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Letters to the Editor

Incident Hepatitis B Virus Infection after Hematopoietic Stem Cell Transplantation in Initially HBV-Seronegative Recipients: Four Cases

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To the editor.

Hepatitis B virus (HBV)-related events after hematopoietic stem cell transplantation (HSCT) are usually discussed in recipients with chronic HBV infection or resolved infection, particularly those who are HBsAg-positive or HBsAg-negative/anti-HBc-positive before transplantation.[1-4] Current international guidance emphasizes HBV screening, prevention, risk-based monitoring, and individualized antiviral management in patients at risk of HBV-related complications.[5,6] In routine practice, recipients who are negative for HBsAg, anti-HBc, and HBV DNA at baseline are often regarded as low risk. We report four initially HBV-seronegative HSCT recipients who subsequently developed new HBsAg positivity with detectable HBV DNA. These events are described as incident HBV infection of uncertain origin, not as HBV reactivation.

From August 2020 to May 2026, 72 patients underwent HSCT at Anqing Municipal Hospital, including 57 autologous and 15 allogeneic HSCT recipients. Among these 72 recipients, 65 had documented negative HBsAg, anti-HBc, and HBV DNA before transplantation. Four recipients with baseline negative HBsAg, anti-HBc, and HBV DNA subsequently developed new HBsAg positivity with detectable HBV DNA during post-transplant follow-up. For center-level descriptive context, these four cases represented 4 of 72 HSCT recipients (5.6%), including 2 of 57 autologous HSCT recipients (3.5%) and 2 of 15 allogeneic HSCT recipients (13.3%). Because this was a single-center retrospective case series and post-HSCT HBV DNA testing was not performed according to a uniform prospective surveillance protocol for all recipients, these figures should not be interpreted as formal incidence estimates.

Clinical data were extracted from medical records. HBsAg, anti-HBc, anti-HBs, and HBV DNA testing were performed by the clinical laboratory of Anqing Municipal Hospital according to routine institutional procedures. HBsAg, anti-HBc, and anti-HBs were measured by enzyme-linked immunosorbent assay (ELISA) using kits from Shanghai Kehua Bio-engineering Co., Ltd. HBV DNA was measured using a commercial assay from Guangzhou Da An Gene Co., Ltd. on a SLAN-96S real-time PCR system, with a lower limit of detection of 30 IU/mL. HBsAg positivity was confirmed by repeated testing during clinical follow-up rather than by a single isolated result. After HBV DNA positivity was detected, anti-HBc was monitored periodically during follow-up. Stored pre-transplant serum samples were not available for repeat testing.

All four patients received blood components during the transplantation hospitalization, within approximately 1 month of HSCT. The transfused products included irradiated apheresis platelets and irradiated red blood cells. All blood components were supplied by the blood station and had passed routine qualification testing before clinical use, including HBV nucleic-acid testing. The detailed analytical sensitivity or lower limit of detection of the blood-station HBV NAT assay could not be retrieved from the available retrospective records. No abnormality related to the supplied blood products was identified in the available transfusion-record review. However, a formal donor-level transfusion look-back investigation, viral sequencing, and stored pre-transplant serum retesting were not available; therefore, transfusion-transmitted infection could not be completely excluded.

In the two allogeneic cases, donors were negative for HBsAg, anti-HBc, and HBV DNA; the donor for Case 2 was also anti-HBs-negative, whereas the donor for Case 3 was anti-HBs-positive by qualitative testing. No patient had a documented HBV vaccination history. IVIG was administered within 1 month of HSCT in Cases 1-3, twice weekly at 10 g per dose, and was not used thereafter. The study was approved by the Ethics Committee of Anqing Municipal Hospital; informed

consent was waived because de-identified retrospective data were used.

The four recipients included two men and two women, with a median age of 56.5 years. Underlying diseases were multiple myeloma in two patients, acute lymphoblastic leukemia in one, and acute myeloid leukemia in one. Two patients underwent autologous HSCT and two underwent allogeneic HSCT. At HSCT, all four cases were HBsAg-negative, anti-HBc-negative, and HBV DNA-negative. Anti-HBs was reported qualitatively: Case 1 was anti-HBs-positive, whereas Cases 2-4 were anti-HBs-negative; quantitative anti-HBs titers were not routinely measured in this clinical setting. None received HBV prophylaxis. Conditioning regimens are summarized in **Table 1**.

New HBsAg positivity occurred 5 to 20 months after HSCT. Detectable HBV DNA was documented in all four cases, with peak levels ranging from 25,750 to 313,000,000 IU/mL. ALT responses were heterogeneous: two patients had biochemical hepatitis, one had only moderate ALT elevation despite the highest HBV DNA level, and one maintained normal ALT despite detectable viremia. This discordance is clinically relevant because ALT may be delayed, blunted, or confounded after HSCT by immunosuppression, GVHD, drug injury, infection, or delayed immune reconstitution. ALT alone should therefore not be used as the only trigger for HBV testing when post-transplant HBV infection is clinically suspected.

All patients received nucleos(t)ide analog therapy after detection of new HBsAg positivity with detectable HBV DNA. Case 1 received entecavir 0.5 mg once daily plus tenofovir alafenamide 25 mg once daily for 1 month as an individualized short-term intensified regimen because the treating physician considered the patient clinically high risk due to hypogammaglobulinemia and severely impaired immune status after HSCT; after HBV DNA declined, treatment was de-escalated to entecavir 0.5 mg once daily monotherapy. Cases 2 and 3 received entecavir 0.5 mg once daily plus adefovir 10 mg once daily for only 1 month as individualized short-term intensified regimens selected by the treating physician in the setting of allogeneic HSCT and long-term immunosuppressive therapy; after HBV DNA declined, therapy was also de-escalated to entecavir 0.5 mg once daily monotherapy for maintenance. Case 4 received entecavir 0.5 mg once daily. Baseline and follow-up HBV resistance testing were not performed. These combination regimens should not be interpreted as preferred long-term strategies. Adefovir is not considered a preferred high-resistance-barrier agent compared with entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide.

In the present series, HBV DNA became undetectable in all four patients within 2 to 3 months after antiviral therapy. HBsAg cleared in Cases 1, 2, and 4, whereas Case 3 remained HBsAg-positive at last follow-up, approximately 15 months after HBV DNA became undetectable. Antiviral treatment was ongoing at last follow-up in all four patients, and all remained alive. Follow-up after initiation of antiviral therapy was 31, 30, 17, and 18 months in Cases 1-4, respectively, with a median of 24 months and a range of 17-31 months. Follow-up after HSCT was 44, 42, 37, and 23 months, respectively, with a median of 39.5 months and a range of 23-44 months. Given reports of recurrent HBV events after nucleos(t)ide analog cessation in allo-HSCT recipients with resolved HBV infection, antiviral discontinuation after HSCT should remain cautious.[7]

Several explanations may account for these events, and the available data cannot establish a single source. Community-acquired HBV infection, transfusion-transmitted infection, donor-derived transmission in allogeneic HSCT, occult HBV infection below assay detection limits, false-negative baseline anti-HBc testing, and laboratory or sample-identification error were all considered. Donor-derived infection was unlikely in the autologous cases and was not supported by donor HBsAg, anti-HBc, and HBV DNA results in the allogeneic cases. Transfusion-transmitted infection was considered because all four patients received blood components during the transplantation hospitalization. However, this route was less likely because all transfused components were supplied by the blood station as qualified irradiated products and had passed routine screening, including HBV nucleic-acid testing. The detailed analytical sensitivity of the blood-station HBV NAT assay could not be retrieved from the available records. Therefore, transfusion-transmitted infection could not be completely excluded in the absence of viral sequencing, stored pre-transplant serum retesting, and a formal donor-level transfusion look-back investigation. Other possible acquisition routes, including community, household, sexual, nosocomial, dialysis-related, or procedure-related exposures, could not be comprehensively assessed retrospectively unless specifically documented.

The interpretation of anti-HBs also requires caution. Case 1 had qualitative anti-HBs positivity at transplantation. Still, a quantitative anti-HBs titer was not documented because anti-HBs was recorded qualitatively in routine care and quantitative titers were not routinely ordered for patients with negative baseline HBV screening. No HBV vaccination history was documented. Case 1 underwent autologous HSCT, and donor anti-HBs status was therefore not applicable. IVIG was administered within 1 month of HSCT, twice weekly at 10 g per dose, which may complicate interpretation of post-transplant anti-HBs results because passively transferred antibodies may be transient and should not be assumed to represent durable immunity after HSCT.[8,9] No post-HSCT HBV vaccination was documented during the available

Table 1. Summary of four initially HBV-seronegative HSCT recipients with new HBsAg positivity and detectable HBV DNA.

Case	Age/Sex	Disease; HSCT type; conditioning	Recipient HBV status at HSCT	Donor HBV status	Post-HSCT exposures	New HBsAg positivity; peak HBV DNA; peak ALT	Treatment and outcome
1	60/M	MM; auto-HSCT; Mel	HBsAg-, anti-HBc-, HBV DNA-; anti-HBs+ (qualitative)	NA	Irradiated AP and RBC within 1 mo of HSCT; IVIG within 1 mo of HSCT (10 g twice weekly)	13 mo; 1,979,000 IU/mL; 266 U/L	ETV 0.5 mg qd + TAF 25 mg qd for 1 mo, then ETV 0.5 mg qd; HBV DNA undetectable at 2 mo; HBsAg cleared at 7 mo; antiviral FU 31 mo; ongoing therapy; alive
2	34/M	ALL; allo-HSCT; etoposide/Flu/Bu/Mel	HBsAg-, anti-HBc-, HBV DNA-; anti-HBs-	HBsAg-, anti-HBc-, anti-HBs-, HBV DNA-	Irradiated AP and RBC within 1 mo of HSCT; IVIG within 1 mo of HSCT (10 g twice weekly); CTX/ATG/FK506	12 mo; 25,750 IU/mL; 458 U/L	ETV 0.5 mg qd + ADV 10 mg qd for 1 mo, then ETV 0.5 mg qd; HBV DNA undetectable at 2 mo; HBsAg cleared at 2 mo; antiviral FU 30 mo; ongoing therapy; alive
3	55/F	AML; allo-HSCT; Flu/Bu/Mel	HBsAg-, anti-HBc-, HBV DNA-; anti-HBs-	HBsAg-, anti-HBc-, HBV DNA-; anti-HBs+ (qualitative)	Irradiated AP and RBC within 1 mo of HSCT; IVIG within 1 mo of HSCT (10 g twice weekly); CTX/ATG/FK506/MP	20 mo; 313,000,000 IU/mL; 125 U/L	ETV 0.5 mg qd + ADV 10 mg qd for 1 mo, then ETV 0.5 mg qd; HBV DNA undetectable at 2 mo; HBsAg persistent at last follow-up; antiviral FU 17 mo; ongoing therapy; alive
4	58/F	MM; auto-HSCT; Mel	HBsAg-, anti-HBc-, HBV DNA-; anti-HBs-	NA	Irradiated AP and RBC within 1 mo of HSCT; no IVIG	5 mo; 265,300 IU/mL; normal ALT	ETV 0.5 mg qd; HBV DNA undetectable at 3 mo; HBsAg cleared at 4 mo; antiviral FU 18 mo; ongoing therapy; alive

Abbreviations: ADV, adefovir; AP, apheresis platelets; Bu, busulfan; ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ALT, alanine aminotransferase; AML, acute myeloid leukemia; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; ATG, antithymocyte globulin; auto-HSCT, autologous hematopoietic stem cell transplantation; CTX, cyclophosphamide; ETV, entecavir; FK506, tacrolimus; Flu, fludarabine; FU, follow-up; GVHD, graft-versus-host disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; Mel, melphalan; MM, multiple myeloma; MP, methylprednisolone; NA, not applicable; NAT, nucleic-acid testing; qd, once daily; RBC, red blood cells; TAF, tenofovir alafenamide. All transfused blood components were supplied by the blood station as qualified irradiated products and had passed routine screening, including HBV nucleic-acid testing; the analytical sensitivity of the blood-station HBV NAT assay could not be retrieved.

follow-up. HBV vaccination or revaccination of HBV-naive HSCT recipients after immune reconstitution remains an important preventive issue and should be considered according to transplant-center practice and international guidance.

These observations suggest that HBV-seronegative HSCT recipients in HBV-endemic settings or with substantial ongoing exposure risks may warrant individualized post-transplant clinical and serological surveillance. However, prospective studies are needed before routine HBV DNA monitoring can be recommended for all anti-HBc-negative HSCT recipients. When new HBsAg positivity with detectable HBV DNA is identified after HSCT, prompt antiviral therapy should be considered, preferably with a high-resistance-barrier nucleos(t)ide analog such as entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide, with duration individualized according to immune recovery, ongoing immunosuppression, virological response, and feasibility of long-term follow-up.[5,6,10,11]

This report is limited by its retrospective, single-center design; small denominator; absence of uniform prospective HBV DNA surveillance; lack of stored pre-transplant serum samples for repeat testing; absence of high-sensitivity anti-HBc or HBsAg retesting, HBcrAg, HBV genotype, viral sequencing, and HBV resistance testing; unavailable analytical sensitivity data for the blood-station HBV NAT assay; absence of a formal donor-level transfusion look-back investigation; and incomplete retrospective assessment of all community or nosocomial exposures. Nevertheless, it identifies a clinically relevant monitoring gap: incident HBV infection with meaningful viral replication can occur after autologous or allogeneic HSCT even in recipients who were negative for HBsAg, anti-HBc, and HBV DNA at transplantation. Post-HSCT HBV surveillance should therefore be dynamic and should integrate baseline serology with evolving transplant-related, treatment-related, and exposure-related risks.

Ethics statement. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Anqing Municipal Hospital (approval number: 2026-087). The requirement for informed consent was waived because of the retrospective nature of the study and use of de-identified clinical data.

Data availability statement. The data supporting the findings of this report are available from the

corresponding author upon reasonable request.

Author contributions. DC contributed to study conception and design. LY collected data. FY analyzed and interpreted the data. DC and HX drafted the manuscript. All authors critically revised the manuscript and approved the final version.

Dangui Chen[1], Lu Yu[1], Fusheng Yao[1] and Haitao Xu[1].

[1] Department of Hematology, Anqing Municipal Hospital, Anqing Medical Center of Anhui Medical University, Anqing 246003, People's Republic of China.

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Correspondence to: Haitao Xu. E-mail: danielxu9@sina.com

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