INTERNAL MEDICINE

□ CASE REPORT □

Late Reactivation of Hepatitis B Virus after Chemotherapies for Hematological Malignancies: A Case Report and Review of the Literature

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Abstract

Reactivation of hepatitis B virus (HBV) is a serious complication of immunosuppressive therapy and cytotoxic chemotherapy. The optimal duration of HBV-DNA monitoring for at-risk patients depends on the clinical features of reactivation, especially the range of potency from therapies to reactivation. We present a case of very late reactivation after chemotherapy for lymphoma and review previous reports of late reactivation cases. We also underscore the significance of developing an indicator for anti-HBV immunity which can be used to determine the optimal monitoring period.

Key words: *de novo* hepatitis, hepatitis B virus, rituximab

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Introduction

Reactivation of hepatitis B virus (HBV) is a serious complication of immunosuppressive therapy and cytotoxic chemotherapy (1). Carriers of HBV (HBsAg-positive) are at higher risk of reactivation than non-carriers, and prophylaxis with anti-viral therapy is applied during and after these treatments (2). While patients who recovered from past HBV infection (HBsAg-negative and HBcAb-positive and/or HBsAb-positive) are at lower risk, they still carry a definite risk of reactivation and usually receive either prophylaxis or preemptive therapy, according to the viral load. Hepatitis in these patients is referred to as *de novo* hepatitis and poses a high risk of progressing to the fulminant form of hepatitis, which is associated with nearly 100% mortality once developed.

A recently developed scheme for managing HBV reactivation has been shown to be highly effective, with a significant suppression rate of *de novo* hepatitis (3). However, sporadic cases of late reactivation, tentatively defined as those that take place more than 12 months after immunosuppressive therapies, have been reported under this management scheme, highlighting unresolved issues that are mainly due to the lack of any way of determining the optimal period for monitoring the viral load after chemotherapy. We herein report a case of very late reactivation of HBV following rituximab-containing therapy for malignant lymphoma and discuss this issue with a review of the literature regarding late HBV reactivation.

Case Report

A 77-year-old man was diagnosed with diffuse large B cell lymphoma stage IIA at low-intermediate risk according to the international prognostic index in July of Year X. A routine examination before treatment revealed positive HBsAb and HBcAb and negative HBsAg and HBV-DNA; we therefore concluded that this patient had previously had an HBV infection and started periodical monitoring of HBV-DNA according to the recommended management scheme in Japan. Six courses of R-CHOP therapy successfully induced

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Table 1. Clinical Profile of HBV Associated Markers.

time (year/month)	X/Jul[a]	X+1/Mar[b]	X+2/Nov[c]	X+4/Jun[d]	X+4/Jul	X+4/Aug
HBsAg (IU/mL)	0			111	0	0
HBsAb (mIU/mL)	52.9			<10		32.1
HBcAb	9.9			11.18	10.19	
IgM HBcAb				0.1		
HBeAg				350	0.4	
HBeAb (%)				0.1	90	
HBV-DNA (log copies/mL)	negative	negative	negative	6.2	<2.1	
HBcrAg				>7.0	4.7	3.9

Abbreviations: HBsAg: hepatitis B surface antigen, HBsAb: antibody against hepatitis B surface antigen, HBsAb: antibody against hepatitis B core antigen, HBeAg: hepatitis B e antigen, HBeAb: antibody against hepatitis B e antigen, HBcrAg: hepatitis B core related antigen

[a] DLBCL was diagnosed.

[b] Six courses of R-CHOP finished.

[c] HBV-DNA monitoring was suspended.

[d] Hepatitis occurred and entecavir was administered.

complete remission.

Since the patient remained negative for HBV-DNA for 20 months after R-CHOP therapy, we suspended further monitoring in November of Year X+2. We continued measuring ALT/AST as a routine laboratory test at outpatient visits. Nineteen months later (June of Year X+4; 33 months after the last session of R-CHOP therapy), this patient presented with increased levels of liver enzymes (ALT 104 IU/L, AST 97 IU/L) that had been within normal ranges one month prior. A further examination revealed reverse seroconversion of HBs (HBsAg 111 IU/mL, HBsAb <10 mIU/mL), and given that the patient had no history of blood transfusions and was sexually inactive, we diagnosed him with *de novo* hepatitis. The lymphocyte counts in the peripheral blood and serum IgG level were within normal limits. Entecavir was started, and the hepatitis resolved promptly leading to rapid suppression of HBV-DNA and HBsAg and recovery of HBsAb (32.1 mIU/mL) within two months. The clinical course of HBV-related markers is shown in Table 1. A further examination revealed that the patient had HBV-DNA genotype B, with a mixed precore mutation (nt1894, 10% mutated and 90% wild) and a wild type core promotor region (nt1972 and nt1974).

Discussion

HBV reactivation and *de novo* hepatitis is a serious condition associated with high mortality and morbidity usually encountered after chemotherapy or immunosuppressive therapy for patients with past HBV infection or HBV carriers (4). In endemic areas of HBV such as Japan, management guidelines are available to prevent *de novo* hepatitis in patients who are to receive therapies that entail immunosuppression (5); this preemptive approach is recommended for HBV non-carrier patients without a detectable viral load (HBV-DNA <2.1 log copies/mL); patients undergo monthly monitoring for HBV-DNA and begin anti-viral therapy when the HBV-DNA titer increases to ≥2.1 log copies/mL, and a prospective study in Japan has demonstrated the efficacy of this strategy in completely suppressing hepatitis (3). However, the success of this preemptive approach depends on the optimal setting of cutoff values for judging reactivation, because a similar approach in Taiwan applying distinct cut-off criteria resulted in the occurrence of 7 *de novo* hepatitis cases out of 150 enrollments (6).

Our case of *de novo* hepatitis that occurred three years after the completion of chemotherapy is striking in that the present preemptive strategy was not able to completely prevent HBV reactivation-related hepatitis. We detected no early signs of reactivation, probably because we stopped HBV-DNA monitoring 18 months after chemotherapy, but this raises a significant issue regarding how long and in whom we should continue measuring viral load over the generally recommended duration of one year, which was tentatively determined based on the observation that most cases of HBV reactivation occurred within one year (7, 8).

In practice, the duration of HBV monitoring for each patient is left to the discretion of each physician. While HBV reactivation has been widely acknowledged recently and the prevalence of the preemptive strategy has significantly suppressed *de novo* hepatitis, sporadic reports of late reactivation (defined as those taking place one year after the final therapy session) have gradually accumulated. However, integrative information such as the incidence and clinical characteristics of late reactivation are lacking, limiting the utility of these reports for enacting effective countermeasures.

A more practical and economically less burdensome solution is to identify those patients who need an extended monitoring period, instead of continuing to monitor the viral load in all patients indefinitely. We therefore searched the PubMed database for late reactivation cases in hematological patients and reviewed them (7-13). The incidence of late reactivation in a prospective cohort under the routine monitoring policy is relatively low, ranging from 0% to 1.1% according to reports [Japanese cohort: 2/269 (3), Taiwanese cohort: 0/150 (6), Hong Kong cohort 3/263 (13)]. However, it would be inappropriate to ignore late reactivation based on its rarity, because *de novo* hepatitis is prone to progressing to fulminant hepatitis, which has a mortality of nearly 100% (4).

Table 2. Cases of Late Reactivatio of HBV after Hemtological Chemotherapies (Transplantation Excluded).

						status at reactivation					
sex	age	disease	treatment	cycles	HBV status before treatment	interval from chemotherapy to reactivation	liver enzymes and serostatus of HBV	HBV genotype and mutation	HBV-DNA	outcome	treatment of reactivation	references
Female	53	DLBCL	R-CEOP	8	HBsAg-, HBsAb+, HBcAb+, HBV-DNA<10 mIU/mL	100 weeks	ALT 28 IU/L, HBsAg-, HBsAb+	ND	310 IU/mL	recovered	entecavir	Seto [13]
Female	84	LPL	R	4	HBsAg-, HBsAb-, HBcAb+, HBV-DNA<10 mIU/mL	80 weeks	ALT 19 IU/L, HBsAg-, HBsAb-	ND	71 IU/mL	recovered	entecavir	Seto [13]
Female	68	DLBCL	R-CVP	4	HBsAg-, HBsAb+, HBcAb+, HBV-DNA<10 mIU/mL	72 weeks	ALT 14 IU/L, HBsAg-, HBsAb+	ND	82 IU/mL	recovered	entecavir	Seto [13]
Female	77	low grade B cell lymphoma	R, R-Flu	9 for R	HBsAg-, HBsAb+, HBcAb-	18 months	AST 1740 IU/L, ALT 1904 IU/L, HBsAg+, HBsAb-HBcAb+, HBeAg+, HBeAb-	genotype D, sT118K	230000 IU/mL	ND	lamivudine	Ceccarelli [11]
Female	78	cutaneous follicular center B cell lymphoma	R	4	HBsAg+, HBsAb-, HBcAb+, HBeAg-, HBeAb+	12 months	ALT 1624 IU/L, HBsAg+, HBsAb-, HBcAb+, HBeAg+, HBeAb-	ND	200000 copies/mL	dead	lamivudine	Perceau [10]
Female	68	DLBCL	R-CHOP	6	ND	1 year	AST 109 IU/L, ALT 88 IU/L, HBsAb+, HBeAg-, HBeAb-*	ND	ND	dead	lamivudine	Garcia [7]
Female	50	malignant lymphoma	R-CV	ND	HBsAg+, HBsAb-, HBcAb+	441 days	AST/ALT elevation	ND	6.9 log copies/mL	recoverd	entecavir	Takahashi [9]
Female	53	malignant lymphoma	R-CHOP +MTX (IT)	ND	HBsAg+, HBsAb-, HBcAb+	539 days	AST/ALT elevation	ND	5.3 log copies/mL	dead	lamivudine	Takahashi [9]
Male	84	malignant lymphoma	R-THP-COP	ND	HBsAg+	1210 days	ND	ND	8.8 log copies/mL	recovered	entecavir	Takahashi [9]
Female	87	MM	MP	ND	HBsAg-, HBsAb+, HBcAb+, HBV-DNA<1.8 log copies/mL	553 days	HBsAg+	ND	8.5 log copies/mL	recovered	entecavir	Takahashi [9]
ND	elderly	DLBCL	R-CVP	6	HBsAg-, HBcAb+	1 year	AST 116 IU/L, ALT 139 IU/L, HBsAg-,	genotype D, G415R, T126T/I, T131A, C139Y, E/D144G	1.7×10^7 IU/mL	recovered	lamivudine	Zoppoli [8]
Male	70	DLBCL	R-CHOP	6	HBsAb+, HBcAb+, HBV-DNA-	21 months	ND	ND	432 IU/mL	recovered	entecavir	Kusumoto [3]
Male	77	DLBCL	R-CHOP	6	HBsAb+, HBcAb+, HBV-DNA-	13 months	ND	no mutation	14 IU/mL	recovered	entecavir	Kusumoto [3]
Male	77	DLBCL	R-CHOP	6	HBsAg-, HBsAb+, HBcAb+, HBV-DNA-	33 months	AST 104 IU/L, ALT 97 IU/L, HBsAg+, HBsAb-, HBcAb+, HBeAg+, HBeAb-	genotype B, nt1894	6.2 log copies/mL	recovered	entecavir	our case

Abbreviations: ND, no data; DLBC, diffuse large B cell lymphoma; LPL, lymphoplasmacytic lymphoma; R, rituximab; Flu, fludarabine; CEOP, cyclophophamide, epirubicin, vincristine, prednisone; CV, cyclophophamide, vincristine; CVP, cyclophamide, vincristine, prednisone; CHOP, cyclophamide, doxorubicin, vincristine, prednisone; THP-COP, pirarubicin, cyclophamide, vincristine, prednisone; MTX, methotrexate; IT, intrathecal; MP, melphalan, predonisone;
* later, converted to HBsAg+ and HBeAg+

Hematopoietic stem cell transplantation is distinct from conventional chemotherapies, in that it involves much deeper immunological suppression and the need for immunosuppressing agents for a long period after allogeneic transplantation. These patients tend to have a much higher incidence of reactivation, and the reactivation time tends to be later than with conventional therapies (12). In such situations, a longer follow up period is recommended and justified. Therefore, we excluded transplant cases from the review, leaving a total of 14 cases (Table 2).

These 14 patients were characterized by advanced age, lymphoid malignancies, and treatment with multiple courses of rituximab-containing therapies. Of note, some of these patients received less intensive or mild therapies, but even rituximab monotherapy and MP (melphalan and prednisolone) therapy caused late reactivation (10, 13), suggesting that the intensity of treatments has little association with the risk of late reactivation. Discrete follow-up of patients with advanced age, lymphoid malignancies, and rituximab-containing therapies is warranted; however, these features are apparently unsatisfactory for the proper characterization of patients at high risk of late reactivation.

Notably, though: whether or not late reactivation is a distinct disease state from typical *de novo* hepatitis remains controversial, as the clinical outcomes differ. Indeed, all 14 of the patients reviewed here received nucleoside analogues (5 lamivudine and 9 entecavir), and 10 were successfully treated, while typical *de novo* hepatitis has a much higher mortality rate. In addition, there are cases of spontaneous reactivation of HBV without any chemotherapies or immunosuppressive therapies who responded to anti-viral therapy promptly (14). These cases hamper determination of the clinical entity of late reactivation. However, it would be prudent to have a discrete follow-up policy in place until the clinical characteristics of late reactivation are clarified.

Alternatively, judgements regarding when to finish monitoring the viral load might be best made based on the immunological status against HBV. This approach seems realistic, considering the difficulties in making an assessment of late reactivation by therapy-associated factors, as discussed above. HBV reactivation is the result of impaired anti-HBV immunity that allows the proliferation of HBV, which is subsequently attacked by the host's immune system when it recovers later. Therefore, it is assumed that we can safely stop monitoring HBV-DNA if we are able to detect the adequate recovery of anti-HBV immunity before an increase in the HBV titer. HBs-Ab is a potent candidate marker for assessing the recovery status of anti-HBV immunity due to its protective nature, and a low HBs-Ab titer is strongly associated with reactivation risk (15). Regarding the optimal threshold of HBs-Ab titer indicating adequate recovery of anti-HBV immunity, 50 mIU/mL has been suggested as a candidate based on prospective observations, where 18 of 19 reactivated cases showed an HBs-Ab titer below 50 mIU/mL at the time of reactivation (13). We believe we can safely stop HBV-DNA monitoring once the HBs-Ab values in can-

cer patients who have received immunosuppressive chemotherapies exceed this threshold. Clear determination of the recovery phase of immunity will require serial measurements of the markers, and clinical trials are needed to prove this concept.

In conclusion, we experienced a case of HBV reactivation over three years after R-CHOP therapy and discussed potential strategies for coping with late reactivation by reviewing similar previous cases. Our report highlights significant issues regarding the adequate monitoring period after chemotherapies for hematological diseases. The accumulation of cases to clarify the shared features is imperative for predicting and coping with late reactivation. The establishment of a reliable marker indicating the sufficient recovery of anti-HBV immunity will be useful as a guide for when to stop monitoring HBV-DNA for preemptive therapy.

The authors state that they have no Conflict of Interest (COI).

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