Fatal HBV Reactivation in a Subject with Anti-HBs and Anti-HBc

Takeji Umemura and Kendo Kiyosawa

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Approximately 3 billion people have been exposed to hepatitis B virus (HBV), and 350 million are chronic carriers worldwide. HBV infection is the primary cause of cirrhosis and hepatocellular carcinoma and one of the major causes of death globally. As medical services improve, many patients, including elderly, and those with cancer, autoimmune diseases or following transplantation for prevention of rejection undergo cytotoxic or immunosuppressive therapy. If these patients have chronic HBV infection, reactivation of HBV is a well-recognized complication (1, 2). HBV reactivation has a broad range of manifestations, ranging from slight, subclinical rises in transaminase activities to severe, potentially fatal fulminant hepatitis. This is a particularly critical issue in countries in the Far East and the tropics, where HBV is endemic.

The clearance of circulating hepatitis B surface antigen (HBsAg) and appearance of antibody to HBsAg (anti-HBs) with normalization of liver function have been generally accepted as evidence of clinical and serologic recovery from acute hepatitis B. However, even in HBsAg negative patients with resolved HBV infection (anti-HBs-positive and/or antibody to hepatitis B core antigen (anti-HBc)-positive), HBV replication has been shown to persist in the liver and in peripheral blood mononuclear cells for decades (3, 4). Hence, HBV reactivation has been reported after transplantation, immunosuppressive therapy, allogenic and autologous hematopoietic stem cell transplantation in this setting (1, 2, 5).

In the last issue of Internal Medicine, Sera et al (6) report a patient who developed hepatitis due to HBV reactivation and eventually died despite administration of lamivudine. This patient was resolved HBV infection such as, HBsAg-negative, and anti-HBs and anti-HBc-positive before immunosuppressive therapy. After chemotherapy including rituximab for malignant lymphoma, the patient developed severe hepatitis with HBsAg seroreversion and HBV DNA positivity in serum. Rituximab is a generally engineered chimeric murine/human monoclonal antibody against the CD20 antigen found on the surface of normal and malignant B lymphomas and is used alone or in combination with cytotoxic therapy. In 2001, Dervite et al (7) first reported a possible relationship between HBV reactivation and rituximab use in a patient with anti-HBs. After that report, some cases of reactivation of HBV in patients following treatment with rituximab that may prove fatal were reported (8-10). Hence, in October 2004, the U.S. Food and Drug Administration (FDA) reported a possible relationship between fulminant hepatitis and rituximab use. Furthermore, according to an abstract in the Proceeding of Shanghai Hong-Kong International Liver Congress, Dr. Lau’s group evaluated the risk of developing HBV reactivation in HBsAg-negative patients after chemotherapy. They followed-up 244 HBsAg-negative patients with lymphoma treated with chemotherapy for a median 12 months. HBV reactivation developed in 8 (3%) of 244 patients and the risk was statistically higher in patients with rituximab-containing regimen. As rituximab has been found to induce profound and durable B cell depletion, CD20-positive cell was 0% in this case. B cells may act as antigen-presenting cells and prime cytotoxic T lymphocyte-specific responses in HBV infection (1). Thus, progressive B cell depletion may also account for the increasing incidence of HBV reactivation as well as cytomegalovirus (1) and parvovirus B19 (12). Hence careful attention must be employed when administering rituximab to patients with chronic hepatitis and resolved HBV infection. It is well known that anti-HBs is necessary to suppress HBV reactivation. However, the role of anti-HBs has not been demonstrated, especially in patients with occult HBV infection. Rituximab affects lymphoma B-cell as well as normal B-cell producing antibody.

The American Association of Study of Liver Diseases (13) has published the recommendations for antiviral prophylaxis of hepatitis B carriers who receive immunosuppressive or cytotoxic therapy as follows: “HBsAg testing should be performed in persons who have high risk of HBV infec-
tion, prior to initiation of chemotherapy or immunosuppressive therapy; Prophylactic antiviral therapy with lamivudine is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy, and maintained for 6 months after completion of chemotherapy or immunosuppressive therapy.” However, there is no available recommendation for individuals with resolved HBV infection who undergo cytotoxic or immunosuppressive therapy. Additionally, in subjects with past HBV infection the incidence and mortality of HBV reactivation have not been fully clarified in Japan. To clarify the mechanism of HBV reactivation receiving cytotoxic or immunosuppressive therapy, we have started a survey which was supported in part by a Grant-in-Aid from the Ministry of Health, Labour and Welfare of Japan. Here, we present the preliminary data from this retrospective study on the incidence and mortality of HBV reactivation in individuals with resolved HBV infection between January 2000 and December 2004. During 4 years, a total of 55 patients with HBV reactivation were seen at 90 hospitals certified by the Japan Society of Hepatology. During the same period, approximately 1,000 patients with acute hepatitis B were diagnosed in those hospitals. Among the patients with HBV reactivation, 27% developed fulminant hepatitis, compared with only 7% in the acute hepatitis B group. Thus, the incidence of fulminant hepatitis in the HBV seroreversion group was significantly higher than in the acute hepatitis B group. Surprisingly, in patients with fulminant hepatitis, the HBV reactivation group had a significantly higher mortality than the acute hepatitis B group (100% vs. 44%). Taken together, these preliminary data of HBV reactivation in one-fourth of HBsAg-negative subjects causing fulminant hepatitis, and the high mortality of these patients, constitute important issues that need attention.

The patient reported in this issue (6) died due to fulminating hepatitis. Additionally, in our survey, many patients developed severe hepatitis and died. In contrast, some groups have reported that hepatic impairment was mild and no direct HBV-related mortality was observed in such cases (14, 15). Hence, we need to clarify this controversy. As Sera et al (6) found the mutations of core promoter and precore regions of HBV gene in their patient, viral characteristics including genotype and mutations should be investigated. We are planning further investigation of this group, including clinical backgrounds and mechanisms of high mortality. Furthermore, a guideline for reactivation prevention and treatment is necessary to manage this problem in patients undergoing or completing cancer therapy in Japan.

References


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