bortezomib-based chemotherapy, and autologous hematopoietic stem cell transplantation (HSCT) was performed thereafter. A 56-year-old male patient with the diagnosis of chronic lymphocytic leukemia had received 6 cures of rituximab-endoxan chemotherapy. Prior to chemotherapy, HBsAg was negative, anti-HBs positive, anti- HBc positive and HBV-DNA was negative in both patients. Approximately one year after chemotherapy, HBV reverse sero-conversion developed in both patients. Resolved HBV infection with undetectable HBV-DNA before chemotherapy or HSCT did not confer HBV reverse sero-conversion. Prior to the creation of regular follow-up or prophylaxis schemes of patients with resolved HBV infection, in whom immune suppressive and anti-cancer treatments or HSCT will be performed, close follow-up of patients for HBV reverse sero-conversion even in late stages after immune suppressive and anti-cancer treatments or HSCT seems beneficial, especially in regions with intermediate or high endemicity for HBV.

Key Words: *Hepatitis B virus; Reverse sero-conversion; Resolved infection; Hematopoietic stem cell transplantation; Rituximab*

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ÖZET

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[1] Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Gastroenteroloji Bilim Dalı, Eskişehir, Türkiye
[2] Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Eskişehir, Türkiye
[3] Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Hematoloji Bilim Dalı, Eskişehir, Türkiye

Hepatit B virüsü (HBV)'ne gelişen immünite ve iyileşme hepatit B yüzey antijeni (HBsAg) yokluğunda hepatit B core antijenine karşı gelişen antikor (anti-HBc) ve/veya hepatit B yüzey antijenine karşı gelişen antikor (anti-HBs) ile belirlenir. Ciddi immün kompromize bireylerde düzelmiş infeksiyonun serolojik kanıtları bulunsa dahi HBV reaktive olabilir. HBsAg gelişimiyle birlikte anti-HBs kaybı tersine serokonversiyon olarak bilinir. Altmış iki yaşında IgG tipi multipl miyelom tanılı kadın hastaya bortezomib bazlı kemoterapi verildi ve bundan sonra otolog hematopoietik kök hücre nakli (HKHN) yapıldı. Elli altı yaşında kronik lenfositik lösemi tanılı bir erkek hastaya altı kür rituksimab-siklofosfamid kemoterapisi verildi. Kemoterapiden önce her iki hastada HBsAg negatif, anti-HBs pozitif, anti-HBc pozitif, HBV-DNA negatifti. Kemoterapiden yaklaşık bir yıl sonra her iki hastada da HBV ters serokonversiyonu gelişti. Kemoterapi veya HKHN'den önce saptanamayan HBV-DNA düzeyleri ile birlikte iyileşmiş HBV infeksiyonu HBV ters serokonversiyonu olmayacağını göstermedi. Özellikle HBV için orta veya yüksek endemik olan bölgelerde, immünsüpresif ve antikanser tedavi veya HKHN uygulanacak hastalar için düzenli izlem ve profilaksi programlarının oluşturulması, immünsüpresif, antikanser veya HKHN tedavisinden sonra geç dönemde olsa bile hastaların HBV ters serokonvesiyonu için yakın takip edilmesi yararlı olacak gibi görünmektedir.

Anahtar Kelimeler: *Hepatit B virüsü; Ters serokonversiyon; İyileşmiş infeksiyon; Hematopoietik kök hücre nakli; Rituksimab*

INTRODUCTION

More than 2 billion people alive today have been infected with hepatitis B virus (HBV) at some time in their lives. Of these, about 350 million remain infected chronically and become carriers of the virus[1]. Chronic HBV infection is one of the most common viral infections, affecting an estimated 6% of the world population. Each year, an estimated one million persons die of complications of chronic HBV infection, including cirrhosis, end-stage liver disease, and hepato-cellular carcinoma[2]. According to World Health Organization (WHO) classification, Turkey is one of the countries with intermediate (2%-8%) endemicity for HBV[3]. Parallel with the growing incidence of auto immune and malignant diseases, there is a tendency in immune suppressive and anti-cancer treatments which might be challenging in patients with occult, inactive, active or resolved HBV infections, especially at intermediate and high endemic regions.

Recovery and immunity to HBV are marked by antibody to hepatitis B core antigen (anti-HBc) with or without antibody to hepatitis B surface antigen (anti-HBs) in the absence of hepatitis B surface antigen (HBsAg). The course and outcome of HBV infection is modulated by the host immune response, and the loss of immune surveillance can cause reactivation of viral replication and exacerbations of disease activity. In the profoundly immune compromised individual, HBV may reactivate even in the presence of serologic evidence of resolved infection. The loss of anti-HBs followed by reactivation with development of HBsAg is known as reverse sero-conversion[2].

Although HBsAg reverse sero-conversion was first reported in the early 1990s, incidence ranges from < 10% to around 20% up to approximately 90%. Patients who show isolated anti-HBc positivity carry a greater risk for HBsAg reverse sero-conversion and majority of the cases in the literature are patients with chronic occult HBV infection. HBsAg reverse sero-conversion in patients with resolved HBV infection is very rare in the literature as case presentations. The risk for HBsAg reverse sero-conversion in patients

with resolved HBV infection undergoing immune suppression remains controversial in the literature. Main risk factor for reverse sero-conversion seems to be the duration and severity of immune suppression. In addition, type of the immunosuppressive drugs and treatment regimens, underlying onco-hematological diseases, hematopoietic stem cell transplantation (HSCT) or graft versus host disease (GvHD) occurrence after HSCT may influence HBsAg sero-reversion[4].

We present two cases of HBsAg reverse sero-conversion in patients with resolved HBV infections, after HSCT and rituximab-endoxan based chemotherapy regiments.

CASE REPORTS

Case 1

A 62-year-old female patient, with the diagnosis of IgG type of multiple myeloma, had received bortezomib based chemotherapy regiments, and autologous HSCT was performed in November 2013. Prior to chemotherapy HSCT HBV serology was as follows: HBsAg negative, anti-HBs positive, anti-HBc positive and HBV deoxyribonucleic acid (DNA) negative. On routine controls, elevation at transaminase levels determined in November 2014 was as follows: aspartate transaminase (AST): 144 U/mL, alanine transaminase (ALT): 183 U/mL. HBV serology was as follows: HBsAg positive, anti-HBs negative and HBV-DNA level was 15.100.000 U/mL. Clinical or laboratory investigations for other causes of chronic liver diseases were negative. Necro-inflammatory activity grade was 7 and fibrosis stage was 2 at liver biopsy. After 12 weeks of tenofovir 1 x 245 mg treatment, transaminase levels were within normal range and -NA level was < 20 U/mL.

Case 2

A 56-year-old male patient, with the diagnosis of chronic lymphocytic leukemia (CLL), had received 6 cures of rituximab-endoxan chemotherapy in July 2012. Prior to chemotherapy HBV serology was as follows: HBsAg negative, anti-HBs positive, anti- HBc positive and HBV-DNA negative. On routine controls, elevation at transaminase levels determined in July 2014 was as follows: AST: 51 U/mL, ALT: 108 U/mL. HBV serology was as follows: HBsAg positive, anti-HBs negative and HBV-DNA level was 54.000.000 U/mL. Clinical or laboratory investigations for other causes of chronic liver diseases were negative. Necro-inflammatory activity grade was 8 and fibrosis stage was 2 at liver biopsy. After 12 weeks of entecavir 1 x 0.5 mg treatment, transaminase levels were within normal range and HBV-DNA level was < 20 U/mL.

DISCUSSION

Several mechanisms have been postulated to explain the phenomenon of reverse sero conversion: re-infection, low levels of HBV replication and the failure of immune surveillance [5].

In our patients, the possibility of re-infection can be eliminated by the abstinence of intra venous drug dependency, inappropriate sexual relationship, unsterile parenteral medical administrations or surgical procedures and infected blood or blood product transfusions. Probability of low level HBV replication can be eliminated by the negativity of HBV-DNA before chemotherapy regiments. Immune suppressive and anti-cancer treatments with B cell depleting agents in HBsAg negative/anti-HBc positive patients is defined as high risk condition with a reactivation risk of > 10%[6]. Pretreatment assessment of HBV-DNA levels is recommended for patients with elevated aminotransferase levels and a viral hepatitis serology resembling resolved HBV infection HBsAg negative, anti-HBs positive, anti-HBc positive[7]. HBV-DNA levels are determined in patients with resolved HBV infection and high risk conditions like treatment with B cell depleting agents or HSCT.

HBV penetrates through the hepatocyte via interaction of envelope proteins with cell receptors, and following penetration, HBV-DNA is released from the nucleocapsid with the help of the cellular enzymes in the cytoplasm, and thereafter, the viral DNA gets into the nucleus and forms a circular structure-covalently closed circular DNA (cccDNA) which is responsible for the formation of pre-genomic RNA and mRNAs

by transcription and crucial for viral replication[8]. In addition, viral DNA integrates to the host peripheral blood mononuclear cells (PBMC) at the acute stages of the infection[9]. Although sero-conversion of HBsAg to anti-HBs was considered as the eradication of HBV, recent data has shown that HBV-DNA remains latent in the liver and in the peripheral blood mononuclear cells after sero-conversion and resolved infection[9,10]. Serologic markers of resolved HBV infection and negativity of HBV-DNA before chemotherapy regiments thought us that the failure of immune surveillance is the mechanism of reverse sero-conversion in our patients.

Most relevant factors to trigger HBV reverse sero-conversion are HSCT and rituximab based chemotherapy regiments[11]. Apart from the human immunodeficiency virus infected individuals, almost all patients with HBV reverse sero-conversion in the literature have a previous history of HSCT or rituximab based chemotherapy regiments administration. Although follow-up and preemptive treatment recommendations for occult, inactive, and active HBV infections before immunosuppressive treatment or anti-cancer cytotoxic chemotherapy are present in European Association for the Study of the Liver (EASL) or American Association for the Study of Liver Disease (AASLD) practice guidelines, there is no recommendation on follow-up protocols or whether nucleoside analogues should be given in patients with resolved HBV infection. In the study by Huang et al., the only study in the literature with preemptive treatment to patients with resolved HBV infection, while no HBV reverse sero-conversion has developed in patients under entecavir prophylaxis, four patients at the control arm of the study have developed HBV reverse sero-conversion[12,13]. Another important issue in this study was that HBV reverse sero-conversion usually happened late after completion of chemotherapy and the risk of HBV reverse sero-conversion can last for 18 months after initiation of chemotherapy[14].

In conclusion, resolved HBV infection with undetectable HBV-DNA before chemotherapy or HSCT did not confer HBV reverse sero-conversion. Prior to creation of regular follow up or prophylaxis schemes of patients with resolved HBV infection, in whom immune suppressive and anti-cancer treatments or HSCT will be performed, close follow-up of patients for HBV reverse sero-conversion even in late stages after immune suppressive and anti-cancer treatments or HSCT seems beneficial, especially in regions with intermediate or high endemicity for HBV.

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Address for Correspondence/Yazışma Adresi

Uzm. Dr. Şafak Meriç ÖZGENEL

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi
İç Hastalıkları Anabilim Dalı
Gastroenteroloji Bilim Dalı
Eskişehir-Türkiye

E-posta: mozgenel@yahoo.com