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Correspondence

Hepatitis B virus (HBV) reactivation in an acute lymphoblastic leukemia patient despite being vaccinated against HBV in infancy

Dear Editor,

Hepatitis B virus (HBV) reactivation is widely recognized as a complication in patients receiving immunosuppressive therapy, including chemotherapy [1]. However, cases of patients experiencing HBV reactivation despite having received HBV vaccination during infancy and obtaining hepatitis B surface antibody (HBsAb) have not yet been reported. In this report, we present a case wherein with high probability HBV reactivated after chemotherapy and hematopoietic stem cell transplantation despite the patient having received HBV vaccination during infancy.

Case: An 18-year-old man presented to our hospital with leukocytosis, anemia, and thrombocytopenia. He was diagnosed with acute lymphoblastic leukemia as confirmed by his bone marrow aspiration result. He had received hepatitis B immune globulin (HBIg) at birth and at 2 months of age as well as an HBV vaccine at 2, 3, and 5 months because his mother was an HBV carrier. His virological status of HBV in serum before chemotherapy was as follows: negative for hepatitis B surface antigen (HBsAg), positive for HBsAb, negative for hepatitis B core antibody (HBcAb), and undetectable for HBV–DNA (Table 1). HBsAb, HBcAb, and HBsAg were examined using chemiluminescent immunoassay, whereas HBV–DNA was examined using TaqMan polymerase chain reaction (PCR) (reference range: from 21.9 IU/mL (detectable) to 173780083 IU/mL). He underwent allogeneic peripheral blood stem cell transplantation (allo-PBSCT) after chemotherapy. The donor of allo-PBSCT was his sister who had also received HBV vaccination during infancy, and her virological status of HBV in serum was the same as his, including undetectable HBV–DNA (Table 1). Graft-versus-host disease was well controlled with medications, namely, cyclosporine and prednisolone, which were gradually reduced in dosage depending on his clinical condition. Serum HBV–DNA was monitored monthly during the treatment, and it was not detected. After 1 year from the patient receiving allo-PBSCT, HBV–DNA became detectable (<21.9 IU/mL) with ALT elevation (33 U/L). The virological profile of HBV at that point was all negative except for HBV-DNA (Table 1). To clarify his and his mother's HBV genotyping, we performed phylogenetic analysis. The extracted HBV–DNA from serum was used for the amplification and direct sequencing of S gene. The target of S gene was amplified by nested PCR and then sequenced. The obtained sequencing products were aligned with Hepatitis Virus Database to determine the genotypes and transmission route. Next, a phylogenetic tree was created using the neighbor-joining method. This system was named as the easy-to-use phylogenetic analysis system (E-PAS) [2]. The amplified S region is a relatively highly conserved area, even under antiviral drug pressure [3,4]. In the original article regarding E-PAS, serum HBV–DNA levels were examined using a commercial-based kit (detection limit <69.2 IU/mL). However, samples with low titer of HBV–DNA under the limit (<69.2 IU/mL) could be effectively amplified. Thus, E-PAS could sufficiently determine the transmission routes even if the conventional diagnosis was negative for HBV–DNA [2]. Phylogenetic analyses clearly revealed that the patient's HBV was identical to his mother's HBV and HBV genotype C. Hence, based on HBV–DNA detection, a diagnosis was made of HBV reactivation in an immunosuppressive condition. In addition, HBV may have got transmitted from mother to child at birth before the child received HBV vaccination. He then started taking entecavir. At the start of entecavir therapy, HBV–DNA was 549.5 IU/mL and gradually became undetectable over the course of therapy.

HBV reactivation can be life-threatening because of the onset of fulminant hepatitis in patients undergoing treatment for cancer and autoimmune diseases [1,5]. HBV reactivation can occur in patients who have been previously infected with HBV besides those who are HBV carriers [1,5,6]. Virological status of HBV-infected patients who have been diagnosed with HBV reactivation has revealed that they mainly test positive for HBcAb and that HBV reactivation rarely occurs in patients who test positive for HBsAb and negative for HBcAb [6]. Furthermore, reactivation of HBV after HBV vaccination has not yet been reported. Thus, the present case is extremely rare, considering that HBV reactivation occurred after chemotherapy and hematological stem cell transplantation despite the patient having received HBV vaccination during infancy and obtaining HBsAb. Based on the patient's history, two hypotheses can be suggested. First, occult HBV infection (OBI) was reactivated. Second, a de novo infection occurred during the post-PBSCT follow-up. On the basis of the virological profile of his mother (HBsAg, 9391.94 IU/mL; HBV–DNA, 8709.6 IU/mL), he could possibly have acquired an HBV infection; however, he initially tested positive for HBsAb. Although his HBsAb disappeared after the PBSCT, he had no contact with his mother's blood or bodily fluids, suggesting that a de novo HBV infection acquired from his mother was highly unlikely. In Japan, patients born of mothers who are HBV carriers had previously received HBIg at birth and at 2 months as well as HBV vaccine at 2, 3, and 5 months. Since October 2013, HBIg and HBV vaccine have been administered at birth, and HBV vaccine has been administered again at 1 and 6 months to complete its course, in accordance with the international standard vaccination. The rate of HBV infection among the immunized infants born of hepatitis B e-antigen-positive mothers according to the old Japanese vaccination schedule was 6.7% [7], suggesting the similar effect as the standard vaccination [8–10]. Therefore, the patient is surmised to have experienced OBI reactivation with a virological profile that was negative for HBcAb, positive for HBsAb, negative for HBsAg, and undetectable for HBV–DNA, even though he underwent the conventional HBV vaccination in Japan. A recent meta-analysis has revealed that HBsAb reduces the risk of HBV reactivation in patients with hematological malignancies [11], and HBsAb titers signifi-

Table 1
The virological status of HBV of the patient and his family.

	Reference range	Patient			Sister	Mother
		Pre-chemotherapy	At the point of reactivation	At the time of entecavir start		
HBsAg	<0.05 IU/ml	<0.01	0.03	0.04	<0.01	9391.94
HBsAb	<10.00	405.00	0.74	3.8	23.47	0.37
HBcAb	<1.00 S/CO	0.05	0.05	0.1	0.08	10.58
HBeAg	<1.00 S/CO	NA	0.274	0.266	NA	0.254
HBeAb	<50%	NA	11.5	0	NA	99.7
HBV-DNA	<21.9 IU/mL (not detectable)	not detectable	<21.9 (detectable)	549.5	not detectable	8709.6

HBsAg: hepatitis B surface antigen, HBsAb: hepatitis B surface antibody, HBcAb: hepatitis B core antibody, HBeAg: hepatits B envelope antigen, HBeAb: hepatitis B envelope antibody, S/CO: signal to cut-off, NA: not available.

cantly decrease after chemotherapy in hematological malignancies [12]. Hence, the present case indicates that HBV reactivation with HBcAb-negative OBI occurs due to the disappearance of HBsAb as a result of PBSCT-related chemotherapy and immunosuppression treatment.

Considering the insights obtained in the present case, we conclude that HBV reactivation should be considered even in patients who have received HBV vaccination during infancy as protection against HBV infection transmitted from their mothers, especially for those under immunosuppressive conditions, such as allo-PBSCT.

Conflict of interest
None declared.

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Complete response of early stage hepatocellular carcinoma in a patient treated with combination therapy of camrelizumab (SHR-1210) and apatinib

Dear Editor,

Hepatocellular carcinoma (HCC) is one of the most common tumors with limited treatments and poor prognosis. Along with the discovery and researches of programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) and associated antibodies, the effectiveness of PD-1/PD-L1 inhibitor on the treatment of HCC is still controversial and remains as a research focus. Here we report a case of early-stage HCC with multiple times of recurrence and a poor response to sorafenib, having a complete response to the combination of camrelizumab (SHR-1210) and apatinib.

A 52-year-old male, having suffered from hepatitis B virus (HBV) infection and associated liver cirrhosis for 30 years, presented for the fifth time with continuously elevated alpha-fetoprotein (AFP) and recurrent tumors. Two years ago, the patient was initially admitted with continuously elevated AFP for 8 months. The imaging examination showed single tumor in S4b with diameter of 1.7 cm and then the patient was diagnosed with HCC, Barcelona Clinic Liver Cancer (BCLC) stage 0. Entecavir therapy for HBV infection had been administrated for 6 months before the admission. A curative liver resection was immediately performed and the patient was well recovered. After that, he received another curative liver resection during the second admission and a curative radiofrequency ablation (RFA) during the third admission respectively, due to tumor recurrence. In the fourth admission, the patient was diagnosed with recurrent HCC (BCLC stage B) and a drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) was performed. Besides, he took sorafenib 200 mg twice daily as an adjuvant therapy for 10 months until the fifth admission, which