Chemotherapy drugs do not affect the production of hepatitis B surface antibodies: A case report

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Received February 4, 2025; Accepted August 20, 2025

DOI: 10.3892/ol.2025.15267

Abstract. Vaccines can stimulate an immune response. However, whether the use of chemotherapy drugs affects the body's production of antibodies after vaccination remains to be studied. This study reports the case of a 49-year-old female patient who first visited Chifeng City Hospital (Chifeng, China) in January 2021 who was likely naturally infected with hepatitis B virus (HBV) during administration of vincristine, doxorubicin and prednisone because the patient was diagnosed with acute lymphoblastic leukemia, recovered spontaneously and developed high levels of anti-hepatitis B surface antibodies (anti-HBs). Due to routine testing for hepatitis B during treatment, the test in February 2022 revealed that the hepatitis B antigen (HBsAg) level was 0.19 (positive). Subsequently, a peripheral blood hepatitis B virus nucleic acid test was performed and the results did not show amplification. In March 2022, the HBsAg quantitative result was 12.8 (positive). The following day, consolidation chemotherapy was performed with the cisplatin, oxaliplatin, doxorubicin, etoposide and tegafur regimen and vincristine treatment was administered in March 2022. In August 2022, the HBsAg quantitative result of the patient was <0.05 (negative) and the anti-HB content was 982 IU/l; 2 days later methotrexate combined with pegaspargase treatment was administered. Overall, the present study showed that chemotherapy did not affect the production of anti-HBs in the patient.

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Key words: hepatitis B virus, acute lymphoblastic leukemia, chemotherapy, elevated transaminases, vaccination

Introduction

Immunization via vaccination not only prevents the spread of infectious diseases in children and adults, but also provides lifelong protection against certain diseases (1). However, whether the use of chemotherapeutic drugs reduces vaccine efficacy remains unclear.

Chemotherapeutic drugs kill hematopoietic cells in the bone marrow, which can cause side-effects such as neutropenia, erythropenia and thrombocytopenia. Due to changes in the immune system, patients with cancer are at a higher risk of becoming infected with pathogens than the general population, and infections in these patients often lead to excessive morbidity and mortality rates (2). This increased risk may be related to a variety of causes, including cancer, chemotherapy and poor nutrition. Although traditional chemotherapy has long been recognized as an effective anticancer treatment, its potentially severe side-effects are also widely recognized, including the marked impairment of immune function (3). In patients treated with platinum-based drugs, such as epirubicin, doxorubicin, paclitaxel and cyclophosphamide chemotherapeutic regimens, the absolute numbers of B-cell subsets significantly decrease between 2 and 12 weeks of treatment (4). By contrast, treatment with methotrexate at various doses for 6 weeks has been shown to result in a decrease in B-cell numbers (5).

B-cells play a key role in adaptive immune responses. These cells are activated in the germinal centers of secondary lymphoid organs to form long-lived memory B-cells, which differentiate into plasma cells following antigen stimulation and produce high-affinity antibodies. The 'Clinical Practice Guidelines for Vaccination of Immunocompromised Hosts'

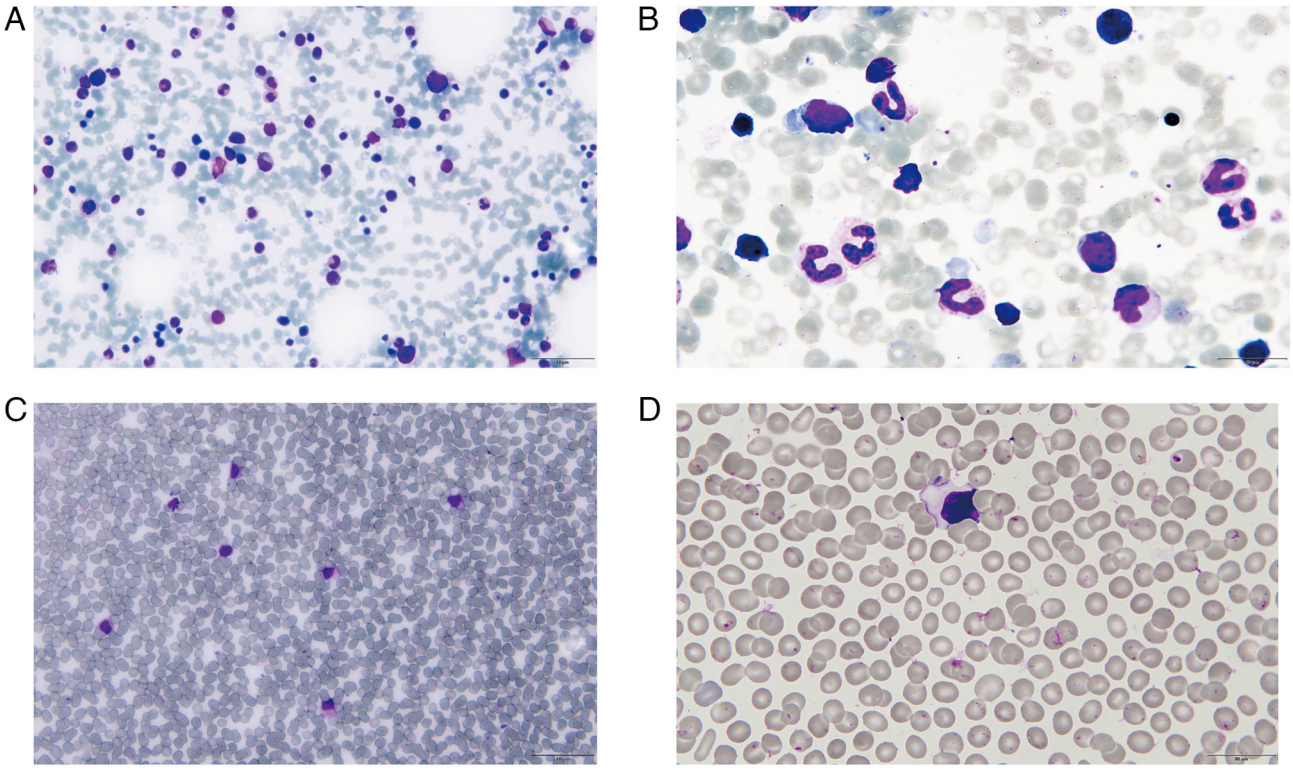

Figure 1. Numerous primitive lymphocytes appear in the bone marrow and peripheral blood. Bone marrow smears from the patient in (A) 10x and (B) 40x magnification. The bone marrow is hyperproliferative or markedly hyperproliferative, with primitive and immature lymphocytes predominating at over 30%. Erythrocytes, granulocytes, and megakaryocytes are markedly decreased. (C) and (D) Peripheral blood smears in (C) 10x and (D) 40x magnification. Leukemic cells vary in size, with an increased nuclear-cytoplasmic ratio and irregular nuclei that may be twisted or folded. Nucleoli are prominent and numerous, with scant cytoplasm. All smears were stained with Wright-Giemsa stain.

issued by the Infectious Diseases Society of America considers that live attenuated vaccines should be administered at least 4 weeks prior to the start of any immunosuppressive treatment (6). In the case that radiotherapy or chemotherapy are performed, vaccination should be terminated due to concerns that live vaccines may cause infection (7). The present study reports the case of a patient who was likely naturally infected with hepatitis B virus (HBV) during chemotherapy, who recovered spontaneously and developed high levels of anti-hepatitis Bs (anti-HBs).

Acute lymphoblastic leukemia (ALL), the disease that the patient was originally treated for, is a malignant disease that originates from B- or T-lymphocytes that proliferate abnormally in the bone marrow. ALL can also invade tissues outside the bone marrow (such as meninges, lymph nodes and peripheral blood) (8). The treatment of ALL usually includes four stages: i) Induction therapy; ii) consolidation therapy; iii) enhancement therapy; and iv) targeted therapy to prevent the relapse of central nervous system leukemia (9). During treatment, patients receive different chemotherapeutic drugs, such as vincristine, cytarabine, mercaptopurine, doxorubicin, methotrexate, cyclophosphamide and L-asparaginase (10).

Case report

The patient in the present study was a 49-year-old woman as of 2024. The vaccination history of the patient was unknown, and the patient began to feel weak in January 2021, accompanied by subcostal and lumbar pain, but did not pay attention to it. The patient received treatment at the Chifeng Municipal Hospital (Chifeng, China). The patient is a woman who was admitted to the hospital for examination in March 2021 and was 46 years old at the time. A peripheral blood examination in March, 2021, revealed the following: i) A total white blood cell (WBC) count of $56.84x10^9$/l (reference interval: $4\text{-}10x10^9$/l); ii) a lymphocyte ratio (L%) of 87.7% (reference interval: 20-40%) and a neutrophil ratio (N%) of 6.95% (reference interval: 50-70%); iii) a total red blood cell (RBC) count of $2.47x10^{12}$/l (reference interval: $3.5\text{-}5.0x10^{12}$/l) and a hemoglobin (Hb) level of 75 g/l (reference interval: 110-150 g/l); and iv) a platelet (PLT) count of $20x10^9$/l (reference interval: $100\text{-}300x10^9$/l). Blood test results revealed that primitive cells accounted for 84% of the cells (reference interval: 0%). The morphological description was that a large number of primitive cells were observed, mature RBCs were of different sizes, no nucleated RBCs or RBC inclusion bodies were observed and the PLTs were relatively few. The bone marrow morphology report was grade 1-2 myeloproliferation, mainly the abnormal proliferation of lymphoid system cells, mature RBCs of different sizes and primitive lymphocytes of the lymphocyte system accounting for 95%. The primitive lymphocytes in the bone marrow smear are of different sizes, with more nuclear chromatin, visible nucleoli, less serous fluid, blue color, no granules, larger nuclei, and darker cytoplasm (Fig. 1A and B). Primitive lymphocytes were also found in the peripheral blood (Fig. 1C and D). The diagnosis of ALL was made. Immunophenotyping revealed that immature cells accounted for 91.6% of all cells expressing CD19, CD38, CD43, CD58,

Table I. Determination of biochemical substance content in peripheral blood.

	Days post admission						
Biomarker name	325	384	405	411	483	Unit	Reference interval
TP	53.00	57.00	46.00	61.00	63.00	g/l	65.00-85.00
ALB	36.00	42.00	29.00	36.00	41.00	g/l	40.00-55.00
GLO	17.00	15.00	17.00	25.00	21.00	g/l	20.00-40.00
A/G	2.12	2.80	1.71	1.44	1.88	-	1.20-2.40
PREA	210.00	330.00	40.00	80.00	170.00	mg/l	180.00-350.00
AST	15.00	21.00	916.00	289.00	18.00	IU/l	13.00-35.00
ALT	13.00	41.00	1,334.00	259.00	12.00	IU/l	7.00-40.00
AST/ALT	1.15	0.51	0.69	1.12	1.53	-	0.25-4.4
ALP	119.00	93.00	477.00	230.00	86.00	IU/l	35.00-100.00
GGT	74.00	104.00	198.00	75.00	88.00	IU/l	7.00-45.00
ADA	10.00	9.00	138.00	210.00	6.00	U/l	1.00-20.00

TP, total protein; ALB, albumin; GLO, glyoxalase I; A/G, albumin/globulin ratio; PREA, prealbumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; ADA, adenosine deaminase.

Table II. Changes in peripheral blood pathogenic diagnostic markers.

	Days post admission					
Marker	189	189	377	524	Unit	Reference interval
HbSAg	<0.05	0.19	12.80	<0.05	IU/ml	Negative <0.05; positive ≥0.05
Anti-HBs	<2.00	6.25	<2.00	982.00	IU/l	Negative <10.0; positive ≥10.0
HBeAg	0.10	0.12	0.97	0.10	COI	Negative <1.0; positive ≥1.0
HBeAb	1.49	1.40	1.62	0.01	COI	Negative >1.0; positive ≤1.0
Anti-HBc	2.37	2.11	0.91	0.01	COI	Negative >1.0; positive ≤1.0
Anti-HBcIgM	0.090	0.063	0.089	-	COI	Negative <1.0; positive ≥1.0

HbSAg, Hepatitis B surface antigen; Anti-HBs, anti-hepatitis B surface antibodies; HBeAg, Hepatitis B e antigen; HBeAb, Hepatitis B e antibody; Anti-HBc, Hepatitis B core antibody; Anti-HBcIgM, Hepatitis B virus core anti-antibody IgM.

CD79a and HLA-DR (human leukocyte antigen DR α chain precursor); some cells expressed CD123, CD81, CD24, CD15, glial antigen 2 and terminal deoxynucleotidyl transferase; there was no expression of CD45, CD5, CD10, CD7, CD56, CD117, CD34, CD33, CD65, CD13, CD66c, CD22, CD20, c/mκ and c/mλ. The IKAROS family zinc finger 1 mutation status was positive.

In March 2021, the patient received 1.4 mg/m^2 of vincristine, 40 mg/m^2 of doxorubicin and 1.4 mg/m^2 of prednisone based on the body surface area (m^2). The aforementioned medication is called VDP chemotherapy regimen. Bone marrow morphology analysis suggested that the patient achieved morphological remission after 15 days of VDP chemotherapy regimen. The day after the first administration of VDP, the test result of HBsAg was <0.05 IU/ml (negative). One intramuscular injection of 3,750 IU pegaspargase was given in April 2021. A further 13 days later, the patient received methotrexate (MTX) chemotherapy at a dose of 1 g/m2 (body surface area), with a total dose of 1.6 g. After 24 h, the MTX concentration in the blood was 0.086 μmol/l. In May 2021, the quantitative result of HBsAg was <0.05 IU/ml (negative). A cyclophosphamide, doxorubicin and methotrexate (CAM) chemotherapy program was administered in June 2021. In July 2021, the patient was treated once with daunorubicin (total dose 30 mg) and cytarabine (total dose 7.2 mg). Subsequently, 10 days later, the quantitative result of HBsAg was <0.05 IU/ml (negative). Subsequently, 18 days later, chemotherapy with 1.4 mg/m^2 vinblastine, 40 mg/m^2 daunorubicin, 800 mg/m^2 cyclophosphamide and 40 mg/m^2 dexamethasone (VDCD) was administered. In August 2021, a single intramuscular injection of high-dose MTX (total dose 2.1 g) and 3,750 IU of pegaspargase was administered. In September 2021, the quantitative result of HBsAg was <0.05 IU/ml (negative). In October 2021, to create conditions for donor stem cell implantation, the patient received 0.8 mg/kg busulfan and 60 mg/kg cyclophosphamide (BUCY) regimen for pre-autologous hematopoietic stem cell transplantation conditioning. Hematopoietic stem cells

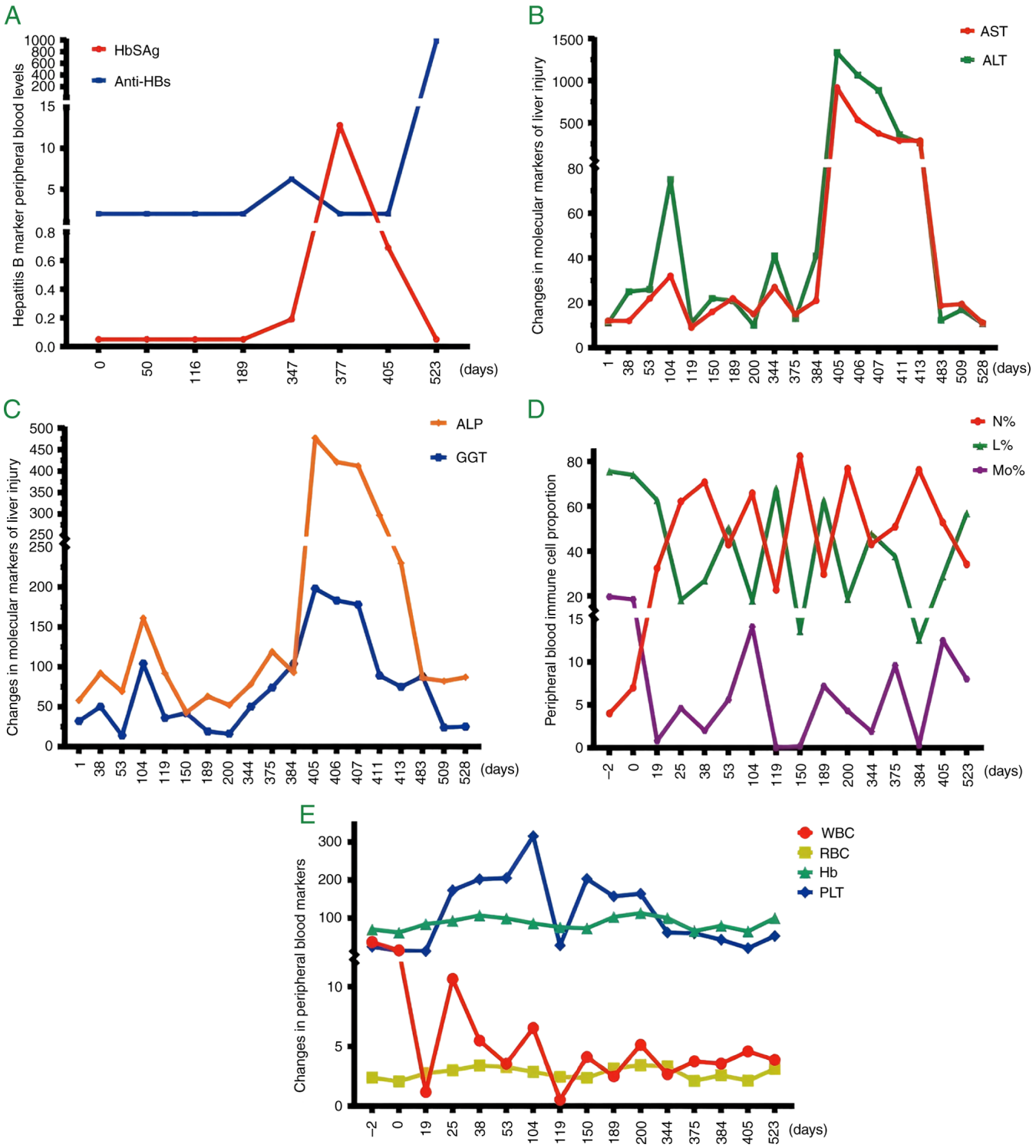

Figure 2. Changes in trends in peripheral blood-related clinical diagnostic markers. (A) Detection of hepatitis B markers HBsAg (IU/ml) and anti-Hbs (IU/l). (B) Detection of ALT and AST levels (unit, IU/l). (C) Detection of ALP and GGT levels (unit, IU/l). (D) Proportion of major immune cells; (E) WBC (10^9/l); RBC (10^{12}/l); Hb (g/l); PLT (10^9/l) content determination. HBsAg, Hepatitis B surface antigen; anti-Hbs, anti-hepatitis B surface antibodies; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; N, neutrophils; L, lymphocytes; Mo, monocytes; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLT, platelet.

were transfused 7 days after the BUCY regimen was administered. In February 2022, the patient was treated once with a regimen of 1.4 mg/m^2 vindesine, 40 mg/m^2 daunorubicin, 800 mg/m^2 cyclophosphamide and 40 mg/m^2 dexamethasone (VICP), and 3,750 IU of pegaspargase intramuscularly. for consolidation chemotherapy. Subsequently, 10 days later, the γ-glutamyl transferase (GGT) test result was 68 IU/l (reference interval: <60 U/l) which indicated a marked increase.

For possible potential blood transfusion treatment, relevant infectious markers are tested before blood transfusion. Subsequently, 7 days later, the HBsAg quantitative level was accidentally detected and was 0.19 IU/ml (positive) and was

Table III. Timeline.

Days post admission	Patient notes
January 2021	Fatigue and subcostal and back pain began to occur.
March 2021	Acute lymphoblastic leukemia was diagnosed and chemotherapy was administered using the VDP regimen. HBsAg test result <0.05 IU/ml (negative).
September 2021	HBsAg test result <0.05 IU/ml (negative).
October 2021	Hematopoietic stem cell infusion
February 2022	Treated with VICP and pegaspargase. The quantitative result of HBsAg detected unexpectedly was 0.19 IU/ml (positive).
March 2022	Chemotherapy was performed using the COATD regimen. The quantitative result of HBsAg was 12.8 IU/ml (positive).
April 2022	Peripheral plasma ALT levels began to increase and soon reached 1334 IU/l. The same changes occur in AST levels. Anti-HBc-IgM levels were significantly increased in peripheral serum.
July 2022	ALT and AST levels in peripheral plasma decreased to within the reference range. Use VD regimen for treatment.
August 2022	The HBsAg quantitative result became <0.05 (negative), and the Anti-HBs content was 982 IU/l.

VDP, vincristine, doxorubicin and prednisone; HBsAg, Hepatitis B surface antigen; VICP, vindesin, daunorubicin, cyclophosphamide and dexamethasone; COATD, cisplatin, oxaliplatin, doxorubicin, etoposide and tegafur; ALT, alanine aminotransferase; AST, aspartate aminotransferase; anti-HBc-IgM, Hepatitis B virus core anti-antibody IgM; VD, vincristine and doxorubicin.

followed by a peripheral blood HBV nucleic acid test; the results revealed that no amplification occurred. In March 2022, the HBsAg quantitative result was 12.8 IU/ml (positive); however, the cisplatin, oxaliplatin, doxorubicin, etoposide and tegafur regimen consolidation chemotherapy was still administered the following day. In April 2022, the alanine aminotransferase (ALT) (reference interval: <35 U/l) levels began to increase slightly, with a test result of 41 IU/l, and the GGT level was 104 IU/l. In April 2022, the possibility of hepatitis B virus infection began to be considered due to a notable increase in transaminase levels [ALT, 1,334 IU/l; aspartate aminotransferase (AST), 1,334 IU/l; and GGT, 198 IU/l] (Table I). The patient developed jaundice and received hepatoprotective treatment with 100-200 mg magnesium isoglycyrrhizinate and 1.8-2.4 g glutathione daily for 3 weeks. Ursodeoxycholic acid and adenosine blue butane sulfonate (the dosage and duration of treatment are unknown) were used for treatment simultaneously, and gradual improvements were observed.

VD (vincristine 1.4 mg/m^2; daunorubicin 30-40 mg/m^2) treatment regimen treatmentwas continued in July 2022. In August 2022, in order to observe whether the patient had liver damage, liver function-related biomarkers were tested, and the results were as follows: ALT, 13.8 IU/l; AST, 17.7 IU/l; GGT, 67 IU/l. Quantitative analysis of blood samples with hepatitis B infection indicators on the second day showed that the HBsAg level had decreased to <0.05 (negative) and the anti-HBs content was 982 IU/l (Table II). The first day of chemotherapy in March 2021, was considered as hospitalization day 0, and some of the collected clinical test data were counted by day to observe the results more intuitively. On day 347, HbSAg was first found to be positive and became negative on day 524. The anti-HBs level significantly increased on day 524 (Fig. 2A and Table SI). The activities of ALT and AST in peripheral serum can reflect the degree of liver damage, which peaked on day 405 and then gradually decreased (Fig. 2B and Table SII). The other two indicators of liver function, ALP and GGT, reached their highest levels on day 405 (Fig. 2C and Table SII). Peripheral blood indices (WBC, N%, L%, Mo%, RBC, Hb and PLT) revealed irregular 'wave-like' changes (Fig. 2D and E; Table SIII). The disease occurrence timeline is presented in Table III.

Discussion

The present study reports the case of an adult patient with ALL who may have been infected with HBV during chemotherapy. The patient subsequently produced corresponding antibodies and successfully achieved clinical self-recovery.

The average incubation period of HBV infection is 60-90 days (11). Infants, children <5 years of age and immunosuppressed adults usually have no obvious clinical symptoms in the case of infection with HBV. In adults with normal immune function, ~95% of infections will be rapidly cleared by the immune system of the body following viral infection (12). Immunosuppressed patients (such as those undergoing hemodialysis and those infected with human immunodeficiency virus) may develop chronic infection from acute infection. Currently, there is no specific treatment available to completely eliminate HBV from the body (13). HBsAg positivity indicates HBV infection. In the case of an acute HBV infection, anti-HBc (IgM and IgG subtypes) in peripheral blood can be detected 1-2 weeks later than HBsAg (14). After a healthy adult is infected with HBV, HBsAg usually disappears within 3-4 months and anti-HBs appear. The presence of anti-HBs usually indicates immunity to HBV infection (15). Occult HBV infection refers to patients who test negative for HBsAg in their peripheral blood, but there is replication-competent viral DNA in their liver and HBV DNA is undetectable in

their serum, which poses a challenge to the study of HBV (16). In the present study, the use of chemotherapy did not affect the production of anti-HBs, although there was no evidence of an occult HBV infection. No information on the disease history of HBV in family members was obtained from medical records of the patient.

B-cells are generally known to produce secretory antibodies during HBV infection and are a key component of the adaptive immune response of the body (17). It is generally believed that the use of chemotherapeutic drugs to treat tumors will have the side-effect of suppressing bone marrow hematopoiesis, leading to a decrease in the number of immune cells, such as B-lymphocytes and a decrease in the ability of B-lymphocytes to respond to immune responses, such as against viruses (18). Notably, there is limited scientific knowledge available as to whether chemotherapeutic drugs will affect the function of lymphoid tissue and cell subsets, and whether they will have long-term effects on the cellular and humoral immune responses of the body. The main drugs used in patients with ALL in the maintenance phase are 6-mercaptopurine and MTX, which can reduce the risk of relapse; however, they also have potentially severe toxic effects, with bone marrow suppression being the most common side-effect (19). Therefore, it can be taken for granted that chemotherapeutic drugs have significant adverse effects on the immune system.

It has long been recognized that chemotherapeutic agents can treat immune diseases. For example, the inactive chemotherapeutic agent, cyclophosphamide, undergoes complex metabolism in the liver to produce cytotoxic metabolites (20). Decades ago, the immunomodulatory effects of cyclophosphamide were discovered in animal models, and its mechanism of action is through the reduction of cell numbers (21). In addition, chemotherapeutic agents can deplete cells known as regulatory T-lymphocytes (Tregs), thereby promoting local antitumor immune responses. There has been renewed interest in the use of cyclophosphamide to deplete human Tregs (22). As Tregs have low levels of intracellular ATP and glutathione, they are considered to be more susceptible to the toxic effects of cyclophosphamide than other T-cells (23). When high-dose corticosteroids are combined with cyclophosphamide to treat severely active lupus nephritis, it can preferentially eliminate naive B cells (24). Notably, cyclophosphamide has no significant effect on class-switched memory B cells, as these cells are normally dormant and do not proliferate (25). Additionally, chemotherapeutic drugs, including cyclophosphamide, doxorubicin, methotrexate, mitomycin C, paclitaxel and vincristine, can improve the function of antigen-presenting cells and increase the antitumor effect of immune cells at low doses (26). Paclitaxel can also directly affect the maturation of dendritic cells (27). Paclitaxel displays lipopolysaccharide-mimicking activity in mice, activates TLR4, and enhances DC activation and cytokine biosynthesis (28).

The majority of vaccination strategies for patients with cancer involve vaccines for influenza, pneumococcal infection, hepatitis B or recurrent herpes zoster. Experience suggests that patients with cancer, or immunocompromised or immunosuppressed patients may require a greater number of vaccine doses and more vaccinations than immunocompetent individuals (29). A previous study of a recombinant herpes zoster vaccine in patients with cancer demonstrated that the overall immune response differed when the first dose of the vaccine was administered prior to chemotherapy compared with when the first dose was administered during chemotherapy (30). However, another study on a recombinant subunit herpes zoster vaccine found that only 15% of patients with hematological malignancies had a detectable serological response (31).

Patients with cancer are more likely to have an immune response following vaccination for coronavirus disease-19 than non-cancer patients. As previously demonstrated, after the third dose of the vaccine in patients with solid tumors, the proportion of patients with neutralization to the Omicron variant increased from 47.8 to 88.9% (32). It has also been found that after two doses of the mRNA vaccine in patients with non-small cell lung cancer, the neutralization response to the Omicron variant was 79-fold lower than that of individuals without cancer (33). Neutralizing antibodies are rarely detected in patients with hematological malignancies after two doses of the Omicron vaccine; however, neutralizing antibodies are detected in ~50% of patients after the third dose (34). Therefore, limited knowledge is available as regards the impact of chemotherapy on the immune system of patients with cancer, particularly with regards to vaccination strategies in the context of chemotherapy.

The present study revealed that a patient accidentally infected with HBV continued to produce protective antibodies against HBV despite taking chemotherapy drugs to reduce the number of lymphocytes in their blood, ultimately achieving clinical cure. This phenomenon highlights the complexity of the human immune system. Further understanding of the immune system is needed to potentially produce effective strategies to enhance antibody production in patients with HBV after vaccination.

Acknowledgements

Not applicable.

Funding

This research was supported by the Natural Science Foundation of Inner Mongolia Autonomous Region (grant no. 2021MS08060), Inner Mongolia Medical University Joint Project (grant nos. YKD2021LH068 and YKD2022LH072) and the Public Hospital Research Joint Fund Science and Technology Project (grant no. 2024GLLH0990).

Availability of data and material

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

LW, FZ and JH wrote the manuscript. YH, FZ and JH provided critical comments on the manuscript content and made substantial contributions to the interpretation of the data.

LW and YH made substantial contributions to the conception and design of the manuscript, identified the clinical cases, assessed the clinical data, verified the case data and reviewed the manuscript. DS and RY analyzed and interpreted the data. HN acquired the data. LW and YH confirm the authenticity of all original data and take responsibility for all aspects of the work, ensuring that any questions regarding the accuracy or integrity of any part of the work were appropriately investigated and resolved (according to ICMJE regulations). All authors read and approved the final version of the manuscript and unanimously agreed that the manuscript could be published.

Ethics approval and consent to participate

This case report (including images and related text) was submitted and published in accordance with the COPE guidelines, strictly following the Declaration of Helsinki and Chinese national policies, and was approved by the Ethics Committee of Chifeng Municipal Hospital (approval no. CK20250101, approved in January 2025).

Patient consent for publication

Written consent was obtained from the patient to publish these details.

Competing interests

The authors declare that they have no competing interests.

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