

Hepatitis B virus reactivation in hepatitis B virus surface antigen negative patients receiving immunosuppression: A hidden threat

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Abstract

AIM: To present the characteristics and the course of a series of anti-hepatitis B virus core antibody (HBc) antibody positive patients, who experienced hepatitis B virus (HBV) reactivation after immunosuppression.

METHODS: We retrospectively evaluated in our ter-

tiary centers the medical records of hepatitis B virus surface antigen (HBsAg) negative patients who suffered from HBV reactivation after chemotherapy or immunosuppression during a 3-year period (2009-2011). Accordingly, the clinical, laboratory and virological characteristics of 10 anti-HBc (+) anti-HBs (-)/HBsAg (-) and 4 anti-HBc (+)/anti-HBs (+)/HBsAg (-) patients, who developed HBV reactivation after the initiation of chemotherapy or immunosuppressive treatment were analyzed. Quantitative determination of HBV DNA during reactivation was performed in all cases by a quantitative real time polymerase chain reaction kit (COBAS Taqman HBV Test; cut-off of detection: 6 IU/mL).

RESULTS: Twelve out of 14 patients were males; median age 74.5 years. In 71.4% of them the primary diagnosis was hematologic malignancy; 78.6% had received rituximab (R) as part of the immunosuppressive regimen. The median time from last chemotherapy schedule till HBV reactivation for 10 out of 11 patients who received R was 3 (range 2-17) mo. Three patients (21.4%) deteriorated, manifesting ascites and hepatic encephalopathy and 2 (14.3%) of them died due to liver failure.

CONCLUSION: HBsAg-negative anti-HBc antibody positive patients can develop HBV reactivation even 2 years after stopping immunosuppression, whereas prompt antiviral treatment on diagnosis of reactivation can be lifesaving.

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Key words: Immunosuppression; Hepatitis B; Anti-hepatitis B virus core antibody positivity; Occult hepatitis B virus infection; Rituximab

Core tip: Patients with occult or resolved hepatitis B

undergoing chemotherapy or immunosuppression are potentially at risk of hepatitis B virus (HBV) reactivation which can be disastrous since it can lead to acute liver failure and death. In this report, we describe the characteristics and outcome in one of the larger series of patients ($n = 14$) with occult or resolved HBV who experienced HBV reactivation after receiving immunosuppression though they were initially HBV surface antigen-negative. Most of patients had received rituximab. We showed that these patients can develop severe HBV reactivation even 2 years after stopping immunosuppression, whereas prompt antiviral treatment on diagnosis of reactivation can be lifesaving.

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INTRODUCTION

Hepatitis B virus (HBV) is a common cause of liver disease, affecting more than 240 million people worldwide^[1]. HBV carriers are traditionally identified by the detection of HBV surface antigen (HBsAg) in their blood. During the past 15 years with the availability of highly sensitive molecular methods, persistence of HBV genomes in HBsAg negative individuals has been clearly proven termed occult HBV infection (OBI).

Accordingly, OBI is defined by the presence of HBVDNA in the liver tissue or also in the serum of HBsAg negative individuals who are either anti-HBc antibodies (Abs) and/or anti-HBs Abs positive or even have negative serological markers^[2-4]. OBI is mainly related to a strong suppression of the viral activity in which the host's immune surveillance is likely to play a major role. Therefore, patients with OBI undergoing strong immunosuppression are potentially at risk of HBV reactivation, a common phenomenon in HBsAg-positive hematological or oncological patients^[5,6]. HBV reactivation has also been reported in patients with OBI treated with synthetic disease modifying antirheumatic drugs (DMARDs) and/or high-dose prednisolone for rheumatic diseases^[7-13]. Especially in the era of targeted immune modulators (commonly referred to as biological response modifiers or "biologics"), which cause profound immunosuppression and are used in the treatment of immunological, inflammatory as well as hematological/oncological diseases, the risk becomes even greater^[14].

The European Association for the Study of the Liver clinical practice guidelines for the management of chronic HBV infection in HBsAg-negative patients with positive anti-HBc Abs who receive chemotherapy and/or immunosuppression suggest HBVDNA determination in

the serum and if undetectable, strict follow-up consisting of alanine aminotransferase (ALT) and HBVDNA testing^[15]. Treatment with potent antivirals with high barrier to resistance (*i.e.*, entecavir or tenofovir) is recommended upon confirmation of HBV reactivation before ALT elevation^[15]. However, there are no surrogates or prognostic markers for impending HBV reactivation, making the follow-up of these patients difficult, since cost-effectiveness of serial and frequent HBVDNA testing has not been documented. For these reasons it is urgent to define the characteristics of these patients with OBI who experience HBV reactivation, when they receive immunosuppression as well as the features of the HBV reactivation itself.

Accordingly, in this case-study we describe the course of 14 patients with OBI who received intense immunosuppression with various biological or non-biological immune modifying agents for diverse pathological entities and experienced HBV reactivation.

MATERIALS AND METHODS

Patients

We retrospectively evaluated in our tertiary centers (Aristotle University Medical School and University of Thessaly Medical School) the medical records of HBsAg seronegative patients who suffered HBV reactivation after chemotherapy or immunosuppression during a 3-year period (2009-2011). Accordingly, we identified 14 patients with occult [anti-HBc (+)/anti-HBs (-)/HBsAg (-), $n = 10$] or resolved [anti-HBs (+)/anti-HBc (+)/HBsAg (-), $n = 4$] HBV infection, who developed HBV reactivation after the initiation of chemotherapy or immunosuppressive treatment. The clinical, laboratory and virological characteristics of the patients were recorded. The mean follow-up of the patients from the time of the diagnosis of HBV reactivation was 8 (range 1-60) mo. Although there are no clear diagnostic criteria for HBV reactivation, we defined HBV reactivation as seroconversion from HBsAg negative to HBsAg positive with serum HBV DNA turning from negative to positive^[16]. Quantitative determination of HBV DNA during reactivation was performed in all cases by a quantitative real time polymerase chain reaction kit (COBAS Taqman HBV Test; cut-off of detection: 6 IU/mL). All patients were anti-hepatitis C virus negative, anti-hepatitis A virus IgG positive, anti-HIV negative at baseline (before the initiation of immunosuppression) as well as at the time of HBV reactivation.

RESULTS

The 10 anti-HBc (+)/anti-HBs (-)/HBsAg (-) patients were all males, whereas 2 out of 4 anti-HBc (+)/anti-HBs (+)/HBsAg (-) patients were females. The median age at diagnosis of HBV reactivation was 74.5 (range 53-82) years, while the median age of the diagnosis of their primary disease and initiation of immunosuppression was 73 (range 49-80) years. The primary diagnosis

Table 1 Characteristics and outcome of the ten hepatitis B surface antigen (-)/anti-hepatitis B virus core antibody (+)/anti-hepatitis B virus surface antigen (-) patients (at baseline) who experienced hepatitis B virus reactivation after immunosuppressive therapy

No.	Age, yr (at reactivation)	Sex	Disease	Type of IMS	Months from start of IMS to HBV reactivation	Months from last treatment cycle to diagnosis of HBV reactivation	HBV-DNA (IU/mL) at diagnosis of HBV reactivation	ALT/Bil/INR at diagnosis of HBV reactivation	Antiviral treatment	Serology at end of follow-up	Outcome
1	77	M	NHL	C, Flud, R	6	3	> 17857000	1472/3.22/1.3	Tenofovir	Anti-HBc (+)	Alive, response ¹
2	71	M	NHL	CHOP-R	8	1	487934	871/8.8/0.87	Entecavir	Anti-HBc (+)	Liver related death
3	74	M	NHL	C, Flud, R	6	1	1310000	73/0.7/0.97	Tenofovir	NA	Alive, response ¹
4	76	M	NHL	R	24	1	> 17857000	374/0.44/1.22	Entecavir	NA	Alive, response ¹
5	81	M	NHL	CHOP-R	30	12	660570	737/1/1.37	No treatment due to spontaneous seroconversion	Anti-HBc (+)/anti-HBs (+) 22 IU/L	Alive, response ¹
6	78	M	Castleman's disease	P, R	12	1 (from last R cycle)	4228720	1536/15.8/1.03	Lamivudine	Anti HBc (+), anti-HBs (+) 189 IU/L	Non-liver related death
7	82	M	CLL	Chl, R, C	22	17 (from last R cycle)	> 17857000	3440/20.8/1.7	Tenofovir	HBsAg (+), anti-HBc (+), HBeAg (+)	Alive, response ¹
8	72	M	Temporal arteritis	P, MTX	6	0	> 17857000	308/0.63/1.03	Tenofovir	NA	Alive, response ¹
9	75	M	Dermatomyositis	P, MTX, AZA, Cyc	15	0	126992	657/1.47/0.86	Entecavir	Anti-HBc (+)/anti-HBe (+)	Alive, response ¹
10	53	M	Kidney transplantation	P, Cyc, Myc	48	0	> 17857000	28/0.96/0.98	Entecavir	HBsAg (+), anti-HBc (+), HBeAg (+)	Alive, response ¹
11	73	F	NHL	CHOP-R	9	4	127000	614/1.2/1.12	Lamivudine	Anti-HBc (+) anti-HBs (+) 183 IU/L	Liver related death
12	68	M	HL	ABVD, CHOP-R, DHAP, HSC transplantation, BEAM	28	16	> 17857000	49/1.1/1.01	Tenofovir	HBsAg (+), anti-HBc (+), HBeAg(+)	Alive, response ¹
13	77	M	Waldenstrom's macroglobulinemia	C, R	36	3 (from last R cycle)	> 17857000	2500/19/1.19	Tenofovir	Anti-HBc (+)/anti-HBs (+) 579 IU/mL	Alive, response ¹
14	64	F	RA	MTX, R	24	2 (from last R cycle)	> 17857000	72/1.02/0.96	Entecavir	NA	Alive, response ¹

¹Clinical and biochemical response to antiviral treatment. HBV: Hepatitis B virus; HBc: Hepatitis B virus core antibody; HBsAg: Hepatitis B virus surface antigen; F: Female; M: Male; NHL: Non-Hodgkin lymphoma; CLL: Chronic lymphocytic leukemia; IMS: Immunosuppression; C: Cyclophosphamide; Flud: Fludarabine; R: Rituximab; CHOP-R: Cyclophosphamide Doxorubicin Vincristine Prednisone-Rednizolon; Chl: Chlorambucil; MTX: Methotrexate; AZA: Azathioprine; Cyc: Cyclosporine; Myc: Mycophenolate. NA: Not applicable.

of 10 patients (71.4%) was hematologic malignancy: six suffered from non-Hodgkin lymphoma, one from Hodgkin lymphoma, one from Castleman's disease, one from chronic lymphocytic leukemia and one from Waldenstrom's macroglobulinemia (Table 1). Regarding the remaining 4 patients, 3 were diagnosed with rheumatological diseases (one with temporal arteritis, one with dermatomyositis and one with rheumatoid arthritis). Finally, the last patient had received kidney transplantation for chronic renal failure due to diabetes mellitus (Table 1). He was anti-HBc (+)/anti-HBs (-)/HBsAg (-) before kidney transplantation and he had received a cadaveric

kidney from an HBsAg (-)/anti-HBc (-) donor.

Eleven out of 14 patients (78.6%) had received rituximab (R) as part of the immunosuppressive schedule regimen (Table 1). The patient suffering from Hodgkin lymphoma (patient 12) had sequentially received diverse schemes of chemotherapy, including combination with R and finally autologous hemopoietic stem cell transplantation (HSCT). The median time from the initiation of immunosuppression till HBV reactivation was 18.5 (range 6-48) mo. The median time from last chemotherapy cycle till HBV reactivation for the 10 out of 11 patients who received R was 3 (range 2-17) mo. Patient 12 was diag-

nosed with HBV reactivation 16 mo after HSCT. The remaining 3 patients experienced reactivation while on immunosuppression containing corticosteroids (Table 1).

The viral load during the diagnosis of HBV reactivation was high in 50% of the patients (above 17857000 IU/mL). The median viral load in the sera of the remaining patients was 574252 IU/mL (range 12700-4228720 IU/mL). The median maximum ALT, aspartate aminotransferase, bilirubin and INR levels during reactivation was 635.5 IU/mL (range 28-3440 IU/mL), 339 IU/mL (range 24-2306 IU/mL), 1.47 mg/dL (range 1-20.8 mg/dL) and 1.075 (range 0.86-1.7), respectively. However, all our patients were asymptomatic during reactivation and were diagnosed in routine laboratory testing.

All but one patients received antiviral treatment with nucleos(t)ide analogues immediately after the diagnosis of HBV reactivation (Table 1). Actually, the median time from the documentation of transaminase rise until treatment initiation was 15 (range 0-180) d. Patient 5 had already achieved seroconversion (disappearance of HBsAg and development of anti-HBs Abs) at diagnosis of HBV reactivation and for this reason he did not receive any treatment.

The HBV serological markers of 10 patients who were tested at the end of follow-up, are shown in Table 1. In more detail, 4 (40%) patients seroconverted to anti-HBs Abs after a median of 10.5 (range 3-60) mo. Three (30%) patients remained HBsAg (+)/HBeAg (+) after 24 mo the two and after 1-mo the third whereas the remaining 3 (30%) patients were anti-HBc (+)/ anti-HBe (+) at the end of follow-up (after 1, 7 and 26 mo, respectively).

Regarding the outcome, 3 patients (21.4%) deteriorated, manifesting ascites and hepatic encephalopathy and 2 (14.3%) of them died due to liver failure. The third died of a non-liver related cause, 60 mo after the diagnosis of HBV reactivation.

DISCUSSION

The natural course of chronic HBV infection is determined by the interplay between virus replication and the host's immune response^[17]. In case of OBI, a long-term persistence in the nuclei of the hepatocytes of the HBV covalently-closed-circular DNA (cccDNA) supports its molecular basis^[18]. In parallel, there is a strong suppression of the viral activity by the host's immune surveillance, which is likely to be the factor of outmost importance. However, this state of suppression of viral replication and gene expression may be discontinued by any kind of immunosuppression, leading to the development of a typical hepatitis B that often has a severe, even fulminant, clinical course.

To the best of our knowledge, this is one of the larger series of patients with OBI or resolved HBV infection who experienced HBV reactivation after receiving immunosuppression. The incidence of such a clinical adversity varies in the literature, depending on the population studied or the immunosuppressive regimen used. Among pa-

tients with OBI and malignancies the reported incidence fluctuates between 2.7%^[6], for conventional regimens and 25%^[19] when R is used. In patients with rheumatologic diseases the incidence of HBV reactivation in resolved infection is rather lower ranging from 2.2%^[12] to 5.2%^[11]. However, in the later study^[11], when only patients treated with biological agents were taken into account, the incidence raised to 11.5%. Our series confirms two points: first the vast majority (71.4%) of the patients were diagnosed with hematologic malignancy and second approximately 80% of the patients had received R, sometime during their course.

R is a monoclonal antibody directed against the CD20 antigen expressed on the surface of normal and malignant B lymphocytes causing apoptosis. B cell plays a key role in the multiple immune responses against HBV: besides the production of neutralizing antibodies, it is an antigen presenting cell and enhances the cytotoxic response of CD8 T lymphocytes. Therefore, its destruction favors dramatically HBV replication. Our series is in accordance with the finding that R is a HBV reactivation risk factor even greater than corticosteroids, since in a series of patients with lymphoma treated with chemotherapy (CMT), the only significant difference between the reactivation group with resolved hepatitis and the group without reactivation was treatment with R^[5]. In addition, three recent reports, including a meta-analysis of 184 case reports, have demonstrated that R containing regimens significantly increased the risk of HBV reactivation in OBI patients by five-fold compared to non-R regimens^[5,19,20].

Since by definition CMT/immunosuppression decreases the ability of the immune system to respond, a period of time is necessary for immune reconstitution and subsequent attack on the liver, where a massive replication of HBV has taken place due to lack of "surveillance"^[16]. For this reason, HBV reactivation often manifests in periods between cycles of CMT/immunosuppressive treatment or at the end of therapy after the recovery of the host immune system^[21]. Therefore, in HBsAg carriers the time between last CMT cycle and HBV reactivation detection is variable: from 1-36 mo, usually ranging between 1 and 4 mo^[22]. From the present study, it seems that the same is true also for resolved HBV infection, since the median time from last cycle to reactivation was 3 mo, although with wide variation from 2 to 17 mo. Therefore, it is crucial to closely follow-up patients with OBI after stopping immunosuppression, especially when they have received R, for at least 2 years. In addition, patients who are in continuous immunosuppression containing corticosteroids without R in the regimen, must be considered as vulnerable as those receiving cycles of CMT, since -especially after corticosteroid tapering- they can develop HBV reactivation at any time even after 4 years, as happened with patient 10 who had received kidney transplantation.

The clinical course of HBV reactivation usually begins with HBV replication, during which serum HBVDNA levels increase and in a second phase hepatitis occurs (2-3

wk after HBVDNA elevation) characterized by increase of transaminases and, occasionally appearance of symptoms such as fatigue, malaise and jaundice^[22]. However, the reactivation can also present with fulminant hepatitis which intimates a poor prognosis. In the present cohort, 1/5 of the patients manifested fulminant liver failure and 14% died. In a recent meta-analysis of case reports and case series of R associated HBV reactivation in lymphoproliferative diseases^[20], the fulminant liver failure rate and, as a consequence, the liver related mortality rate among the HBcAb (+)/HBsAg (-) cases was between 20% and 50%. The low mortality in our present case series could be attributed to the immediate initiation (within a median of 15 d of antiviral treatment after transaminase elevation. In many circumstances, this is not the case, since these patients are, frequently, not recognized as a reactivation high-risk group, leading to an underestimation of hepatitis due to HBV^[23].

The vast majority of our patients received tenofovir or entecavir, drugs with high barrier to resistance. This can be justified by considering that current guidelines^[15] recommend therapy with nucleoside analogue for at least 6-12 mo after discontinuation of chemotherapy and patients with hematological malignancies receive long term therapeutic regimens so they will probably demand long term use of antiviral treatment with the risk to develop treatment-resistant HBV variants if treated with lamivudine.

Male sex has been reported to be a significant factor associated with the risk of developing HBV reactivation in HBsAg (-) cancer patients on chemotherapy^[24,25]. Interestingly, 12 out of 14 patients in the present study were male, which is in accordance with previous studies^[19] on OBI patients. Male sex along with old age (median age at reactivation 74 years) could define two characteristics of OBI patients who reactivated after immunosuppression. It is unfortunate that blood samples were not available in our patients, for HBVDNA testing at baseline before the institution of immunosuppression, since in a recent study^[26], HBVDNA testing had a 90% ability to forecast persistent HBsAg negativity in HBVDNA negative patients showing that highly sensitive serum HBVDNA testing had better performance than serological tests in predicting HBsAg reappearance.

In conclusion, patients with OBI who develop HBV reactivation after immunosuppression are more likely to have received R as a component of their treatment for their underlying disease, are more frequently older males and they can experience hepatitis due to HBV reactivation even 2 years after stopping the immunosuppressive therapy. Immediate start of antiviral treatment with potent antivirals after transaminase elevation and diagnosis of HBV reactivation with HBVDNA testing is of utmost importance in order to prevent deterioration and fulminant liver failure leading to lethal outcome. Two strategies could be adopted in order to prevent HBV reactivation in OBI patients: baseline and serial HBVDNA testing during and at least one year after the end of immunosuppressive treatment^[23] or pre-emptive treatment

with antivirals in all anti-HBc Abs (+) patients with or without resolved infection particularly when R is used. However, clinical evidence to date is not informative for determining optimal frequency and duration of such HBVDNA monitoring, whereas, concerning pre-emptive treatment, there are issues such as drug resistance and cost effectiveness, which also need to be addressed. Therefore, further studies to better define the characteristics of OBI patients who are “prone” to reactivation after receiving immunosuppression are needed, while in parallel establishment of new, precise guidelines on how to handle these patients seems to be extremely urgent considering the high mortality rate of a disease which can be effectively managed.

COMMENTS

Background

Patients with occult hepatitis B, defined by the presence of hepatitis B virus (HBV)-DNA in the liver tissue or also in serum of hepatitis B virus surface antigen (HBsAg) negative individuals, undergoing strong immunosuppression are potentially at risk of HBV reactivation, a common phenomenon in HBsAg-positive hematological or oncological patients. HBV reactivation can be disastrous for the patient since it can lead to acute liver failure and death.

Research frontiers

The characteristics of these patients with occult HBV infection who experience HBV reactivation, when they receive immunosuppression as well as the features of the HBV reactivation itself need urgently to be defined. Until now few studies have accessed these topics mainly as case reports.

Innovations and breakthroughs

This is one of the larger series of patients with occult or resolved HBV infection who experienced HBV reactivation after receiving immunosuppression. The incidence of such a clinical adversity varies in the literature, depending on the population studied and, accordingly, on the immunosuppressive regimen used. This study confirms that the vast majority of these patients are being diagnosed with hematologic malignancy and the patients usually have received rituximab, sometime during their course.

Applications

Clinical evidence to date is not informative for determining optimal frequency and duration of HBV DNA monitoring during immunosuppressive treatment in patients with occult or resolved HBV infection. In addition, concerning pre-emptive treatment given in all these patients, there are issues such as drug resistance and cost effectiveness, which need to be addressed. Therefore, further studies to better define the characteristics of occult HBV infection patients who are “prone” to reactivation after receiving immunosuppression are needed.

Peer review

The excellent manuscript is of utmost importance and clinical relevance as it throws light on a frequently faced issue on handling of cases with occult HBV infection undergoing immunosuppression.

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