CASE REPORT

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Reactivation of Hepatitis B Virus Infection 66 months after Rituximab Therapy for Chronic Lymphocytic Leukemia, Emphasis on Interplay between Infection, Drugs and Disease Biology

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ABSTRACT

Hepatitis B virus (HBV) reactivation (HBVr) in patients receiving immunosuppression is an evolving topic. American Gastroenterology Association (AGA) have reported a guideline for the management of patients with certain HBV status who will undergo immunosuppression with regard to patient's HBV status as well as the category and duration of immunosuppression. Here we are presenting a case with CLL who have received rituxmab with bendamustine 66 months before, developing HBVr with an emphasis on the discussion pathophysiological process of the disease itself, not just the treatment course. 59 years old male patient diagnosed with CLL and chronic asymptomatic HBV infection received 3 lines of treatment under viral prophylaxis in 13 years. 66 months after the last treatment with rituximab, HBV reactivation developed and treated with dual antiviral therapy. During this period a decrease in lymphocyte count was observed concurrent with transaminase elevation. As the reactivation was controlled, lymphocyte counts increased back to pre-flare levels. While the patient had impaired antibody related immune response since monoclonal B cells are nonfunctional, an attempt to improve T cell related response may be resulted with both to the clearance of lymphocytes (as they were decreased) and the immune reaction of necroinflammation in the hepatocytes were triggered.

Key Words: Hepatitis B Reactivation, Chronic Lymphocytic Leukemia, Rituximab

Introduction

Hepatitis B virus (HBV) reactivation (HBVr) in patients receiving immunosuppression is an evolving topic. Terminology of HBV status include active carrier (AC) who are HbsAg positive with elevated HBVDNA (>2000IU/mL), occult HBV carrier (OBI) who are HbsAg negative but Anti HBc positive with absent HBVDNA and positive or negative AntiHBs, inactive carrier (IC) HbsAg positive but HBVDNA is absent or <2000IU/mL (1).

American Gastroenterology Association (AGA) have reported a guideline for the management of patients with certain HBV status who will undergo immunosuppression with regard to patients' HBV status as well as the category and duration of immunosuppression Prior to immunosuppressive treatments, all patients should be screened for HBV with HbsAg, AntiHBs, and AntiHBc (2). Patients who are HbsAg positive should also be assessed with HBVDNA as a baseline evaluation and likewise, HbeAg and AntiHBe should also be evaluated (3).

In patients with hematologic disorders, benign conditions such as immune thrombocytopenia and autoimmune hemolytic anemia require prolonged corticosteroid treatments and are regarded as high risk for reactivation. Patients receiving chemotherapy such as alkylating agents, B cell depleting agents and high dose corticosteroids are regarded as high risk while patients receiving tyrosine kinase inhibitors and moderate dose corticosteroids are regarded as moderate risk while traditional immunosuppresants such as metotrexate, azathiopurine, cytarabine and other antimetabolites are regarded as low risk.

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The reactivation of HBV is observed typically in patients with a forementioned HBV status as immunosuppresive treatments influencing the activity of B cells as well as T cells leading to an intensification of HBV replication. Within hepatocytes, HbsAg and HBVDNA levels increase, and with the withdrawal of immunosuppression, a rebound activity in T cells result with hepatocyte destruction, just like the immune reconstitution syndrome (IRIS) in hepatosplenic candidiasis, where the liver lesions appear after the increase in the neutrophyl count of the patient.

Patients receiving immunosuppresive treatments like antiCD20, rituximab to develop HBVr long after the cessation of the treatment as long as 60 months (4-5). Here we are presenting a case with Chronic Lymphocytic Leukemia (CLL) who have received rituxmab with bendamustine 66 months before, developing HBVr with an emphasis on the discussion pathophysiological process of the disease itself, not just the treatment course.

Case Report

59 years old male patient diagnosed with CLL and chronic asymptomatic HBV infection in 2005. Initial laboratory included leucocyte 24800/mm3, lymphocyte 20900/mm3, hemoglobin 14.2 g/dL, platelets 156.000/mm3. HbsAg was positive. From 2005 to 2008, he did not receive treatment for either condition. In 2008, lymphocyte doubling time shortened, leucocyte count 50900/mm3, lymphocyte 48900/mm3, hemoglobin 14.6 g/dL, platelets 184.000/mm3, HbsAg negative, AntiHBs positive (11.3 mIU/mL), AntiHBcTotal positive, HBVDNA <100 IU/mL, no cytogenetic abnormalities were observed by FISH, and patient received 6 cycles of fludarabin cycophosphamide with lamivudine 100mg/days. Till 2012 he was on routine 3 months' follow up without treatment. In 2012, due to lymphocyte doubling time shortening to 4 months, and laboratory revealed leucocyte 274000/mm3, lymphocyte 229000/mm3, hemoglobin 13.8 g/dL, platelets 156000/mm3, HbsAg negative, AntiHBs negative, AntiHBcTotal positive, HBVDNA 20Iu/mL, FISH analysis revealed 13 q deletion and patient received 4 cycles of rituximab and bendamustine, again on lamivudine prophylaxis prolonged 1 year after the end of treatment. After 4 cycles of rituximab and bendamustine in 2012, bone marrow recovery was in 18 months. After this treatment, constantly hypogammaglobulinemia and increase in monoclonal lymphocytosis on a slow pace were observed. Till 2017 he did not receive any chemotherapy for CLL. During a routine follow up, lymphocyte count was decreased, liver transaminases were observed to be elevated as ALT 900 IU/mL AST 411 IU/mL and serology was repeated. HbsAg has become positive, AntiHBs negative, HBVDNA 12.700.000/IU/mL antiDelta negative. He was hospitalized for acute viral hepatitis B reactivation and combination of lamivudin and tenofovir treatment was started. During his follow up, liver transaminases were elevated to the peak levels of ALT 2600 IU/mL and AST 1200IU/mL. Prothrombin time reached a maximum level of 17 seconds. After 3 weeks of treatment, transaminase levels trended towards a decrease, while lymphocyte count trended to increase back and the patient was discharged with tenofovir only. At the 4th month follow up, HBs Ag was negative with a high titer for AntiHBs (>1000 mIU/mL). Regarding CLL status, the same monoclonal B cells with FISH analysis showing 13q deletion only were determined. The time table of the patient's course was summarized in Figure 1. Informed consent was obtained from the patient for being included in the study.

Discussion

The immunogenic mechanism of HBV infection is complex. In normal population, after the entrance of HBV virus, the outcomes may be either; 1. infection may be rapidly eliminated, most expectedly in an immunocompetent individual, or 2. viral DNA may integrate in the hepatocyte and persist indefinitely but in a state that replication is minimally active but under control and last, 3. host immune system may be unable to eradicate or control the infection and this condition leads to chronic liver disease. As a result of these mechanisms, patients present with certain laboratory features which are defined as AC, OBI or IC a.k.a "low replicative chronic HBV infection" (1).

When a hematological malignancy is included in the picture, the immunologic pathways are altered due to reasons such as, the disease biology and as well as the treatments used for this malignancy and their short term and long term consequences. For the last 30 years, treatments of hematologic malignancies and their effects on HBV status are documented by retrospective analyses and are categorized as high-intermediate and low risk treatments for HBVr. Especially monoclonal

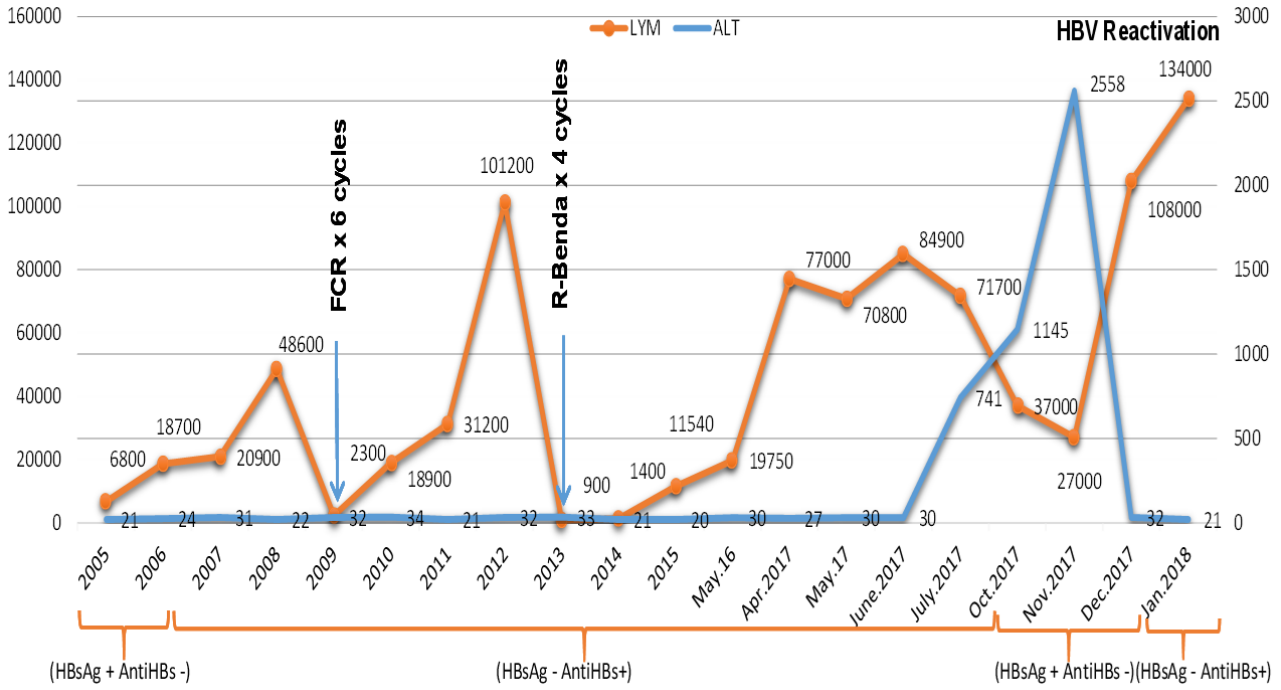

Fig. 1. The course of the patient in regard to lymphocyte count, alanine aminotransferase level and HBV serology status

antibodies, which are also may be regarded as B cell depleting agents and corticosteroids are now accepted as high risk treatments (6-9). In this regard, the mechanism of action of each drug will bring consequences on HBV-host interplay. Bendamustine, an alkylating agent with a benzimidazole ring as purine analog leads to cell death via single and double strand DNA crosslinking and is active towards dividing cells with a half life of 40 minutes. On the other hand, rituximab, which is a monoclonal antibody directed towards the CD20 antigen on the surface of B lymphocytes, activates complement dependent B cell toxicity and to human Fc receptrs mediating cell death through an antibody dependent toxicity. After the completion of all treatment cycles, rituximab is still detectable in serum up to 3 to 6 months and B cell depletion effect is sustained up to 6 to 9 months. Halflife elimination depends on the underlying disease as, an indolent B lymphoproliferative disorder CLL, it is 32 days while for high grade nonHodgkins lymphomas it is nearly 22 days.

The knowledge of HBV infection includes a latent infection can maintain the T cell response for decades and unresponsiveness of these T cells to HbeAg and HbcAg may result in ineffective cytotoxic T cell lysis of infected hepatocytes. So the interplay between HBV infection and B cell depletion after rituximab is much more complex, involving the Tcell mediated immunity which may be explained with the monoclonality of CLL cells bearing T cell surface antigen, CD5.

As the HBVr risk tend to decrease in the long run, after the completion of hematologic treatment under prophylactic antiviral treatment, late onset HBVr are reported (5). In our case, it was 66 months after the completion of rituximab in combination with bendamustine despite another additional year of antiviral treatment. Despite the pharmacokinetic knowledge of rituximab half life elimination prolonged in low grade B-lymphoproliferative disorder CLL, 66 months is still extreme. The lymphocytes in the peripheral blood of patients with CLL are monoclonal, mature-looking but nonfunctional cells, which can not differentiate towards plasma cells and also cannot present antigens, which means, are not protective for effective immune response.

The intriguing finding was the decrease in the lymphocyte count during the HBVr active period, the trough level of lymphocytes were as low as 27.000/mm3 when the ALT level was on its peak, 2600 U/L. This finding led us towards the hypothesis that, the patient is still hypogammaglobulinemic, which means antibody related immune response is still compromised since monoclonal B cells are nonfunctional, but an improved T cell related response may be developed against both to the clearance of lymphocytes (as they were decreased) and the immune reaction of necroinflammation in the

hepatocytes were triggered. The antiviral drugs used in the treatment of the flare (lamivudin and tenofovir) are well studied drugs with known adverse effects which do not include lymphocytosis.

The risk of treatments of hematological malignancies on HBVr is solid. Real life data suggests this risk may be categorized according to the potency of the treatment, as much as they may be understood. But the missing point lies within the first steps of HBV infection. Though the individuals may seem to be immuno competent, the outcomes of HBV encounter differ. It may be eliminated, remain silent under control or may exceed the immune system and lead to hepatic failure. This complexity becomes more complex with the addition of hematological malignancy and more complex still with the treatments.

Our case may lead to ideas of further studies on the interplay between the disease biology of hematological malignancy and HBV infection before the treatment enters the screen.

Conflict of interest: all authors declare that they have no conflict of interest

Authors' contributions: EU have collected the data, is the primary hematologist of the patient and wrote the paper, HU is the gastroenterologist, responsible for the treatment of HBV prophylaxis and the reactivation. HG had edited the paper and the data. MB collected the data and edited the paper. AMD has edited the data and the manuscript.

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