Case Report

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Occult Hepatitis B Reactivation After Chemoteraphy: A Case Report

Kemoterapi Sonrası Okkült Hepatit B Reaktivasyonu: Olgu Sunumu

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ABSTRACT

Occult hepatitis B virus (HBV) infection is defined as the detection of HBV genome in the liver and/or serum in HBsAg(-) individuals. Most patients with occult HBV infection are asymptomatic and are usually diagnosed during screening. Occult HBV infection is clinically significant because it spreads through blood transfusion and organ transplantation and triggers the reactivation of HBV in immunosuppressive patients. In this paper, we present a 63-year-old patient with occult hepatitis B who was scheduled for chemotherapy due to Hodgkin's lymphoma, and developed hepatitis B reactivation after chemotherapy while being HBsAg(-) and anti-HBs(-) before chemotherapy.

Key Words: Occult hepatitis B, reactivation, immunosuppression

ÖZET

Okkült hepatit B virüs (HBV) enfeksiyonu HBsAg(-) kişilerde HBV genomunun karaciğer ve/veya serumda tespit edilmesi olarak tanımlanmıştır. Okkült HBV enfeksiyonuna sahip hastaların büyük bir çoğunluğu asemptomatik olup genellikle tarama sırasında tespit edilirler. Okkült HBV enfeksiyonunun kan transfüzyonu ve organ transplantasyonu ile geçmesi, immünosupresif hastalarda HBV'nin reaktivasyonuna neden olması klinik önemini arttırmaktadır. Hodgkin lenfoma nedeniyle kemoterapi alması planlanan, kemoterapi öncesi HbsAg(-), anti-HBs(-) iken, kemoterapiyi takiben hepatit B reaktivasyonu gelişen 63 yaşında okkült hepatit B olgusu sunulmuştur.

Anahtar Kelimeler: Okkült hepatit B, reaktivasyon, immünsupresyon

Introduction

Occult hepatitis B virus (HBV) infection is defined as the presence of low-level HBV-DNA in serum and/or liver in HBsAg (-) individuals. Serum HBV-DNA levels are usually lower than 104 copy/ml. Anti-HBc and/or anti-HBs antibodies are detected positive in some of occult hepatitis infections. Both antibodies are negative in a significant number of patients (1).

Occult HBV infection is usually associated with anti-HBc positivity, though anti-HBC antibody positivity is rarely possible. While occult HBV infection can be observed after healing of acute hepatitis B, it can also develop after hepatitis B surface antigen (HBsAg) seroclearance with spontaneous or anti-viral therapy in patients with cirrhosis or chronic hepatitis (2).

The chance of detecting HBV DNA in Ag(-) individuals has increased with the development of highly sensitive molecular techniques. This condition was first defined in the 1980's in patients with hepatocellular carcinoma (HCC) or chronic hepatitis but anti-HCV(-) or who had no obvious underlying reason. In later years, it was discovered that occult HBV infection can be observed in individuals without liver disease, whose liver function tests are completely normal. The clinical and biological spectrum of occult HBV infection is not fully known. The prevalence of HBV-DNA positivity in HBsAg(-) individuals is closely associated with the prevalence of HBV infections (3,4,5).

Studies have shown that occult HVB infection is more frequent in some patient groups, including: Patients with cryptogenic cirrhosis, patients with HCC, immunosuppressed patients, hemodialysis patients, intravenous drug user patients, type 2 diabetes mellitus patients and patients with chronic hepatitis C (6,7,8,9,10,11,12).

In many studies in the literature, the prevalence of occult HBV infection is high in immunosuppressed populations. This finding suggests that suppressed immune response against HBV has a role in the development of the occult form of HBV infection (8,13,14,15). In this study, we present a patient who was negative for HBsAg and anti-HBsAg before chemotherapy and had hepatitis B activation after chemotherapy, and was suspected of having occult hepatitis B.

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Case

In July 2012, HBsAg(-), anti-HBs(-), anti-HCV(-), and anti-HIV(-) were detected before chemotherapy in a 63-year-old male patient who had been scheduled to undergo Adriblastina, Bleomycin, Vinblastine, Deticene (ABVD protocol) due to stage 4 Hodgkin's lymphoma. After the first course of ABVD treatment in August 2012, the patient's levels were detected at AST: 17 U/L, ALT: 24 U/L, T.bil: 0.5 mg/dL, D.bil: 0.3 mg/dL. After the second treatment in September 2012, the patient had slightly elevated transaminase levels: AST: 41 U/L, ALT: 64 U/L. Since AST: 750 U/L, ALT: 1628 U/L, GGT: 183 U/L, ALP: 138 U/L, T.bil: 1.7 mg/dL, D.bil: 1.2 mg/dL were detected during the follow-up one week after treatment, the patient was transferred to the gastroenterology department. Physical examination revealed, the following: general condition: medium; sclera icteric, liver and spleen nonpalpable; HbsAg(+), anti-HBs(-), anti-HBc IgM(+), HBeAg(-), anti-HBe(+), anti-HAV IgM (-) anti-HDV(-), anti-HCV(-) in viral indicators. In his follow-ups, the following were obtained: AST: 2732 U/L, ALT: 3487 U/L, GGT: 168 U/L, ALP: 131 U/L, T.bil: 13 mg/dL, D.bil: 10 mg/dL, prothrombin time (PT): 21 second INR: 1.5.

Occult hepatitis B reactivation was considered since HBsAg and anti-HBs were negative before chemotherapy; and after chemotherapy, HBsAg and anti-HBc IgM were positive, which was accompanied by the development of a severe acute hepatitis B manifestation. HBV DNA could not be determined as the patient was transferred to another center. Because of progressive PT extension, it was considered that the patient might need transplant. Therefore, he was transferred to a transplant center and lamivudine treatment was initiated. Since liver enzymes and PT were decreased in his follow-ups, the patient did not undergo transplant and was taken back to our outpatient follow-up. In the first month of treatment, the results were as follows: AST: 30 U/L, ALT: 31 U/L, ALP: 66 U/L, GGT: 41 U/L, T.bil: 1.7 mg/dL, D.bil: 1.2 mg/dL, PT: 16 seconds, INR: 1.12. In the third month of lamivudine treatment in February 2013, AST: 22 U/L and ALT: 14 U/L, were within normal limits. The decision was made to continue chemotherapy with lamivudine prophylaxis, and the patient was taken into outpatient follow-up.

Discussion

Hepatitis B is a very common worldwide infection. Reactivation is proposed to have an association with morbidity and mortality in patients receiving immunosuppressive treatment until antiviral prophylaxis is conducted (16). Patients who recover after acute hepatitis B may have HBV genome for a long time. After many years following acute hepatitis B resolution, histological patterns of mild necroinflammation and even fibrosis can be seen without any clinical or biochemical evidence of liver disease (17). In infected hepatocytes, the presence of covalently closed circular (ccc) DNA serves as a reservoir for future infections and causes continuation of HBV infection. Occult HBV infection is defined as the presence of HBV-DNA in liver tissue in patients for whom HBsAg cannot be detected serologically (18). HBV reactivation risk varies depending on the presence of previous HBV infection and the degree of immunosuppression developed due to chemotherapy (19). HBsAg and anti-HBsAg were investigated and obtained as negative, as a result of routine tests before chemotherapy was performed for our patient, but anti-HBc total was not.

When determining the optimal strategy for prevention and treatment of hepatitis, it is important to deeply understand the characteristics of HBV reactivation, the clinical course and the risk factors (19). The diagnosis of acute hepatitis B is based on the detection of HBsAg and IgM anti-HBc. During the initial phase, markers of HBV replication, HBeAg and HBV DNA, are present. Resolution of infection is accompanied by the disappearance of HBV DNA, HBeAg to anti-HBe seroconversion and, then, HBsAg to anti-HBs seroconversion. As acute hepatitis B resolves, anti-HBe appears after anti-HBc, but before anti-HBs. It usually disappears earlier than anti-HBs. Occult HBV infection refers to the presence of HBV DNA in the absence of detectable HBsAg. Occult HBV infection can be classified into 2 groups: seropositive occult HBV infection (anti-HBc and/or anti-hepatitis B surface (anti-HBs) positive) and seronegative occult HBV infection (anti-HBc and anti-HBs negative), on the basis of the HBV antibody profile (20,21). HBV-DNA and anti-HBc IgG could not be determined but since HbeAg was (-), anti-HBe was (+), the case was accepted as reactivation of occult hepatitis B. In our case; HBsAg and anti-HBs prior to chemotherapy were negative and anti-HBc was not checked. Anti-HBc was positive in our patient after reactivation. Since HBsAg may be negative and anti-HBs may be negative in some patients, anti-HBc should be checked in order to minimize the risk of reactivation. Moreover, close follow-up is life saving in terms of reactivation, since all parameters may be negative in a small number of patients.

The important viral risk factors in terms of HBV reactivation include HBV-DNA level and HBV-related serum markers, ccc DNA, genotype and gene mutations (19). Patients with chronic HBV infections are at risk for HBV reactivation in the presence of clinical conditions, such as using anti-CD20 antibody, immunosuppression due to solid-organ or stem cell transplantation, and chemotherapy for cancer (22). When HBV-infected patients with lymphoma undergo chemotherapy or immunotherapy, HBV reactivation may develop (23). Since our patient was in this risk group, he was followed closely after chemotherapy.

The keys to prevent HBV reactivation are identification of patients with HBV infection before immunosuppressive treatment, initiation of prophylactic antiviral treatment in patients with moderate or high risk for HBV reactivation, and close follow-up of patients for whom prophylactic antiviral treatment is initiated at the first sign of HBV reactivation. However, the majority of patients infected with HBV are unaware of the infection and risk factors, and doctors usually do not have enough time to evaluate systemic risk factors for HBV before starting immunosuppressive therapy. Rapid initiation of antiviral treatment can be life saving in reactivation diagnosis since HBV reactivation may develop even two years after the end of immunosuppression in HBsAg-negative and anti-HBc-positive patients (24). Prophylactic lamivudine reduces the morbidity and mortality associated with HBV reactivation (23). Early initiation of lamivudine treatment in our patient was probably life saving.

In conclusion, occult HBV infection is clinically significant since it causes HBV reactivation in immunosuppressed patients. The case of occult hepatitis B in our patient who was scheduled

to receive chemotherapy due to Hodgkin's lymphoma and was HBsAg(-), anti-HBs(-) before chemotherapy, and developed hepatitis B reactivation after chemotherapy suggests that it is necessary to investigate anti-HBc antibody (and HBV-DNA level if required) and, if positive, to give prophylaxis before chemotherapy; and to initiate anti-viral treatment as early as possible in case of HBV reactivation.

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