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BRIEF REPORT

Mortality Secondary to Fulminant Hepatic Failure in Patients with Prior Resolution of Hepatitis B Virus Infection in Japan

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Hepatitis B virus (HBV) reactivation in patients with resolved HBV infection was found in 23 (4%) of 552 newly hepatitis B surface antigen–positive patients in Japan. Because one-fourth of cases develop into fulminant hepatic failure and mortality is 100%, management of HBV reactivation in patients with resolved HBV infection should be discussed.

Reactivation of hepatitis B virus (HBV) is becoming a well-recognized complication in patients with chronic HBV infection who are undergoing cytotoxic chemotherapy or immunosuppressive therapy [1–5]. HBV reactivation has a variety of manifestations, ranging from subclinical increases in transaminase activity to severe and potentially fatal fulminant hepatic failure (FHF). Because clinical studies have demonstrated that lamivudine therapy reduces the rate of HBV reactivation and mortality [6–9], prophylactic antiviral therapy is advised for HBV carriers at the onset of chemotherapy [10].

The clearance of hepatitis B surface antigen (HBsAg) and the appearance of antibody to HBsAg, with normalization of liver function, is generally accepted as evidence of clinical and serologic recovery from acute hepatitis B. However, HBV replication has been shown to persist at low levels in the liver for decades [11–13], which may explain the recent increase in the rate of HBV reactivation in patients with resolved infection during or after chemotherapy and transplantation [1, 5, 14–16]. Although reactivation led to FHF and even death in some cases [17–22], the incidence of and mortality associated with HBV reactivation have not been fully clarified in this context. Recently, a prospective study [23] from Hong Kong revealed that 3.3% of HBsAg-negative patients developed HBV reactivation after chemotherapy. In Japan, because ~20% of individuals are positive for at least 1 HBV marker [24], HBV reactivation during or after immunosuppressive treatment may become a critical issue in the near future. Thus, we investigated the mortality associated with and prevalence and clinical significance of HBV reactivation in Japanese patients with resolved HBV infection in a multicenter, cross-sectional study.

Methods. In 2005, we sent a questionnaire to 230 hospitals certified by the Japan Society of Hepatology; this included questions about patients who had become newly positive for serum HBsAg from January 2000 through December 2004 [25]. A total of 1239 patients were registered by 93 hospitals (40%). Of those patients, 55 were recorded as having experienced HBV reactivation after having resolved HBV infection, and the remaining 1184 patients were classified as having acute hepatitis B. Sixty-three (68%) of 93 hospitals responded to a second survey and provided information on 552 patients enrolled in this study; 23 of these patients developed HBV reactivation, and 529 had acute hepatitis B.

HBV reactivation was defined (according to a slight modification of the report by Hui et al. [23]) as a decrease in the level of antibody to HBsAg that was associated with the reappearance of HBsAg, a 3-fold elevation of serum alanine aminotransferase (ALT) level above normal, and detection of HBV DNA in serum during or after chemotherapy. The diagnoses of acute hepatitis B and FHF were defined as reported elsewhere [26]. Patients with other liver diseases were excluded. Serum HBV markers were determined as reported elsewhere [26]. Serum levels of HBV DNA were determined with use of Amplicor HBV Monitor kits (Roche Diagnostics) at each hospital when the patients were admitted. HBV genotypes were determined with use of the PCR-invader method, with genotype-specific probes [27]. This study was approved by the ethics committees of appropriate institutional review boards. Informed consent was obtained from each patient in accordance with the Helsinki Declaration.

The Mann-Whitney U test was used to analyze continuous variables. The χ^2 test with Yate's correction was used for analysis of categorical data. In cases in which the number of patients was <5, Fisher's exact test was used. $P \leq .05$ was considered to

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be statistically significant. Statistical analyses were performed using SPSS, version 15.0J (SPSS).

Results. We first compared the demographic, clinical, and virologic features of the 23 patients who experienced HBV reactivation with those of the 529 patients with acute hepatitis B (table 1). The reactivation group had a significantly higher median age and median serum HBV DNA level ($P < .001$) and significantly lower peak ALT and albumin levels ($P < .001$). Although HBV genotype was not determined for one-half of the patients with acute hepatitis B, marked differences in the distribution of genotypes were seen; HBV type A occurred less frequently ($P = .003$) among patients with HBV reactivation than among those with acute hepatitis. However, HBV type B occurred more frequently among patients with HBV reactivation ($P < .001$).

FHF was more common among patients with HBV reactivation than among those with acute hepatitis ($P = .048$). Of the 23 cases of HBV reactivation, 6 (26%) resulted in liver-related death, 11 (48%) resolved, and 6 (26%) led to chronic hepatitis B. In contrast, of the 529 cases of acute hepatitis B, 490 (93%) were self-limited, 16 (3%) became chronic, and 21 (4%) resulted in death. These results revealed that liver-related mortality was significantly higher in the group with HBV reactivation than in the group with acute hepatitis ($P < .001$).

We then compared the clinical features of FHF between the groups (table 2). Patients with HBV reactivation had a higher median age, significantly lower peak ALT levels ($P = .006$), higher HBV DNA levels ($P = .035$), and higher mortality ($P = .031$) than did patients with acute hepatitis B.

Malignant lymphoma–associated morbidity was significantly higher among patients with HBV reactivation who developed FHF than among those who did not develop FHF (table 3). A rituximab-containing treatment regimen was administered to all patients who experienced FHF, compared with only 4 (22%) of 18 patients who did not experience FHF ($P = .004$). Lamivudine was administered to 16 (89%) of 18 patients who did not experience FHF and to all patients who experienced FHF at 7 and 20 days after hospital admission, respectively; this suggests that lamivudine treatment could not prevent FHF after HBV reactivation. Eventually, liver-related mortality occurred exclusively in patients who experienced FHF. There were no statistically significant differences between the 2 subgroups regarding HBV markers.

Discussion. Although a prospective study by Hui et al. [23] revealed that the incidence of HBV reactivation among HBsAg-negative patients after chemotherapy was 3.3%, there are no data available on HBV reactivation in Japan. In our nationwide cross-sectional study, a total of 552 newly HBsAg-positive patients were registered from 63 tertiary care hospitals. Overall, HBV reactivation was found in 4% of patients with resolved infection after chemotherapy. Serum and liver samples were not available before chemotherapy for most of these patients; therefore, we were unable to prove specifically whether reactivation was a result of occult or acute HBV infection. However,

Table 1. Demographic and clinical characteristics of patients with hepatitis B virus (HBV) reactivation, compared with those of patients with acute hepatitis B.

Characteristic	Patients with HBV reactivation	Patients with acute hepatitis B	*P*
Age, median years (95% CI)	63 (39–83)	33 (19–64)	<.001
Male sex	14/23 (61)	374/529 (71)	NS
Peak ALT level, median IU/L (95% CI)	929 (137–2441)	2300 (299–6626)	<.001
Peak bilirubin level, median mg/dL (95% CI)	10.3 (0.3–58.6)	6.4 (1.0–23.7)	NS
Lowest albumin level, median g/dL (95% CI)	3.2 (2.1–3.7)	3.6 (2.7–4.2)	<.001
Most prolonged PT%, median % (95% CI)	65.0 (10.2–121.4)	75.0 (11.0–103.1)	NS
HBV DNA level, median log copies/mL (95% CI)	7.5 (4.0 to >7.6)	5.5 (2.6 to >7.6)	<.001
Genotype			
A	0/19 (0)	57/232 (25)	.003
B	8/19 (42)	27/232 (12)	<.001
C	11/19 (58)	141/232 (61)	NS
Other	0/19 (0)	7/232 (3)	
Treatment			
Lamivudine	20/23 (87)	118/529 (22)	<.001
IFN	5/23 (22)	12/529 (2)	<.001
Fulminant hepatic failure	5/23 (22)	45/529 (9)	.048
Liver-related death	6/23 (26)	21/529 (4)	<.001

NOTE. Data no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; NS, not statistically significant; PT, prothrombin time.

Table 2. Demographic and clinical characteristics of patients with hepatitis B virus (HBV) reactivation who experienced fulminant hepatic failure (FHF), compared with those of patients with acute hepatitis B who experienced FHF.

Characteristic	Patients with FHF		*P*
	With HBV reactivation	With acute hepatitis B	
Age, median years (95% CI)	63 (47–64)	48 (18–72)	.029
Male sex	3/5 (60)	26/45 (58)	NS
Peak ALT level, median IU/L (95% CI)	907 (359–1823)	5995 (589–11,858)	.006
Peak bilirubin level, median mg/dL (95% CI)	20.8 (10.2–45.7)	9.9 (4.9–30.5)	.099
Lowest albumin level, median g/dL (95% CI)	2.6 (2.1–3.0)	2.9 (1.9–3.9)	NS
Most prolonged PT%, median % (95% CI)	22.0 (8.7–32.3)	16.0 (0.2–37.0)	NS
HBV DNA level, median log copies/mL (95% CI)	7.6 (5.6 to >7.6)	5.7 (2.6 to >7.6)	.035
Genotype			
A	0/5 (0)	2/16 (13)	NS
B	1/5 (20)	3/16 (19)	NS
C	4/5 (80)	11/16 (69)	NS
Received lamivudine treatment	5/5 (100)	29/45 (81)	NS
Liver-related death	5/5 (100)	21/45 (47)	.031

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; NS, not statistically significant; PT, prothrombin time.

because all patients were negative for HBsAg and positive for antibody to hepatitis B core antigen before treatment, we presumed that reactivation was occult in nature.

In our study, patients who experienced HBV reactivation were significantly older and had lower serum albumin levels, compared with patients with acute hepatitis B. The immune status of many patients may have been further decreased by cytotoxic chemotherapy. Approximately 20% of the patients who experienced HBV reactivation developed FHF. Surprisingly, mortality was 100%, implying that FHF in these cases is severe. Both the prevalence of and mortality associated with FHF were significantly higher among patients who experienced HBV reactivation than among those with acute HBV infection. Although the group with HBV reactivation also had lower albumin levels at the onset of lamivudine therapy, the development of FHF could not be predicted from this study. Thus, it is crucial to prevent FHF in patients with HBV reactivation with use of agents other than—or complimentary to—lamivudine. Unfortunately, preemptive therapy is not recommended because of the difficulties in detecting reactivation. Hui et al. [23] recommended monthly testing of HBV DNA levels and immediate antiviral therapy when levels are 100-fold the levels before chemotherapy. However, this strategy is still controversial [28, 29] and needs testing in a randomized study.

A recent study revealed that HBV type Bj and G1896A mutations were independently associated with a fulminant outcome in patients with acute HBV infection [30]. However, HBV genotype, serum HBV DNA level, or mutations in G1896A or A1762T/G1764A did not influence the development of FHF in patients who experienced HBV reactivation in this study. HBV reactivation in patients infected with HBV genotype A was also not found in this study, which may be explained by the fact that this genotype occurs in only 1.7% of patients with chronic hepatitis B in Japan [31].

Because our study and other studies [23] have confirmed that HBV reactivation can be fatal, we need to emphasize greater testing of HBV markers, including antibody to hepatitis B core antigen, antibody to HBsAg, and HBV DNA levels before administration of chemotherapy, especially therapy containing rituximab. Patients with resolved HBV infection should be routinely monitored for liver function and HBV DNA levels, and antiviral therapy should be administered immediately when evidence of HBV reactivation is found.

In conclusion, HBV reactivation is found in 4% of newly HBsAg-positive patients with resolved HBV infection in Japan. One-fourth of cases of HBV reactivation develop into FHF, and mortality is extremely high. Because our study was unable to distinguish HBV reactivation from occult HBV infection and could not clarify whether antiviral therapy was effective, a prospective study is being planned to clarify the mechanism of HBV reactivation and the benefits of antiviral therapy.

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Table 3. Demographic and clinical characteristics of patients with hepatitis B virus (HBV) reactivation who did and did not experience fulminant hepatic failure (FHF).

Characteristic	Patients with HBV reactivation		
	Experienced FHF (n = 5)	Did not experience FHF (n = 18)	P
Age, median years (95% CI)	63 (47–64)	63 (39–78)	NS
Male sex	3 (60)	11 (61)	NS
Peak ALT level, median IU/L (95% CI)	907 (359–1823)	1016 (124–2524)	NS
Peak bilirubin level, median mg/dL (95% CI)	20.8 (10.2–45.7)	7.6 (0.3–24.9)	.094
Lowest albumin level, median g/dL (95% CI)	2.6 (2.1–3.0)	3.3 (2.2–3.6)	.015
Most prolonged PT%, median % (95% CI)	22.0 (8.7–32.3)	77.5 (18.0–101.8)	<.001
ALT level,[a] median IU/L (95% CI)	176 (83–1035)	266 (58–1690)	NS
Bilirubin level,[a] median mg/dL (95% CI)	0.7 (0.4–7.2)	0.7 (0.3–13.6)	NS
Albumin level,[a] median g/dL (95% CI)	3.4 (2.5–3.5)	3.9 (2.8–4.5)	.035
PT%,[a] median % (95% CI)	42.2 (16.4–46.4)	83.7 (38.7–123.5)	NS
HBV DNA level, median log copies/mL (95% CI)	7.6 (5.6 to >7.6)	7.5 (4.0 to >7.6)	NS
Genotype			
Bj	1 (20)	7/14 (50)	NS
C	4 (80)	7/14 (50)	NS
Mutation			
G1896A	4 (80)	5/12 (42)	NS
A1762T/G1764A	2 (40)	2/12 (17)	NS
Non-Hodgkin lymphoma	5 (100)	8 (44)	.046
Received a rituximab-containing treatment regimen	5 (100)	4 (22)	.004
Treatment			
Lamivudine	5 (100)	16 (89)	NS
IFN	1 (20)	4 (22)	NS
Liver-related death	5 (100)	1 (6)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; NS, not statistically significant; PT, prothrombin time.

[a] Laboratory data are from the start of lamivudine therapy.

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