

Hepatitis B reactivation after therapy for non-Hodgkin lymphoma: a case report with review of literature

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SUMMARY

The natural course of hepatitis B virus (HBV) infection depends on the immune status of the host. In cancer patients, as the consequence of immune suppression due to chemotherapy and malignant disease itself, the balance between replicative potential of the virus and immune response of the host is disrupted leading to acute HBV infection or reactivation. We present a case of HBsAg positive, diffuse large B cell gastric lymphoma patient CD20+ staged IB, treated with six cycles of R-CHOP protocol and two cycles with rituximab monotherapy. Five months after the successful anti-cancer treatment, patient developed reactivation of chronic HBV infection (ten-fold increase in liver enzymes, HBsAg+, IgM antiHBc+, HBeAg(-), and HBV DNA 5×10^6 copies/ml). Antiviral therapy with lamivudine was started. Four weeks after the antiviral therapy initiation liver enzymes were in normal ranges. One year after the start of antiviral treatment HBV DNA PCR test did not detect any viral particles. The patient is in complete remission of malignant disease, and still receiving therapy with lamivudine. HBV screening in cancer patients is necessary in order to provide a prompt antiviral therapy and to prevent postponement or even cessation of planned anticancer treatment. HBsAg positive patients should start prophylactic antiviral treatment before the start of immunosuppressive treatment. Chemotherapy protocols consisting rituximab and corticosteroids significantly increase the risk of reactivation. If reactivation is diagnosed in course of chemotherapy, the therapy should be stopped and antiviral treatment should be applied as soon as possible. Treatment with lamivudine is continued at least 6 months after the chemotherapy end.

Key words: Hepatitis B; Recurrence; Lymphoma, Non-Hodgkin; Antineoplastic Protocols; Lamivudine

INTRODUCTION

It is estimated that 1/3 of the world population is infected with hepatitis B virus (HBV) and that about 350 to 400 million people have chronic HBV infection (1). The natural flow of HBV infection depends on the immune status of the host. As the consequence of chemotherapy as well as malignant disease itself, the balance between replicative potential of the virus and immune response of the host is disrupted. In states of immune deficiency an uncontrolled, free replication of the virus starts, leading to acute HBV infection or reactivation, depending on previous hepatitis B surface antigen (HBsAg) status (2). Reactivation of HBV is defined as increase in serum HBV DNA for more than $1 \log_{10}$ copies/ml in comparison to the level before the therapy was initiated; or an absolute increase in HBV DNA level higher than $6 \log_{10}$ copies/ml; or conversion of HBV DNA in serum from negative to positive. Viral reactivation causes acute exacerbation of chronic hepatitis, which is defined as threefold increase in serum levels of alanine aminotransferase (ALT) in at least 5-day period (3). Reactivation can be divided into three separate phases. Initially, specific T cell and B cell immune control is lost during intensive cytotoxic and immunosuppressive chemotherapy. Increase in viral replication occurs and can be estimated by the rise in HBV DNA in serum, with minimal activity of ALT. After the chemotherapy or immunosuppressive therapy is discontinued, the functionality of the immune system is restored (immune reconstitution), cytotoxic T lymphocytes recognize the viral antigen of hepatocyte membrane, and infected cells are destroyed. The third phase is the recovery phase, when ALT levels are normalized and HBV markers return to the levels prior to chemotherapy. In some cases, the immune reconstitution does not occur and the increase in HBV DNA is not accompanied by development of acute hepatitis, or it is extremely

severe and can be even lethal. In some patients, the recovery phase is not experienced, liver disease progresses and it can violate liver function (4). Reactivation can occur in HBsAg negative patients, who have HBV markers indicating previous infection with HBV (anti-HB core antibody (anti-HBc) and/or anti-HBs) (5). Reactivation of HBV in patients previously recovered from hepatitis B is enabled by covalently closed circular DNA (cccDNA), which is the most resistant part of virus, implanted in hepatocyte after the infection (6).

Risk factors for HBV reactivation can be classified in two groups: (1) viral: higher HBV DNA load in serum, amount of cccDNA in hepatocytes, non-A HBV genotype, precore and core promoter mutations (causes of HBeAg negative chronic hepatitis); and (2) host factors: male gender, young age, lymphoma, use of corticosteroids, rituximab, absence of anti-HBs antibody before chemotherapy or decrease in anti-HBs during chemotherapy (6). The highest risk factors of HBV reactivation are type of malignancy and type of chemotherapy administered (7).

We reported a case of HBsAg positive, gastric lymphoma patient, who developed reactivation of HBV infection after the completion of chemotherapy.

CASE REPORT

Male patient, 46 years old, was diagnosed for diffuse large B cell gastric lymphoma, CD20+ staged IB. In course of preparation for chemotherapy, he did not give any significant medical history including HBsAg positivity. He was treated with six cycles of R-CHOP protocol (rituximab, cyclophosphamide, vincristine, and prednisone) and two cycles of rituximab monotherapy. After the treatment was ended, the patient was in complete remission of malignant disease. Five months later, during routine

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check-up he complains of fatigue, nausea, and joint pain. Laboratory findings presented ten-times the upper limit of the normal range (ULN) in liver enzymes, hepatic synthetic function was normal, HBsAg+, IgM antiHBe+, HBeAg(-) and HBV DNA 5×10^8 copies/ml in serum. Initially, the patient was suspected to have acute hepatitis B infection. However, epidemiologic poll as well as thorough medical history overview revealed that the patient was diagnosed with hepatitis B infection in the year 1980. Finally, diagnosis of reactivation of chronic hepatitis B was established and therapy with lamivudine 100 mg per day was started. Patient's subjective complaints subsided and 4 weeks after the antiviral therapy initiation level of liver enzymes were in normal ranges. One year after the start of antiviral treatment HBV DNA PCR test did not detect any viral particles. The patient is still HBsAg positive and receiving therapy with lamivudine. He is in complete remission of malignant disease.

REVIEW OF THE LITERATURE AND DISCUSSION

Reactivation of HBV has been mostly reported in patients with hematologic malignancies, and lymphoma patients are at highest risk for reactivation (8). One of the reasons is a fact that non-Hodgkin lymphomas (NHL) are associated with HBV and HCV. HCV is one of the well-recognized etiological factors of lymphoproliferative diseases, while positive association between HBV and NHL is evident; however details of this relation are not fully understood. Marcucci and authors speculate of possible mechanisms of lymphomagenesis; HBV particles or HBV antigens can be synthesized and assembled by hepatocytes and probably by lymphocytes. HBV particles can then infect other lymphocytes in lymphoid organs. Infectious particles integrate in the host genome, leading to overexpression of cellular oncogenes or downregulation of the expression of tumor suppressor genes. Moreover, HBV antigens can also induce chronic antigenic stimulation (CAS). Infection, integration, and CAS are proposed to be causally linked to lymphomagenesis in concurrence to other yet undefined risk factors (9, 10).

Our patient knew he had been HBsAg positive for at least 20 years. This data correlates to the facts indicating that HBV and HCV induced lymphomagenesis is a long process lasting for more than 15 years (the mean age of 23 years since diagnosis of HCV infection until NHL diagnosis) (10).

An increase in transaminases occurred 5 months after the cessation of chemotherapy. In HBsAg positive patients, reactivation can occur between the cycles or only after the end of chemotherapy. This period varies from one month up to 36 months, most commonly ranges between 1 to 4 months (11, 12). In patients with high HBV DNA viral load, reactivation can occur soon after the chemotherapy start. In HBsAg negative (anti-HBe positive) patients, reactivation can be diagnosed mostly after the completion of chemotherapy, the longest period reported is 8.5 months after the completion of oncology treatment (12).

Our patient experienced increase in liver enzymes along with general symptoms: fatigue, weakness, nausea, and arthralgia. HBV reactivation can be symptomatic or asymptomatic. The most usual clinical manifestations of hepatitis are fatigue, nausea, and jaundice. However, ascites, hepatic encephalopathy, and coagulopathy can occur as a consequence of life-threatening fulminant hepatitis and cholestatic fibrosing hepatitis (7, 13). In some patients reactivation can be subacute and resolves

spontaneously, while in others it can progress to undetectable persistent infection (12).

All types of medications used in treatment of malignancies can be involved in HBV reactivation starting with classic cytostatic all the way to the modern monoclonal antibodies, as they all have immunosuppressive activity. R-CHOP protocol consists of several drugs related to HBV reactivation, with rituximab and corticosteroids as the most prominent ones (7). Corticosteroids can raise the risk of HBV reactivation from 38% up to 78% (14). Besides being general immunosuppressants, they enhance HBV replication through glucocorticoid-responsive element, transcriptional promoter in HBV genome. High doses of corticosteroids reduce function of suppressor and helper T lymphocytes and enhance primary B cell function (15, 16). Reactivation of HBV was reported in cases of long-term low dose corticosteroid therapy (17).

Rituximab is a monoclonal antibody aiming CD20 antigen, expressed in over 95% of normal and malignant B cells (18). HBV replication is under control of HBV-specific cytotoxic T lymphocytes, while B-lymphocytes are antigen-presenting cells. Durable depletion of B lymphocytes induced by rituximab enables HBV to escape the cytotoxic T lymphocytes control, hence leading to uncontrolled viral replication (12). Pei et al. reported that 80% of their study population of rituximab treated patients without antiviral prophylaxis has developed HBV reactivation (19). Protocols consisting of both drugs: rituximab and corticosteroids raise the risk of reactivation significantly, so in cases of HBsAg negative patients this risk rises from 1 to 2.3% up to 12.2 to 23.3% (6, 13).

Hepatitis is often diagnosed only after the beginning of oncology treatment when the complications of such treatment have already aroused. Therefore, in case of liver dysfunction without present metastatic liver disease, one has to consider possible hepatotoxicity and infections with hepatotropic viruses (HCV, HBV, HAV, CMV, EBV, and others) (7).

Our patient has manifested the criteria for diagnosis of HBV reactivation (high HBV DNA viral load in serum, trifold increase in ALT, symptoms of hepatitis). If reactivation is diagnosed in course of chemo- or immunosuppressive therapy, the therapy should be stopped and antiviral treatment should be applied as soon as possible, or antiviral drug should be replaced with antiviral with high barrier to viral resistance (20). Since our patient was not treated with antiviral drug, we introduced lamivudine and achieved biochemical and viral suppression.

According to the current guidelines for prevention, treatment, and follow-up of hepatitis B, all HBsAg positive patients should start prophylactic antiviral treatment before the start of immunosuppressive treatment (1 to 2 weeks) (7, 18, 21, 22). The most commonly applied antiviral drug for HBV reactivation prevention is lamivudine, cheap drug with good tolerance profile. Lamivudine significantly reduces the risk of HBV reactivation; the prevalence of reactivation is 0 to 8.6% in patients with antiviral prophylaxis, comparing to 50% in patients without lamivudine prophylaxis (7, 23). Treatment with lamivudine is continued at least 6 months after the chemotherapy end, or 12 months for patients treated with monoclonal antibodies or bone marrow transplant. In patients with high HBV DNA level before chemotherapy start lamivudine is applied even longer; i.e. 12 months after the normalization of ALT levels, undetectability of HBV DNA in serum, and anti-HBe seroconversion (in HBe positive patients), or in

accordance with the guidelines for treatment of chronic active hepatitis B (7, 12, 18, 21, 22). In course of lamivudine treatment HBV mutations can occur, so it is necessary to monitor HBV DNA levels and in cases of resistance, lamivudine should be replaced with other potent antiviral with high barrier to resistance (tenofovir or entecavir) (21, 22).

Although there are clear recommendations for testing of all oncology patients for HBV markers, it is still debated of pharmaco-economic advantages of this practice. A cost-effectiveness analysis of hepatitis B virus screening of patients with lymphoma before chemotherapy (R-CHOP protocol), published in 2012, speaks in favor of this practice. It reduces the reactivation rate 10 times and has lower costs of treatment than screening only high-risk patients or total screening avoidance (24).

CONCLUSION

HBV screening in cancer patients is inevitable in order to provide a prompt antiviral therapy, as well to prevent postponement or even cessation of planned oncologic treatment with all the consequences to cancer patient. Besides HBsAg, screening should consist of anti-HBc and anti-HBs status. Anti-HBc positivity marks previous HBV exposure, so if there is a high risk of viral reactivation (bone marrow transplantation, biologic therapy, etc.) such patients adequate anti-HBV prophylaxis. Anti-HBs positivity in serum represents immunity to HBV infection and prophylaxis is not obligatory except in patients in high risk for HBV reactivation. These patients should be closely monitored for anti-HBs in course of chemotherapy, and in case of drop in anti-HBV level, antiviral drugs should be introduced in treatment. Recommendations for HBV prevention are clearly defined in 2009 and 2012 European and American clinical practice guidelines for treatment of chronic HBV infection (21, 22, 25). The American Society of Clinical Oncology ASCO published in 2010 Provisional Clinical Opinion for chronic HBV infection screening in cancer patients and recommends testing of all patients in heightened risk for this infection as well as if highly immunosuppressive treatment or rituximab protocols are planned (26).

Conflict of interest

We declare no conflicts of interest.

REFERENCES

- Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat.* 2004;11:97-107.
- Lau G.K. Hepatitis B reactivation after chemotherapy: two decades of clinical research. *Hepatol Int.* 2008;2(2):152-62. Epub 2008 Mar 5.
- Hoofnagle JH. Reactivation of hepatitis B. *Hepatology.* 2009;49 Suppl 5:S156-S165.
- Hui CK, Cheung WW, Zhang HY, Au WY, Yueng YH, Leung AY, et al. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. *Gastroenterology.* 2006;131:59-68.
- Kusumoto S, Tanaka Y, Ueda R, Mizokami M. Reactivation of hepatitis B virus following rituximab-plus-steroid combination chemotherapy. *J Gastroenterol.* 2011;46(1):9-16. Epub 2010 Oct 6.
- Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat Rev Clin Oncol.* 2012; 9(3):156-66.
- Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer.* 2004; 90(7):1306-11.
- Marcucci F, Spada E, Mele A, Caserta C.A, Pulsoni A. The association of hepatitis B virus infection with B-cell non-Hodgkin lymphoma – a review. *Am J Blood Res.* 2012;2(1):18-28.
- Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. *Blood.* 2011;117(6):1792-8. Epub 2010 Oct 19.
- Duberg AS, Nordström M, Törner A, Reichard O, Strauss R, Janzon R, et al. Non-Hodgkin's lymphoma and other nonhepatic malignancies in Swedish patients with hepatitis C virus infection. *Hepatology.* 2005;41(3):652-9.
- Manzano-Alonso ML, Castellano-Tortajada G. Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy. *World J Gastroenterol.* 2011;17(12):1531-7.
- Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. *Int J Hematol.* 2009;90(1):13-23. Epub 2009 Jun 23.
- Ceballos-Viro J, López-Picazo JM, Pérez-Gracia JL, Sola JJ, Aisa G, Gil-Bazo I. Fibrosing cholestatic hepatitis following cytotoxic chemotherapy for small-cell lung cancer. *World J Gastroenterol.* 2009;15(18):2290-2.
- Cheng AL, Hsiung CA, Su JJ, Chen PJ, Chang MC, Tsao CJ, et al; Lymphoma Committee of Taiwan Cooperative Oncology Group. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology.* 2003;37(6):1320-8.
- Tur-Kaspa R, Burk RD, Shaul Y, Shafir DA. Hepatitis B virus DNA contains a glucocorticoid-responsive element. *Proc Natl Acad Sci USA.* 1986;83:1627-31.
- Hanson RG, Peters MG, Hoofnagle JH. Effects of immunosuppressive therapy with prednisolone on B and T lymphocyte function in patients with chronic type B hepatitis. *Hepatology.* 1986;6:173-9.
- Bae JH, Sohn JH, Lee HS, Park HS, Hyun YS, Kim TY, et al. A fatal case of hepatitis B virus (HBV) reactivation during long-term, very-low-dose steroid treatment in an inactive HBV carrier. *Clin Mol Hepatol.* 2012;18(2):225-8. Epub 2012 Jun 26.
- Mastroianni CM, Lichtner M, Citton R, Del Borgo C, Rago A, Martini H, et al. Current trends in management of hepatitis B virus reactivation in the biologic therapy era. *World J Gastroenterol.* 2011;17(34):3881-7.
- Pei SN, Chen CH, Lee CM, Wang MC, Ma MC, Hu TH, et al. Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol.* 2010;89(3):255-62. Epub 2009 Aug 21.
- Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology.* 2006;43:209-20.
- Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):661-2.
- European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol.* 2012; 57(1):167-85. Epub 2012 Mar 20.
- Katz LH, Fraser A, Gafter-Gvili A, Leibovici L, Tur-Kaspa R. Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis. *J Viral Hepat.* 2008;15(2):89-102.
- Zurawska U, Hicks LK, Woo G, Bell CM, Krahn M, Chan KK, et al. Hepatitis B virus screening before chemotherapy for lymphoma: a cost-effectiveness analysis. *J Clin Oncol.* 2012;30(26):3167-73. Epub 2012 Jun 18.

- 25 Maticič M, Poljak M. Slovenske nacionalne usmeritve za preprečevanje reaktivacije hepatitisa B pri bolnikih, ki potrebujejo imunosupresivno zdravljenje. Slovene national guidelines for the prevention of hepatitis B reactivation in patients undergoing immunosuppressive therapy. *Zdravniški Vestnik*. 2010;79(9).
- 26 Artz AS, Somerfield MR, Feld JJ, Giusti AF, Kramer BS, Sabichi AL, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening inpatients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol*. 2010;28(19):3199-202. Epub 2010 Jun 1.