Clinical Case Report

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Hepatitis B virus infection in an HBsAb-positive lymphoma patient who received chemotherapy

A case report

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Abstract

Rationale: Tumor chemotherapy could weaken the immune system of patients, which might enhance the body sensitivities to the exogenous pathogens, among which the hepatitis B virus (HBV) infection should be concerned because of the higher chances of infection and the severe outcomes, especially in East Asia. The titer level of hepatitis B surface antibody (HBsAb) higher than 10 IU/L is considered to offer immunocompetent individuals adequate protection. However, whether this level is enough to the tumor patients during chemotherapy remains unclear.

Patient concerns: A 58-year-old female lymphoma patient was admitted to our hospital for asthenia, nausea, vomiting, and abnormal liver function lasting over 1 week and diagnosed as acute hepatitis B. The patient just finished a course of chemotherapy with CHOP regimen and had recent record (78.61 IU/L) of HBsAb positive. The only risk of infection we could found was that the patient had received blood transfusion shortly after chemotherapy from a donor who was recovering from an asymptomatic acute HBV infection.

Intervention: The patient was administered with entecavir and glycyrrhizic acid agent, and then the disease was resolved successfully with hepatitis B surface antigen serological conversion.

Lessons: Tumor chemotherapy might have weakened the immune system of the patient and enhanced the body sensitivities to hepatitis B virus, then led to the infection. We concluded that HBsAb-positive status, at least "weakly positive," might not enough to provide protection for tumor patients on chemotherapy though this level was enough for health individuals and donors recuperating from subclinical acute hepatitis B might be another potential risk of HBV infection.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTL = cytotoxic T lymphocyte, ELISPOT = enzyme-linked immunospot assay, HBcAb = hepatitis B core antibody, HBeAg = hepatitis B e antigen, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HBVDNA = hepatitis B virus-deoxyribonucleic acid, PBMCs = peripheral blood mononuclear cells, TBIL = total bilirubin.

Keywords: chemotherapy, hepatitis B surface antigens, hepatitis B, lymphoma

1. Introduction

Tumor chemotherapy can weaken the immune system of patients, which not only induces the reactivation of latent infections, such as tuberculosis bacteria, hepatitis B virus, and cytomegalovirus, but also enhances the body sensitivities to the exogenous pathogens.[1–3] Different antitumor drugs have different influence mechanisms to the immune system, including myelosuppression, cytotoxicity, and antiproliferation and apoptosis-induced effects. The hepatitis B virus (HBV) infection is an issue that should be concerned during and after tumor chemotherapy, one reason is the higher chances of HBV infection in tumor patients, especially in East Asia, and another reason lies in the fact that HBV infection in immune compromised patients may lead to severe outcomes, such as liver failure.[1,4] Several studies have indicated that the tumor patients undergoing chemotherapy with inactive HBV infection, which is defined as negative or low virus load and normal liver enzyme could develop active viral replication and liver function damage.[2] The same findings even could be seen in patients with single hepatitis B core antibody (HBcAb) positive.[3] Tumor chemotherapy may impress the specific antiviral immune response and disrupt the balance of immune system and HBV. Studies found that common chemotherapy drugs, such as cyclophosphamide and prednisone, could suppress the HBV specific humoral and cellular immunity via different mechanisms.[5–6] Based on above, the risk of HBV infection is greatly increased during and after tumor chemotherapy. This is why the tumor patients undergoing chemotherapy were listed as one of high risk groups in the guidelines of China and world health organization and were recommended to accept prophylactic injection of HBV vaccine and monitor the antibody level to maintain effective immune protection.[7–8]

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2. Case presentation

Here we report a 58-year-old Chinese woman with lymphoma was admitted to our hospital for asthenia, nausea, vomiting, and abnormal liver function lasting over 1 week. On admission, her serology was found to be positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), negative for hepatitis B surface antibody (HBsAb) and negative for antibodies of hepatitis C virus, hepatitis A virus, hepatitis E virus, and human immunodeficiency virus. Her serum blood hepatitis B virus-deoxyribonucleic acid (HBVDNA) concentration was 2.05×10^6 copies/mL (limit of detection by polymerase chain reaction: 500 copies/mL). Her alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL) levels were 581 U/L (normal 0–45 U/L), 324 U/L (normal 0–37U/L), and 38.4 μmol/L (normal 0–19.1 μmol/L), respectively. Her albumin, globulin, α-fetoprotein, and complete blood counts were all within the upper limits of normal. The enhanced computed tomography scan of the upper abdomen showed no abnormal imaging result. Based on typical clinical findings and previous history, the patient was diagnosed as acute hepatitis B. Then, the patient was administered for antiviral treatment with entecavir (0.5 mg daily) and glycyrrhizic acid agent. After 4 weeks' treatment, her serum ALT and AST levels were decreased to almost normal limits and the HBVDNA concentration fell below detectable levels (500 copies/mL). Six weeks after entecavir therapy initiation, the patient presented E antigen serological conversion and her HBsAg disappeared after 9 weeks. Twelve weeks after treatment, her hepatitis B surface antibody (HBsAb) was tested for positive and then stopped entecavir administration (Fig. 1).

It's worth noting that the patient had been vaccinated against hepatitis B 8 years ago and had reliable records of HBsAb positive. The latest test for HBsAb was nearly 8 weeks before hospitalization, when she was preparing to receive tumor chemotherapy. The exact titer was 78.6 IU/L, far more 7 times than 10 IU/L, the level which should provide enough protection and no need for revaccination according to the guidelines or position papers from the United States, China and World Health Organization (WHO).[7–9] In addition, her HBcAb and hepatitis B e antibody (HBeAb) levels were found to be negative, which suggested that HBsAb positive result was probably not to the result from postinfection immunity but vaccination.

About 4 months ago, the patient was diagnosed as diffuse large B-cell lymphoma and then received the CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) regimen. Significant side effects included anorexia, hair loss, and decreased leukocytes and platelets, whereas liver enzyme and bilirubin remained normal all the time. Symptomatic hepatitis B virus infection appears about 4 weeks after the chemotherapy ends. Calculating based on the patient's medical history and the incubation period of hepatitis B virus infection, the time point when she required the infection should be during the chemotherapy or in a very short time after it. Then, we decided to investigate her medical history in details even earlier from her latest HBsAb tested positive. According to her narration, she rested at home most of the time without suspect contact and injury. No invasive manipulation was executed during this period. Only one platelet unit was transfused for improvement of thrombocytopenia during the course of chemotherapy, about 5 weeks before the patient developed obvious acute hepatitis related symptoms. The donor's tests were recorded as bellows: normal liver function, weakly positive for HBsAb (6.82 IU/L), and negative for HBsAg, HBcAb, and HBeAb.

We then found the blood donor and asked for another investigation about 12 weeks after donating. The donor is a 28-year-old unmarried healthy male who had no history of hepatitis B and was not received hepatitis B virus vaccination. Like before, liver function test was normal and HBVDNA concentration was lower than the detectable limit (500 copies/mL). Surprisingly, obvious changes were found in serological markers of HBV, including HBsAb (255.82 IU/L), which was much higher than that tested 12 weeks ago, weakly positive HBcAb and positive HBeAb, which were all negative before blood donating. Based on above data, we concluded that the donor should be an asymptomatic acute HBV infected person and were recovering when he donated blood 12 weeks ago.

3. Discussion

Cyclophosphamide and doxorubicin are all nonspecific cell cycle antineoplastic drugs, which can interact with or inhibit

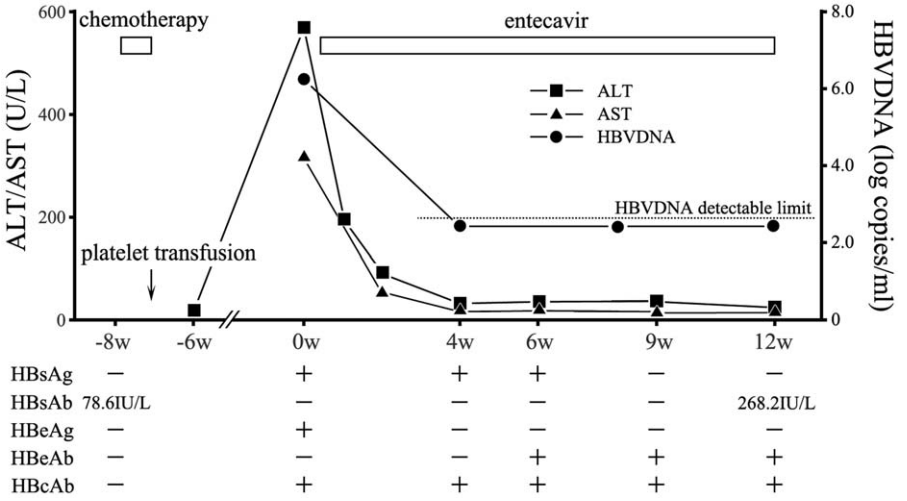

Figure 1. Time courses of alanine aminotransferase (ALT), aspartate aminotransferase (AST), hepatitis B virus-deoxyribonucleic acid (HBVDNA) levels, and hepatitis B serological markers (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb). The time admitted to the hospital was considered as 0 week.

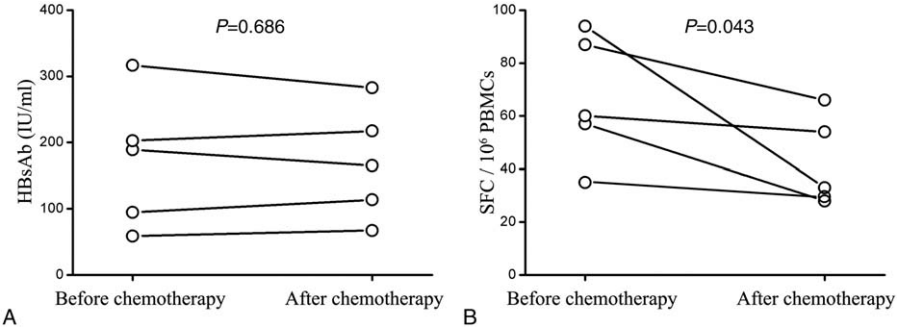

Figure 2. The effects of chemotherapy on HBV specific humoral and cellular immune responses in HBsAb-positive diffuse large B-cell lymphoma patients. A, The changes of HBsAb titers (IU/mL) in lymphoma patients before and after chemotherapy (n = 5). B, ELISPOT data showing the number of IFN-γ SFCs per million peripheral blood mononuclear cells (PBMCs) on stimulation with HBV S region peptide 335–343 (WLSLLVPFV, 20 μg/mL), recombinant human interleukin-2 (rhIL-2, 50IU/mL) along with proper concentrations of rhIL-7 and rhIL-15 for 48 hours in lymphoma patients before and after chemotherapy (n = 5). *P* values are shown.

intracellular DNA and RNA and block the proliferation of cells.[10] Quick proliferative cells, including tumor cells and marrow cells and immune cells are more sensitive to this kind of drugs. Vincristine can inhibit microtubule assembly and induce tubulin self-association into coiled spiral aggregates, which are prone to influencing the same kinds of fast dividing cells as cyclophosphamide. Prednisone, as a kind of glucocorticoids, is thought to have a general suppressive effect on immunity, especially on specific cellular and humoral immune responses.[6] Interestingly, however, The HBV serological protective marker HBsAb had been found much higher than 10 IU/mL before the patient accepted the chemotherapy, which is considered to have full protective effect on hepatitis B virus. Because of the retrospective analysis, we couldn't understand if the HBsAb titer of this patient declined after chemotherapy. To evaluate whether tumor chemotherapy could exert influence on the level of antibody, we selected 5 diffuse large B-cell lymphoma patients with HBsAb positive, detected the antibody levels before and after they underwent chemotherapy with CHOP regimen. The small-sample study and the case report above were approved by the International Review Board of Bethune International Peace Hospital. Both written and oral consents were obtained before the patients were rolled, and relevant data provided to the researchers were anonymized. Surprisingly, no obvious changes of HBsAb levels were found before and after chemotherapy (Fig. 2A). We also detected HBsAg epitope-specific cytotoxic T lymphocyte (CTL) responses by enzyme-linked immunospot assay (ELISPOT), which were achieved by patients' peripheral blood mononuclear cells (PBMCs) incubated with HBV S region peptide 335–343 (WLSLLVPFV, 20 μg/mL), recombinant human interleukin-2 (rhIL-2, 50IU/mL) along with proper concentrations of rhIL-7 and rhIL-15 for 48 hours. Results showed that dramatic drops of epitope-specific CTL responses could be found after tumor chemotherapy ended (Fig. 2B). In theory, chemotherapy drugs above can inhibit both innate and specific immune responses. But for the intracellular microorganisms, such as hepatitis B virus, specific cellular immunity may play a key role in keeping the virus from invading and replicating.[11] This may explain why tumor patients receiving chemotherapy are prone to be infected with hepatitis B virus. For the tumor patients undergoing chemotherapy, HBsAb level beyond 10 IU/mL might not be used as security criteria and could not provide adequately protective effect.

In the retrospective investigation, we highly doubt that this patient's HBV infection was from a blood donor who was recuperating from subclinical HBV infection, for the patient received the donor's platelets because of chemotherapy induced thrombocytopenia. Interestingly, the donor showed HBsAb weakly positive and liver function normal before blood donating, whereas when we investigated after 6 weeks dramatic increase of HBsAb titer was marked and HBcAb and HBeAb both turned positive. We concluded that the donor suffered from subclinical HBV infection might still carry a tiny amount of HBV virus in the peripheral blood though HBsAg serological convention had occurred. We usually think that the risk of HBV infection via blood transfusion mainly come from the window period of donors.[12] Although this case hinted that the recovery stage of acute HBV infection might be regarded as occult HBV infection and be another dangerous period to the blood donors. Occult HBV infection is very easily misdiagnosed because of HBsAg negative, even along with HBsAb positive. The higher requirements should be put forward to screen blood donors, especially for the immune compromised recipients, such as tumor patients receiving chemotherapy.

Though the weak HBsAb titer might be not enough to provide protection for tumor patients on chemotherapy, the effective protection level of HBsAb remains uncertain. Additional case reports and detailed mechanisms will be needed in the future.

4. Conclusions

The case reported here demonstrated that tumor chemotherapy with the CHOP regimen might have weakened the immune system of this lymphoma patient and enhanced the body sensitivities to hepatitis B virus, then led to the infection, though she had a reliable record of HBsAb positive. We concluded that HBsAb-positive status, at least "weakly positive," might not enough to provide protection for tumor patients on chemotherapy though this level was enough for health individuals. This case also suggested that the blood from donors recuperating from subclinical acute hepatitis B might still be infectious and cannot easily be screened though general serological methods before donation. This period might be another potential risk of transfusion transmitted HBV infection besides "window phase."

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