Acute viral Hepatitis B infection after hematopoietic stem cell transplantation in a vaccine-immune patient

AVHB in an immunocompromised patient

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Abstract
Hematopoietic stem cell transplantation is an increasingly common treatment method for benign and malignant hematological diseases. However, infections before and after transplantation are the most important causes of morbidity and mortality, working against the developments in diagnosis and treatment. The regeneration of the immune system after stem cell transplantation spans a period of 12-18 months and the risk of bacterial, fungal, and viral infection development is highest in the first 1-2 years after transplantation. While hepatitis B virus (HBV) reactivation is well defined in patients receiving immunosuppressive therapy in the literature, cases of acute viral hepatitis B (AVHB) development during immunosuppressive therapy are limited. Therefore, we present a case of AVHB developing after immunosuppressive therapy in a patient who was immunized against the HBV vaccine.

Keywords
Hematopoietic Stem Cell Transplantation, Acute Viral Hepatitis B, Vaccination
Introduction
Hematopoietic stem cell transplantation (HSCT) is an increasingly common treatment method for benign and malignant hematological diseases. However, working against the developments in diagnosis and treatment, infections before and after transplantation are the most important causes of morbidity and mortality due to cytopenia, immunoablation, and immunosuppression [1]. The regeneration of the immune system after stem cell transplantation spans a period of 12-18 months and the risk of bacterial, fungal, and viral infections is highest in the first 1-2 years after transplantation. Late hepatic complications seen after HSCT are associated with drugs, chronic graft-versus-host disease, hepatitis B, hepatitis C, and increased iron burden [2].

Although the hepatitis B virus (HBV) and hepatitis C virus (HCV) frequently cause viral hepatitis in patients undergoing HSCT, the adenovirus, herpes simplex virus, varicella-zoster virus, echovirus, and cytomegalovirus are other relevant pathogens [3]. HBV reactivation may develop in patients undergoing systemic cytotoxic chemotherapy and solid organ or stem cell transplantation, as well as those who use immunosuppressive agents. It is thought that immunosuppressive therapies cause HBV reactivation, and as the immune system begins to be activated following the treatment, it may cause severe liver damage and failure or death in patients [4]. While HBV reactivation has been well defined in patients receiving immunosuppressive therapy in the literature, cases of development of acute viral hepatitis B (AVHB) during immunosuppressive therapy are limited [4]. Therefore, we present a case of AVHB that developed after immunosuppressive therapy in a patient who was immunized against the HBV vaccine.

Case Report
A 55-year-old female patient presented to the hematology outpatient clinic with complaints of weakness and dark urine color. She had undergone HSCT with the diagnosis of acute myeloid leukemia 7 months ago. Methylprednisolone, cyclosporine, tacrolimus, and mycophenolate mofetil were prescribed for the patient for immunosuppression after transplantation. System examinations were normal. In the laboratory, HBsAg positivity, anti-HBs negativity, anti-HBc IgM positivity, anti-HBc IgG positivity, HBeAg positivity, anti-HBe positivity, thrombocytes of 139,000 U/L, alanine aminotransferase (ALT) of 699 U/L, aspartate transaminase (AST) of 393 U/L, international normalized ratio of 1.07, alkaline phosphatase of 255 IU/mL, gamma-glutamyl transpeptidase of 288 IU/mL, total bilirubin of 0.49 mg/dL, and direct bilirubin of 0.22 mg/dL were observed. Hepatitis D and C co-infection was not detected. An abdominal ultrasound showed an increase in liver size and a decrease in parenchymal echogenicity. The patient, who was HBsAg-negative, anti-HBs-positive (20 IU/mL), and anti-HBC IgG-negative in an evaluation performed before the transplantation, had been vaccinated for HBV 3 years ago. Risk factors for AVHB infection were investigated, but no risk factors were detected except bone marrow transplantation and blood products given during this period. There was no history of tooth extraction, operation, or suspicious sexual contact. She was admitted to the infectious diseases service considering AVHB and oral treatment of tenofovir disoproxil fumarate at 1 × 245 mg/day was started. During follow-up, HBV DNA was detected at 106.437 IU/mL.

After the patient's clinical condition improved during follow-up, ALT of 206 U/L, AST of 60 U/L, and coagulation test results were within normal limits at the end of the seventh day. The patient was discharged and outpatient clinic control was recommended. At a control visit at the first week after discharge, ALT was 36 U/L and AST was 23 U/L. Tenofovir treatment was continued. At the end of the third month, at an outpatient clinic control visit, HBsAg negativity, anti-HBs negativity, anti-HBc IgM positivity, anti-HBc IgG positivity, HBeAg negativity, anti-HBe positivity, HBV DNA negativity, ALT of 27 U/L, and AST of 19 U/L were determined. At the end of the sixth month, the patient was found to be HBsAg-negative, anti-HBs-positive, and HBV DNA-negative with ALT of 20 U/L and AST of 18 U/L. Tenofovir treatment was discontinued at the end of the seventh month (Figure 1).

Discussion
Acute viral hepatitis is a systemic viral infectious disease with liver inflammation and necrosis. Viral hepatitis is an important health problem that is common in the world and in our country [5]. Around the world, approximately two billion people are infected with HBV, and it is estimated that approximately 248 million people develop chronic liver disease related to HBV [6]. In our country, the HBsAg positivity rate is between 2% and 7%, placing Turkey among the middle endemic countries in terms of HBV infection [5].

HBV infection is an important problem in patients undergoing HSCT. In particular, patients with HBsAg positivity and latent infection are at high risk for viral reactivation after transplantation. After myeloablative therapy and during immunosuppressive therapy, most recipients of HBV-infected HSCT show only slight elevations in transaminases due to suppression. The viral load in the liver gradually increases, possibly leading to severe hepatitis during immune reconstruction. Approximately 12% of patients treated with HBV-infected HSCT may have fulminant liver failure. Acute infection can also be acquired by transfusion of infected blood products [4]. Since our patient was HBsAg-negative and anti-HBc IgG-negative before HSCT, acute HBV infection developed, not HBV reactivation. Blood transfusion is a risk factor for our
patient in terms of AVHB, and we believe that HBV transmission was due to infected blood transfusion due to exposure to many blood product transfusions before and after HSCT. All chemotherapy and immunosuppressive therapy candidates should be screened for HBsAg, anti-HBs, and anti-HBc before immunosuppressive therapy. It is recommended to vaccinate HBV-seronegative patients. Anti-HBs positivity is seen in two-thirds of HBsAg-negative and anti-HBc IgG-positive patients. There was no significant difference between anti-HBs-positive and anti-HBs-negative groups in terms of HBV reactivation and it is therefore not recommended to make inferences regarding reduction of or protection against the risk of reactivation based on anti-HBs positivity or titers [7]. After intensive chemotherapy treatments, the anti-HBs antibody titer may decrease due to the destruction of antibodies producing B lymphocytes after chemotherapy. In a previous study, it was found that in nine patients with hematological malignancies, HBsAg and anti-HBc negativity, and immunity against HBV before chemotherapy, anti-HBs negativity was seen after chemotherapy. It was also reported that anti-HBs titers before chemotherapy were low in all of these patients. The antigenic stimulation caused by the vaccine is less potent compared to exposure to the virus, making these patients more susceptible to acute HBV infection [8]. Necessary screening was performed before HSCT for our patient with observation of HBsAg and anti-HBc negativity and anti-HBs positivity.

In our patient, the anti-HBs titer was not monitored after transplantation and acute HBV infection developed as the patient’s anti-HBs antibodies became negative after HSCT. The antibody titer provided by the vaccine was low (20 IU) in our patient, similar to cases in which antibodies became negative after immunosuppressive therapy, as in the study of Yağcı et al. [8]. It is recommended that all patients be evaluated for re-vaccination requirements at 6 and 12 months after HSCT. Vaccine response is better at 1 year after HSCT [1]. Hepatitis B vaccination was not administered for our patient because immunosuppressive treatment was continuing. Preventing the risk of acute or subacute liver failure is the main treatment goal in patients with acute hepatitis B. Various cohort studies show that early antiviral therapy with nucleos(t)ide analogues in severe cases can prevent progression to acute liver failure and subsequent liver transplantation or mortality. However, this effect is not seen if antiviral treatment is initiated late in the course of severe acute hepatitis B [7]. It is recommended that the use of nucleos(t)ide analogues in patients without immune deficiency and with AVHB infection be evaluated on a patient-by-patient basis (https://www.vhsd.org/tr/article/desc/48317/tu-riye-viral-hepatitler-tani-vetedavi-kilavuzu-2-7.html). The clinical course was mild in our case and liver functions returned to normal values in a short time. Tenofovir treatment was given to our patient despite the possibility of acute infection progressing seriously due to the underlying immunosuppression. Our patient was evaluated in terms of HBV infection before HSCT and was found to be immunized with the vaccine against HBV. However, after HSCT, due to immunosuppressive therapies the antibody became negative and the patient presented with AVHB. HBV infection in immunocompromised hosts can cause serious morbidity and mortality. It should not be forgotten that anti-HBs may become negative after immunosuppressive treatment in patients with antibodies against hepatitis B infection, and all patients with HSCT should be re-evaluated in terms of vaccination after transplantation.

Scientific Responsibility Statement
The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

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