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Illuminating and Instructive Clinical Case

Fatal Hepatitis B Virus Reactivation Following Immunosuppressive Therapy in a Patient with an Atypical Hepatitis B Virus Serological Profile: A Case Report

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Abstract

Hepatitis B virus (HBV) reactivation is a well-recognized complication in patients with lymphoma receiving immunosuppressive therapy, particularly rituximab-containing regimens. We describe a 58-year-old man with diffuse large B-cell lymphoma and an atypical baseline HBV serological profile: hepatitis B surface antibody (anti-HBs) positivity (102.00 U/L), antibody to hepatitis B core antigen negativity, a low-level hepatitis B surface antigen (HBsAg) result (0.35 COI, reported as negative by the local laboratory), and undetectable HBV DNA. Thirteen days after initiation of the fourth cycle of modified R-CHOP (rituximab, cyclophosphamide, pirarubicin, vinorelbine and dexamethasone) chemoimmunotherapy, the anti-HBs titer had decreased to 1.31 S/CO, the HBsAg level to 0.02 S/CO, and HBV DNA was not reassessed until reactivation. Approximately 16 weeks after treatment completion, the patient developed fatigue, anorexia, and jaundice. HBsAg increased from 28.66 S/CO to 8,048.30 IU/mL, hepatitis B e antigen became positive, and HBV DNA increased to 1.94×10^9 IU/mL. Despite treatment with tenofovir alafenamide fumarate and plasma exchange, the patient died of refractory liver failure and hepatic encephalopathy. These findings suggest that atypical serological profiles may not reliably indicate a low risk of severe HBV reactivation during intensive immunosuppressive therapy. Comprehensive pretreatment risk assessment and long-term monitoring of anti-HBs titers, HBsAg, and HBV DNA during and after therapy may facilitate earlier detection and intervention.

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Introduction

Immunosuppression-related hepatitis B virus (HBV) reactivation has received increasing clinical attention because of the widespread use of potent immunosuppressive agents, including chemotherapeutic drugs, molecularly targeted therapies, and immune checkpoint inhibitors.[1,2] HBV reactivation occurs in 20%–70% of patients with non-Hodgkin lymphoma and can lead to severe hepatitis, liver failure, and death.[3]

According to the 2025 American Gastroenterological Association Clinical Practice Guideline,[4] HBV reactivation in high-risk populations is defined as either the reappearance of HBV DNA in patients with previously undetectable levels or a ≥10-fold increase in HBV DNA from baseline. Reactivation results from the loss of immune control over viral replication in patients who are positive for hepatitis B surface antigen (HBsAg) or antibody to hepatitis B core antigen (anti-HBc) and is typically triggered by iatrogenic or disease-related immunosuppression. The risk of HBV reactivation is influenced by host factors (male sex, older age, and cirrhosis), disease- and treatment-related factors (lymphoma, hematologic malignancies, and breast cancer; use of glucocorticoids, anthracyclines, rituximab, and tumor necrosis factor-α inhibitors), and viral factors (high viral load, hepatitis B e antigen (HBeAg) positivity, HBV genotype, hepatitis C virus coinfection, and occult HBV infection).[5,6]

Current major international guidelines provide clear recommendations regarding antiviral prophylaxis for patients with chronic HBV infection and selected patients with resolved HBV infection who receive high-risk immunosuppressive therapy.[1,4,7] However, the clinical significance and optimal management of atypical HBV serological profiles that fall outside conventional risk categories remain incompletely understood. Here, we report fatal HBV reactivation in a 58-year-old man with diffuse large B-cell lymphoma (DLBCL) who developed fulminant hepatic failure 16 weeks after completing rituximab, cyclophosphamide, pirarubicin, vinorelbine, and dexamethasone (modified R-CHOP) chemoimmunotherapy. His unusual baseline HBV serological profile comprised a low-level HBsAg result (0.35 COI, reported as negative by the local laboratory), hepatitis B surface antibody (anti-HBs) positivity, negative anti-HBc, and undetectable HBV DNA. This report examines potential mechanisms underlying HBV reactivation and discusses challenges in risk stratification, prevention, and monitoring, thereby highlighting the clinical importance of recognizing atypical HBV sero-

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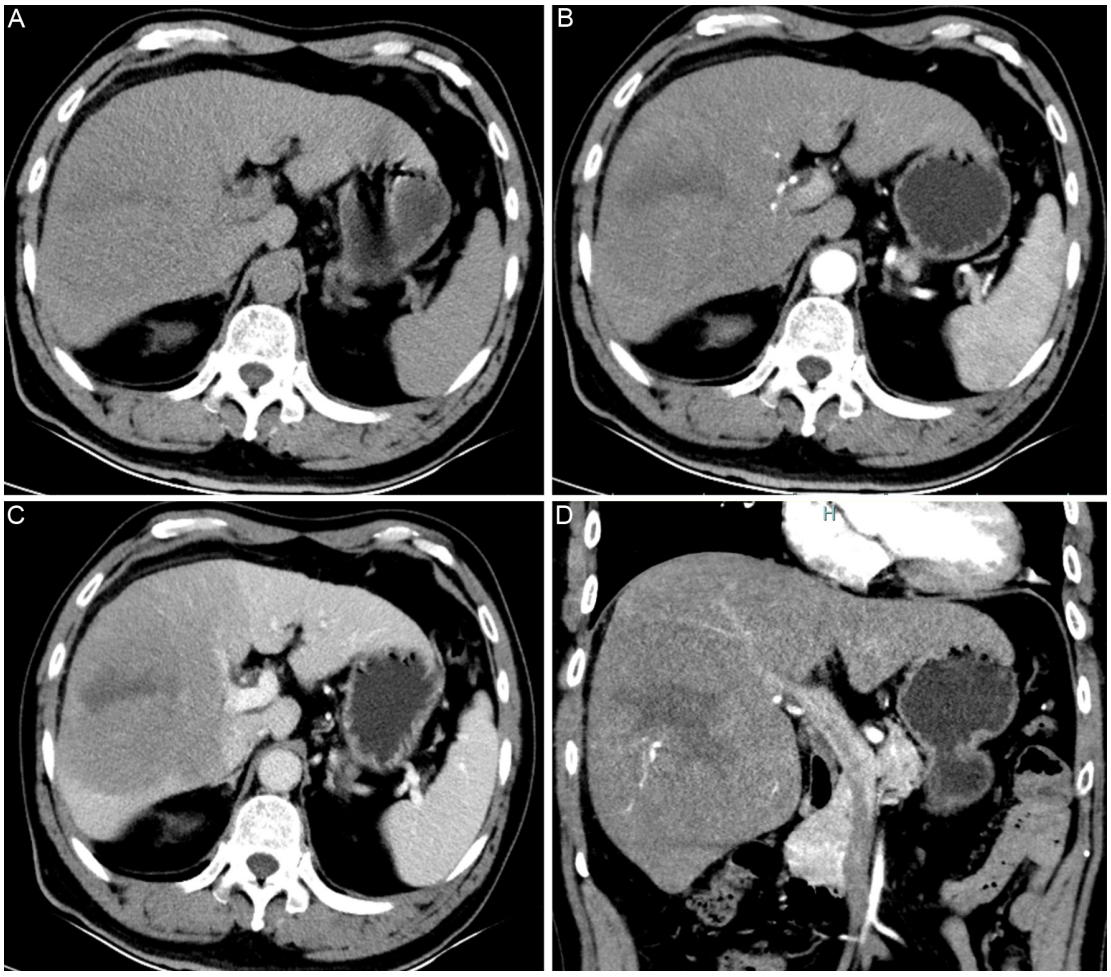


Fig. 1. Abdominal contrast-enhanced computed tomography (CT) images obtained when the hepatic space-occupying lesion was detected. (A) Unenhanced CT image shows a mass-like, slightly hypodense lesion in the right hepatic lobe, measuring approximately 11 × 10 cm, with heterogeneous density and ill-defined margins. (B) Arterial-phase image shows mild enhancement within the lesion, with non-enhancing necrotic areas. (C) Portal venous-phase image shows clear demarcation of the lesion from the adjacent normal hepatic parenchyma, with enhancement comparable to the arterial phase and compression and displacement of the adjacent portal vein. (D) Coronal image shows vessels coursing through the lesion.

logical profiles in patients receiving intensive immunosuppressive therapy.

Case presentation

Chief complaints

The patient had been diagnosed with lymphoma seven months earlier and had experienced fatigue for approximately half a month.

History of present illness

Seven months before the current admission, a 58-year-old man presented to a local hospital with a one-month history of recurrent fever and dull pain in the right upper quadrant. Abdominal contrast-enhanced computed tomography revealed a space-occupying hepatic lesion (Fig. 1). On November 25, 2024, biopsy of the liver mass was performed, and pathological examination confirmed DLBCL of the non-germinal-center subtype. The patient began modified R-CHOP chemoimmunotherapy (rituximab 700 mg on day 0; cyclophosphamide 1.2 g, pirarubicin 85 mg, vinorelbine 40 mg, and dexamethasone 15 mg on days 1–5) on December 3, 2024, and received four cycles. The final cycle was initiated on February 11, 2025.

Baseline HBV serological profile

Before initiation of chemoimmunotherapy (November 18, 2024), HBV serological markers were tested at the local hospital using a Roche electrochemiluminescence immunoassay. The results showed an atypical profile, including anti-HBs positivity (102.00 U/L), a low-level HBsAg result (0.35 COI, reported as negative; reference range: negative <1.00), HBeAg negativity (0.08 COI), antibody to hepatitis B e antigen positivity (1.12 COI), anti-HBc negativity (0.01 COI), and immunoglobulin M antibody to hepatitis B core antigen (anti-HBc IgM) negativity (0.06 COI). HBV DNA was undetectable in two separate tests: one at the local hospital on November 18, 2024 (lower limit of detection, 20 IU/mL), and one at a provincial hospital on November 21, 2024 (lower limit of detection, 3 IU/mL). Tests for antibodies to hepatitis C virus and human immunodeficiency virus, as well as markers of autoimmune liver disease, were negative.

Table 1. Dynamic changes in the patient's HBV serological markers

Date	Event	HBsAg	anti-HBs	HBeAg	anti-HBe	anti-HBc	anti-HBc IgM	HBV DNA
Nov 18, 2024	Baseline	0.35 COI	102.00 U/L	0.08 COI	1.12 COI	0.01 COI	0.06 COI	Undetectable (<20 IU/mL)
Dec 12, 2024	9 days after initiation of Cycle 1	0.31 COI	76.50 U/L	0.10 COI	1.16 COI	0.01 COI	0.06 COI	–
Feb 1, 2025	9 days after initiation of Cycle 3	0.35 COI	36.60 U/L	0.09 COI	1.31 COI	0.01 COI	0.06 COI	–
Feb 24, 2025	13 days after initiation of Cycle 4	0.02 S/CO	1.31 S/CO	0.04 S/CO	2.33 S/CO	1.60 S/CO	–	–
Jun 11, 2025	Reactivation	28.66 S/CO	0.01 S/CO	7.85 S/CO	4.53 S/CO	0.99 S/CO	–	1.94×10^9 IU/mL
Jun 18, 2025	Admission	8,048.30 IU/mL	20.86 mIU/mL	5.81 S/CO	2.00 S/CO	17.12 S/CO	0.07 S/CO	3.05×10^8 IU/mL

HBV serological markers and HBV DNA levels at six key time points from baseline (November 18, 2024) to admission (June 18, 2025). The anti-HBs titer progressively decreased during modified R-CHOP chemoimmunotherapy, and HBV reactivation occurred approximately 16 weeks after treatment completion (June 11, 2025). Cycle 1, Cycle 3, and Cycle 4 refer to cycles of modified R-CHOP chemoimmunotherapy. No serological testing was performed after Cycle 2; therefore, no data point is shown for Cycle 2. Samples from Cycles 1 and 3 were tested at the local hospital; samples from Cycle 4 and reactivation were tested at the provincial hospital; the admission sample was tested at Hangzhou Xixi Hospital. Values are presented as reported by each hospital using their respective assay platforms and units. HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBc, antibody to hepatitis B core antigen; anti-HBc IgM, immunoglobulin M antibody to hepatitis B core antigen; HBV DNA, hepatitis B virus DNA; COI, cutoff index; S/CO, signal-to-cutoff ratio; U/L, units per liter; mIU/mL, milli-international units per milliliter; IU/mL, international units per milliliter; Undetectable, below the lower limit of detection (<3 IU/mL); –, not tested; modified R-CHOP, rituximab, cyclophosphamide, pirarubicin, vinorelbine, and dexamethasone.

Serological monitoring during chemoimmunotherapy

HBV serological markers were monitored at selected time points during chemoimmunotherapy. Testing was performed at different hospitals: the cycle 1 and cycle 3 samples were tested at the local hospital, and the cycle 4 sample was tested at the provincial hospital. HBV DNA was not assessed during this period. Nine days after initiation of the first cycle of chemoimmunotherapy (December 12, 2024), the anti-HBs titer had decreased to 76.50 U/L, and the HBsAg level was 0.31 COI (negative; reference range: negative <1.00). The second cycle was initiated on December 28, 2024. No additional serological testing was performed after this cycle. Nine days after initiation of the third cycle (February 1, 2025), the anti-HBs titer had decreased further to 36.60 U/L, and the HBsAg level was 0.35 COI (negative). Thirteen days after initiation of the fourth and final cycle (February 24, 2025), the anti-HBs titer had decreased sharply to 1.31 S/CO, and the HBsAg level had decreased to 0.02 S/CO (negative, reference range: negative <1.00).

HBV reactivation and clinical deterioration

On June 3, 2025, approximately 16 weeks after completion of chemoimmunotherapy, the patient developed fatigue, anorexia, and jaundice of the skin and sclerae. These symptoms progressively worsened. On June 11, 2025, laboratory testing showed acute liver injury: an alanine aminotransferase (ALT) level of 56 U/L (reference range, 9–50 U/L), an aspartate aminotransferase (AST) level of 66 U/L (reference range, 15–40 U/L), a total bilirubin level of 254.3 μmol/L (reference range, 0–23 μmol/L), and an alkaline phosphatase level of 165 U/L (reference range, 30–120 U/L). Marked serological changes were observed: anti-HBs became undetectable, HBsAg and HBeAg became positive (28.66 S/CO and 7.85 S/CO, respectively), anti-HBc was 0.99 S/CO and HBV DNA level increased sharply to 1.94×10^9 IU/mL. The prothrombin time was prolonged to 26.6 s. Oral tenofovir alafenamide fumarate (25 mg daily) was initiated, and the patient was transferred to Hangzhou Xixi Hospital Affiliated to Zhejiang Chinese Medical University on June 18, 2025.

History of past illness

The patient had a 20-year history of primary hypertension managed with nifedipine sustained-release tablets (20 mg daily) and a 5-month history of type 2 diabetes. The diabetes had been treated with oral hypoglycemic agents (specific medications unknown), which he discontinued after his fasting and postprandial blood glucose levels normalized. He denied any prior history of hepatitis B. Twenty years earlier, he had undergone surgery for a right lower limb fracture and received intraoperative plasma and platelet transfusions. He had never received hepatitis B vaccination.

Personal and family history

His personal, marital, and reproductive histories were unremarkable, and he denied intravenous drug use or alcohol consumption. His father died at an advanced age; his mother died of liver cancer of unknown etiology; his sister was HBsAg-positive; and his brother was healthy.

Physical examination on admission

On admission (June 18, 2025), the only notable finding was jaundice of the skin and sclerae. No other abnormalities were identified.

Laboratory data on admission

Laboratory testing on admission (June 18, 2025) showed a total bilirubin level of 273.33 μmol/L (reference range, 0–23 μmol/L), a direct bilirubin level of 214.34 μmol/L (reference range, <6.84 μmol/L), an AST level of 68 U/L (reference range, 15–40 U/L), an ALT level of 36 U/L (reference range, 9–50 U/L), a γ-glutamyl transferase level of 57 U/L (reference range, 10–60 U/L), an alkaline phosphatase level of 150 U/L (reference range, 30–120 U/L), a total bile acid level of 365.1 μmol/L (reference range, 0–13 μmol/L), a blood ammonia level of 64 μmol/L (reference range, 9–30 μmol/L), a prothrombin time of 22.7 s (reference value, 12.6 s), and an international normalized ratio of 2.12. Changes in HBV serological markers are shown in Table 1: HBsAg, 8,048.30

IU/mL; anti-HBs, 20.86 mIU/mL; HBeAg, 5.81 S/CO; anti-HBc, 17.12 S/CO; anti-HBc IgM, negative (0.07 S/CO); and antibody to hepatitis B e antigen, positive (2.00 S/CO). Real-time quantitative fluorescence polymerase chain reaction showed an HBV DNA level of 3.05×10^8 IU/mL, and the HBV RNA level exceeded 1×10^8 IU/mL. Test results for immunoglobulin M antibody to hepatitis A virus, antibody to hepatitis C virus, immunoglobulin M antibody to hepatitis E virus, and human immunodeficiency virus were negative. The antinuclear antibody titer was 1:100.

Diagnosis and treatment

The patient was diagnosed with HBV reactivation complicated by acute liver failure. Oral tenofovir alafenamide fumarate (25 mg daily) was continued, and plasma exchange was initiated. However, his condition continued to deteriorate. By June 26, 2025, liver function indices had worsened markedly: total bilirubin, 396.68 μmol/L; direct bilirubin, 286.95 μmol/L; AST, 73 U/L; ALT, 34 U/L; total bile acid, 378.7 μmol/L; blood ammonia, 88 μmol/L; prothrombin time, 29.7 s; and international normalized ratio, 2.81. Abdominal computed tomography showed diffuse hepatic hypodensity (approximately 35 Hounsfield units), suggesting extensive hepatocellular necrosis. On June 27, 2025, further deterioration was observed: total bilirubin, 403.66 μmol/L; direct bilirubin, 269.68 μmol/L; prothrombin time, 31.3 s; and international normalized ratio, 2.97. The patient developed grade III hepatic encephalopathy, manifested by confusion, asterixis, and drowsiness. Despite treatment with L-ornithine-L-aspartate, lactulose, and rifaximin, he died of refractory liver failure and hepatic encephalopathy on June 29, 2025.

Discussion

This report describes a rare, fatal case of HBV reactivation in a 58-year-old man with DLBCL who developed fulminant hepatic failure 16 weeks after completing modified R-CHOP chemoimmunotherapy. The baseline HBV serological profile was atypical and could easily have been overlooked: undetectable HBV DNA, negative anti-HBc, positive anti-HBs, and a low-level HBsAg result (0.35 COI, reported as negative). An anti-HBs titer above 100 U/L has been associated with a reduced risk of HBV reactivation.[8,9] However, this case suggests that apparently protective HBV serological features may not reliably indicate a low risk of reactivation during profound immunosuppression. The combination of anti-HBs positivity and a low-level HBsAg result (reported as negative) represents an atypical profile whose relevance to reactivation risk may be underrecognized.

HBV reactivation in this patient may have involved a complex interplay between host immune dysfunction and viral factors. First, rituximab, the B-cell-depleting anti-CD20 monoclonal antibody component of R-CHOP, depletes B cells through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, impairing antibody production and reducing humoral protection.[10–12] In this patient, the anti-HBs titer decreased sharply from 102.00 U/L at baseline to 1.31 S/CO at thirteen days after initiation of the fourth cycle of modified R-CHOP chemoimmunotherapy, falling below the conventional protective threshold. Other components of the modified R-CHOP regimen may have further compromised antiviral immunity. Cyclophosphamide, anthracyclines, and corticosteroids suppress T-cell function and weaken immune surveillance of infected hepatocytes.[13,14] Together, impairment of humoral and cellular immunity may create profound immunodeficiency that facilitates HBV reactivation. Second, the patient denied any prior history of hepatitis B and had no history of hepatitis B vaccination or intravenous drug use. However, he had undergone surgery for a right lower limb fracture with intraoperative plasma and platelet transfusions 20 years earlier, a potential route of HBV exposure. His mother died of liver cancer of unknown etiology, and his sister was HBsAg-positive. Together with the baseline low-level HBsAg result (0.35 COI, reported as negative), these factors raise the possibility of previous HBV exposure. Although direct evidence of persistent HBV infection was unavailable, previous exposure may have resulted in persistence of intrahepatic covalently closed circular DNA,[15,16] which can serve as a stable viral reservoir and regain transcriptional activity during immunosuppression, leading to renewed viral replication.[5] Third, although direct sequencing data were unavailable, the low HBsAg level at baseline (0.35 COI), which decreased further to 0.02 S/CO during chemoimmunotherapy, suggests a possible contribution of viral immune-escape mechanisms. Mutations in the HBV *S* gene, particularly within the "a" determinant of the major hydrophilic region, can alter HBsAg conformational epitopes and enable viral variants to evade neutralization by residual anti-HBs.[17–19] These mutations may also affect HBsAg expression, secretion, or antigen recognition, reducing detectability in conventional serological assays and resulting in a low-level or borderline HBsAg result despite persistent virus. In this patient, profound immunosuppression, possible viral persistence, and potential viral immune escape may have acted together to trigger HBV reactivation in this patient despite apparently protective serological features.

Beyond these mechanistic considerations, this case has potential clinical implications for HBV risk stratification and management. Major international guidelines, including the 2025 European Association for the Study of the Liver and American Gastroenterological Association recommendations, classify patients receiving B-cell-depleting therapies as being at high risk and recommend antiviral prophylaxis. However, these recommendations primarily address patients with HBsAg positivity or resolved HBV infection (HBsAg-negative/anti-HBc-positive).[4,8] The clinical significance of atypical HBV serological profiles that do not conform to conventional risk categories remains incompletely understood. Both baseline HBsAg and anti-HBc were tested at a local hospital using a Roche electrochemiluminescence immunoassay. HBsAg was 0.35 COI, a low-level result reported as negative (reference range: negative <1.00); anti-HBc was also negative (0.01 COI). Although assay sensitivity data were unavailable, these negative results were considered more likely to reflect the patient's true serological status than false-negative results. With the concurrent positive anti-HBs (102.00 U/L) and undetectable HBV DNA, the patient was assessed as low risk, and antiviral prophylaxis was not started. The combination of findings created an atypical profile that complicated assessment of the patient's virological status and reactivation risk. Intensive immunosuppressive therapy may cause a rapid decline in anti-HBs titers and create a period of increased vulnerability. Whether this reduction in humoral protection can be offset by passive immunization with hepatitis B immunoglobulin (HBIG) or booster vaccination remains unresolved. Although HBIG combined with nucleos(t)ide analogues has an established role in preventing HBV recurrence after liver transplantation,[20] its efficacy for preventing reactivation in nontransplant immunosuppressed patients with declining anti-HBs titers has not been established in high-quality randomized controlled trials. HBV escape mutants have been reported in anti-HBs-positive, anti-HBc-negative patients with lymphoma receiving immunochemotherapy, and these

variants may evade vaccination and passive HBIG immunization.[15,21] In a recent fatal case of HBV reactivation in a patient with lymphoma and a similar serological profile, next-generation sequencing identified the D144E mutation in the major hydrophilic region of HBsAg, which was associated with immune escape.[22] Given the availability of well-tolerated, effective antiviral agents and real-world evidence supporting prophylactic antiviral therapy in immunosuppressed patients,[23] preemptive antiviral therapy combined with systematic virological surveillance remains the preferred preventive strategy, whereas passive immunization requires further prospective evaluation. This case suggests that an atypical HBV serological profile may not exclude a latent viral reservoir, and for such profiles, a lower threshold for initiating antiviral prophylaxis may be considered.

HBV reactivation associated with intensive immunosuppressive therapy can progress rapidly and pose substantial management challenges. In this case, initiation of tenofovir alafenamide and plasma exchange did not reverse progressive liver failure. These findings highlight the need for thorough baseline HBV assessment and continuous surveillance throughout immunosuppressive therapy. Current guidelines recommend baseline testing with a complete HBV serological panel and HBV DNA quantification before treatment.[4,8] In HBV-endemic regions, high-sensitivity virological screening and assessment of risk factors, including a family history of HBV infection and the HBV status of close contacts, may improve risk stratification.[24] During immunosuppressive treatment, high-risk patients should undergo protocol-based surveillance, with HBsAg, quantitative anti-HBs, and HBV DNA assessed every 1–3 months to detect early antibody decline and viral breakthrough.[4] For patients receiving B-cell-depleting agents, antiviral prophylaxis should continue for 12–18 months after drug discontinuation, with liver function and HBV DNA monitored every 3–6 months during prophylaxis and for at least 12 months thereafter.[25] Late-onset HBV reactivation can occur more than two years after cessation of rituximab-based chemoimmunotherapy.[26] One prospective study reported a 2-year cumulative reactivation rate of 41.5%, with reactivation occurring as late as 100 weeks.[27] These findings support extended monitoring to detect rare but potentially fatal late reactivation, particularly in patients with atypical serological profiles.

Conclusions

This case suggests that patients with atypical HBV serological profiles characterized by a low-level HBsAg result (reported as negative), anti-HBs positivity, negative anti-HBc, and undetectable HBV DNA at baseline may remain susceptible to severe or fatal reactivation during intensive immunosuppressive therapy. This pattern complicates risk assessment and may not be fully captured by current risk-stratification frameworks. The fatal outcome underscores the need for clinical vigilance, comprehensive baseline evaluation, and longitudinal monitoring of HBsAg, anti-HBs titers, and HBV DNA during and after immunosuppressive treatment. Further studies are needed to clarify the virological basis and clinical significance of this atypical presentation and to optimize prevention and monitoring strategies.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (FL, RW), acquisition of data (FL, HY), analysis and interpretation of data (FL, CL, SL, RW), drafting of the manuscript (FL, RW), critical revision of the manuscript for important intellectual content (XF, SL, RW), administrative, technical, or material support (XF, SL), and study supervision (SL, RW). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

This study was approved by the Ethics Committee of Hangzhou Xixi Hospital Affiliated to Zhejiang Chinese Medical University (Hangzhou Xixi Hospital Ethics Review Approval No. 2026-032). Written informed consent for publication was obtained from the patient's next of kin. This study was conducted in compliance with the Declaration of Helsinki.

Data sharing statement

The data that support the findings of this case report are available from the corresponding author upon reasonable request.

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