De novo hepatitis B infection in a HBsAg-negative patient with chronic lymphoproliferative disorder

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ABSTRACT

HBV reactivation is becoming an important cause of morbidity and mortality in patients with hematologic malignancies undergoing chemotherapy, at highest risk being HBsAg positive patients (active or inactive chronic HBV infection). The occult carriers of HBV have a lower risk, but recent data reveal that reactivation risk is increasing and complications like fulminant hepatic failure and even death can occur. Pre-emptive antiviral therapy is the current standard for HBs Ag positive patients, but for occult carriers routine antiviral prophylaxis is recommended only in certain circumstances.

We report a case of „de novo” hepatitis B in a patient with non-Hodgkin’s lymphoma and an unknown occult carrier status, which experienced viral reactivation after 5 month of combined fludarabine therapy. Lamivudine was initiated when HBs Ag seroreversion occurred and the outcome was good; she was then able to continue chemotherapy with rituximab-based regimen, maintaining antiviral treatment.

Keywords: screening, de-novo hepatitis B, occult HBV infection, lymphoma

INTRODUCTION

Hepatitis B represents a major health problem; 2 billion people have serological evidence of prior or current HBV infection (1), among approximately 350 million persons being chronic carriers (2). The prevalence is varying worldwide; Romania is thought to have intermediate endemicity 5-7% (3). The prevalence of HBV infection in immunocompromised patients it is not known precisely, because HBV screening is not performed at a large scale. HBV reactivation represent a common complication in cancer patients undergoing chemotherapy and its importance is revealed by potential severity (1). The clinical features may vary from asymptomatic hepatitis to fulminant hepatic failure and death (4). Close and careful monitoring is necessary to recognize reactivation of hepatitis B in order to prevent fatal complications.

CASE REPORT

We report the case of a 57-years old female, with no significant past medical history, admitted to Hematology Department in July 2008 to investigate for chronic fatigue (with onset in January 2008) and splenomegaly. No B signs were present. Complete blood count revealed
leukocytosis with lymphocytosis (4,000/mmc lymphocytes), mild anemia, mild thrombocytopenia; renal and liver tests were in normal ranges; peripheral blood immunophenotyping and immunohistochemical tests on bone marrow biopsy establish the Small Cell Non-Hodgkin Lymphoma lymphocytic type diagnosis; the stage was IV A according to Ann Arbor staging system. As in every case of chronic lymphoproliferative disorders, we screened for viral infections – HBs Ag was negative, antibody for HCV – negative and antibody for HIV also negative.

The patient received 6 courses of Fludarabine/Cyclophosphamide (FC) every 28 days, with no significant complications during therapy, except few episodes of mild neutropenia, but with no need to delay therapy.

In January 2009 she was evaluated and partial response was established. In June 2009, 5 month after chemotherapy was ended, she returned with intense fatigue, jaundice, pancytopenia and deteriorated liver function – AST 834 U/l, ALT 865 U/l, TB 1.75 mg/dl. The patient was addressed to Infectious Diseases Department, where a reactivation of HBV infection was diagnosed: HBsAg positive, HBeAg positive, anti-HBs IgG-type positive and HBV-DNA level was 50.100 UI/ml. It was excluded acute HBV infection (anti HBC IgM negative), HDV co-infection, EBV and CMV infections.

Lamivudine 100 mg per day was started and in October 2009 the liver tests returned to almost normal ranges, HBs Ag became negative and HBV-DNA was 12 UI/ml.

At this point, we considered that therapy may be continued and the patient received 8 courses of R-CVP (Rituximab, Cyclophosphamide, Vincristine, Prednisone) between November 2009 – June 2010, followed by Rituximab maintenance every 2 month, with good clinical and hematological evolution (complete response was obtained), and also liver function remained in normal ranges and undetectable HBV-DNA was revealed during therapy (last assessment in April 2010). Treatment with lamivudine was continued.

Despite the good response to therapy, the outcome was not favorable, the patient died in March 2011 because of a respiratory infectious complication.

**DISCUSSION**

HBV reactivation is a common complication in HBsAg positive patients receiving anticancer therapy, with a incidence ranging from 20% to 57% (5,6); it is defined by increment of serum HBV-DNA and ALT level (7). For patients with resolved (HBs Ag negative, antibody anti-HBs antigen positive, +/- antibody anti-HB core antigen

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*FIGURE 1.* At diagnosis time and during chemotherapy, the liver tests were in normal ranges; “de novo” hepatitis B was diagnosed 5 month after chemotherapy, which was a delayed reactivation of an undiagnosed occult carrier state; after Lamivudine introduction, liver tests return to normal
positive) and occult hepatitis B (HBs Ag negative, antibody anti HB core antigen positive), the incidence of reactivation is less frequent (8); the term for HBV reactivation in this subset of patients is de novo hepatitis, defined by increase of HBV-DNA more than $10^5$ copies/ml, HBsAg seroreversion (reappearance of HBs Ag) and threefold elevation of ALT on 2 consecutive measurements 5 days apart (8).

In our patient, the serological status of HBV infection was assessed only by screening for HBsAg, not for antibodies to HBsAg and HbcAg; in 2008, this complete screening was not a routine in our practice.

Some international guidelines recommend that patients who should receive chemotherapy should be screened for HBsAg, anti-HbC and HBs antibodies – AASLD (American Association for the Study of Liver Diseases) (9), CDC (Centers for Disease Control and Prevention) (2), Canadian Guidelines (10), whereas others recommend screening for HBsAg and HbcAb – EASL (European Association for the study of the Liver) (11), Scottish Liver Society (12). Interestingly, ASCO (American Society of Medical Oncology) advises HBsAg +/- HbcAb screening in specific categories of patients – those “at risk” for HBV (meaning the physician should identify precisely this subset of patients) and those undergoing “highly” cytotoxic or immunosuppressive therapy (stem cell transplant, Rituximab) (13).

Despite of all of these guidelines, there are several reports regarding the current practice in HBV screening; only 13% of oncologists screen every patient for HBV and 11% screen occasionally – data from a survey sent to the American Medical Association-registered oncologists (14); another retrospective US study revealed that cancer patients were not tested for HBV, only 17% being screened for HBsAg and HbcAb before chemotherapy (15); in another US study only one third of patients have had HBV serology performed before receiving Rituximab containing regimens (16); Wang et al performed a retrospective study about HBV screening in cancer patients, and only 17.1% received pre-chemotherapy HBV testing (17).

In Hematology and Oncology Centers from Romania, HBV screening is not performed on large scale (personal observation), and if it is, only HBsAg is generally searched for. This problem is a consequence of the absence of national recommendations regarding the correct screening. At present, in hemat-oncology ESMO recommendations are followed; HBV screening is suggested, but it is not specified in which way. The assessment of proper HBV serological status is important. Until recently, only HBsAg positive patients were considered at high risk for HBV reactivation; nowadays, even HBsAg / HbcAb “patients may experience HBV reactivation, especially after Rituximab therapy; their prevalence among chronic lymphoproliferative disorder patients and reactivation rate are variable: 21% prevalence and 10% reactivation in a case-series with a 1-year follow-up performed in a hospital from Hong Kong (18), 35% and 6% respectively in a study of Fukushima et al (19),
44% and 25% respectively in a prospective study of Yeo et al (20), 62.3% and 3.3% respectively in the study of Hui et al (8) – all of these studies conducted in Asian countries, with high HBV endemicity. Similar prevalence was found in Europe: 36% prevalence and 2.7% reactivation in Targhetta’s study (21) and 27% and 10% respectively in the study of Bedognetti et al (22), even if western countries are HBV low endemic areas. In the light of these data, occult HBV carriers undergoing chemotherapy should be monitored closely to detect viral reactivation.

The status of anti-HBs antibodies should be assessed also; patients having anti-HBs levels >10 UI/l are at lowest risk for reactivation, but not completely protected against it. During chemotherapy their titer can decrease (23). Their absence have been considered risk factor for viral reactivation in patients with lymphoma and occult/resolved hepatitis B receiving R-CHOP (20,24).

We can presume that our patient have had occult/resolved HBV infection at the time of hematological diagnosis and she developed „de novo“ hepatitis B infection after chemotherapy.

The general mechanism of reactivation caused by chemotherapy implies few steps: chemotherapy increases virus replication and HBV spreading in hepatocytes and suppresses the cellular immune response to the virus; after chemotherapy withdrawal, the immune response reconstitution leads to destruction of infected hepatocytes (25).

The typical clinical course of HBV reactivation is different between HBs Ag positive and negative patients; in a study of Yeo et al (26), serum HBV-DNA was undetectable at the time of ALT peak, and it peaked prior to ALT by 2 weeks in the first category of patients; in HBsAg negative patients, serum HBV-DNA peaked by 8–12 weeks before HBsAg seroreversion and 12–28 weeks before ALT increase (8). Regarding our patient, this specific reaction pattern is important, because if we would knew she had occult/resolved HBV infection, we would monitored more carefully not only ALT level (which was in normal ranges for a long time), but the HBV-DNA level, because the real reactivation is starting with HBV-DNA elevation; at this point we should institute antiviral therapy, in order to prevent fulminant hepatic failure and death. In Hui et al study, de novo HBV related hepatitis was independently associated with a higher risk of fulminant hepatic failure (8). Fortunately, the patient responded well to Lamivudine therapy, even if it was given after hepatitis clinical picture occurred.

Another possible option for the patient would be antiviral prophylaxis, which could be instituted before chemotherapy. The current recommendations do not support the antiviral prophylaxis in HBs Ag negative patients; DNA-HBV level should be assessed and if it is positive, prophylaxis should be started in occult carriers (11).

Reactivation could be induced by many agents; the most incriminated are biological agents, including Rituximab, a chimeric anti-CD20 monoclonal antibody, approved for treatment of B cell non-Hodgkin’s lymphoma. Rituximab is considered an independent risk factor for “de novo” HBV related hepatitis after chemotherapy (8). Fludarabine, a nucleoside analogue, in our case used in combination with an alkylating agent, induces a profound and prolonged immunosuppression, with a decrease of CD4 and CD8 lymphocytes, predisposing to opportunistic infections (27,28). This profound immunosuppression induced by fludarabine might favor a high rate of HBV replication (29). Most cases of HBV reactivation after fludarabine therapy were reported in HBsAg positive patients (29); there are very few reports about HBV reactivation in HBsAg negative/HBc Ab positive patients (30).

Even if the majority of the above studies were referring to HBV reactivation after Rituximab containing regimens, Mandalà et al consider that Fludarabine represent “high risk” chemotherapy, together with Rituximab, dose-dense regimens, induction of acute leukemia and for HBsAg negative/HBc Ab positive patients receiving Fludarabine recommend Lamivudine prophylaxis started before chemotherapy, continued up to 12 month after stopping therapy (1).

In our case, because the HBV screening was not performed correctly, we were not able to establish that the patient was an occult HBV carrier, to assess the risk for viral reactivation and to plan any antiviral prophylaxis; thus, she experienced HBV reactivation which responded well to lamivudine therapy, being able to continue therapy with Rituximab based regimen. Because of association of Lamivudine during chemotherapy, she did not develop a new HBV reactivation.

**CONCLUSIONS**

Proper HBV serologic status assessment should be implemented by national recommendations. Occult HBV carriers should be considered for antiviral prophylaxis regardless of chemotherapy type, to avoid viral reactivation.
REFERENCES


3. Grigorescu M. – Tratat de hepatologie, 2004; p.375


30. Toscanini F., De Leo P., Calcagno G. et al. – Hepatitis B reactivation in a HBsAg-negative, HBcAb-positive patient receiving fludarabine for the treatment of chronic lymphocytic leukemia. Hepatol 2011, article ID 258791, 3 p