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Case Report

A case of Atypical Occult Hepatitis B Infection (OBI) with HBsAg Negativity and High Anti-HBs Titer: Clinical implications

Lin Duan[1], Yiyang Li[2], Sining Xing[3], Meichen Liu[4], Xiaodan Liu[5]

SUMMARY

A 72 years old male patient was admitted presenting with upper abdominal distension and pain for one day. He had a 20-year history of hypertension and a 10 years history of hepatitis B, which he reported had been cured. Laboratory tests revealed a distinctive serological profile characterized by HBsAg negativity, anti-HBs positivity (714.2 mIU/ml), anti-HBe positivity, and anti-HBc positivity. However, HBV DNA was tested positive (5.962×10^2 IU/mL). The imaging studies revealed a heterogeneous space-occupying lesion in the left hepatic lobe. This case challenges the conventional perception that "a high anti-HBs titer is indicative of protective immunity and successful viral clearance". The patient underwent resection of the lesion and received regular follow-up postoperatively.

KEYWORDS: Genetic Diagnosis, HBsAg Negativity, High anti-HBs Titer, Humoral Immune Escape, HBV DNA Positivity, Occult Hepatitis B Infection (OBI).

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INTRODUCTION

Occult Hepatitis B Infection (OBI) is defined as an infectious state in which hepatitis B surface antigen (HBsAg) is negative in serum, whereas HBV DNA is detectable in liver tissue or serum. Globally, OBI affects approximately 1.5%–31% of HBsAg-negative individuals.[1,2] According to expert consensus,[3] the diagnosis of OBI is based on three criteria: negative serum HBsAg; detectable HBV DNA in liver tissue or serum; and detection of serological markers of past infection (anti-HBc ± anti-HBs). The clinical hazards of OBI manifest primarily in three aspects: an increased risk of liver disease progression (with a 3.8-fold higher risk of cirrhosis or hepatocellular carcinoma (HCC) compared with the general population), viral reactivation under immunosuppression (with a rate of 30%–50% in elderly patients), and the potential for blood-borne transmission. As a region with intermediate HBV endemicity, China has an estimated 75 million chronic HBV carriers, among whom undiagnosed OBI may present significant public health concerns.[4] This article reports an atypical OBI case presenting with an high anti-HBs titer (714.2-mIU/ml) ; the contradictory serological and virological findings observed in this case offer important implications for clinical perception.

CASE REPORT

Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Affiliated Hospital of Hebei University (Ethics Approval No: HDFYLL-KY-2022-020; dated December 29, 2022). Patient informed consent was obtained for the publication of this case report.

A 72 years old male patient was admitted due to "upper abdominal distension and pain for one day

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without obvious inducement, accompanied by nausea and vomiting". Abdominal pain was relieved after vomiting, with no fever or chills. He had a 20 years past medical history of hypertension and took medications regularly; he reported that he was diagnosed with hepatitis B ten years ago and that the disease had been cured. On physical examination, the abdomen was soft, with tenderness (+) noted in the upper abdomen. No rebound tenderness was observed, and the liver and spleen were non-palpable. HBV serological markers (chemiluminescence immunoassay, CLIA, Abbott Architect i2000SR chemiluminescence immunoassay system with its original reagents; LoD for HBsAg: 0.05 IU/mL) showed the "245-positive" pattern: HBsAg negative, anti-HBs positive (714.2-mIU/ml; reference value: >10-IU/ml indicates protective efficacy), HBeAg negative, anti-HBe positive, and anti-HBc positive. HBV DNA (polymerase chain reaction, PCR, Roche COBAS TaqMan HBV DNA Test, v2.0): positive (5.962×10^2 IU/mL).

Multi-platform re-verification was conducted as follows: Virological confirmation, in which HBV DNA was re-tested using PCR assays from two different manufacturers, with both yielding positive results.

Serological confirmation, in which the hepatitis B serological markers were independently re-analyzed using two distinct CLIA platforms, consistently showing an HBsAg-negative and high anti-HBs-positive pattern; tumor marker assays showed an elevated carcinoembryonic antigen (CEA) level of 5.50 ng/mL, while alpha-fetoprotein (AFP) and carbohydrate antigen 199 (CA19-9) levels were within normal ranges (Table-I).

Upper abdominal computed tomography (CT) and MRI revealed a heterogeneous echo mass in the left hepatic lobe (Fig.1-2). The patient was finally diagnosed with OBI and a space-occupying lesion in the left hepatic lobe. The patient underwent resection of the space-occupying lesion in the left hepatic lobe; postoperative pathology indicated moderately differentiated hepatocellular carcinoma (without capsule invasion). Postoperatively, entecavir was administered for antiviral therapy, and regular monitoring of HBV DNA (which decreased to an undetectable level three months postoperatively) and imaging re-examinations were conducted.

DISCUSSION

The core particularity of this case lies in the coexistence of an high anti-HBs titer (714.2-mIU/ml) and positive HBV DNA (5.962×10^2 IU/mL), thereby undermining the conventional cognition that "high antibody titer equates to viral clearance". For such mutant strains, the false-negative rate of HBsAg detection using dual-reagent enzyme-linked immunosorbent assay (ELISA)/CLIA is as high as 70%, giving rise to "detection escape". Furthermore, high-titer anti-HBs loses its neutralizing capacity due to its inability to recognize the mutant antigen, leading to "humoral immune escape".[5,6]

The patient reported having achieved "hepatitis B cure" a decade prior, and routine serological tests were consistent with the profile of the "recovery phase"; however, OBI and HCC were ultimately diagnosed,

Table-I: Key laboratory findings at diagnosis.

Test Category	Parameter	Result	Reference Range / Interpretation
Hepatitis B Serology	HBsAg	Negative	<0.05 IU/mL
	Anti-HBs	Positive	714.2 mIU/mL (>10 indicates protective)
	HBeAg	Negative	-
	Anti-HBe	Positive	-
	Anti-HBc	Positive	-
HBV Virology	HBV DNA	Positive	5.962×10^2 IU/mL
Tumor Markers	AFP	2.59 ng/mL	0-7.0 ng/mL
	CEA	5.50 ng/mL	0-5.0 ng/mL
	CA19-9	12.30 U/mL	0-27 U/mL
Key Liver Function Tests	ALT	56 U/L	9-50 U/L
	AST	48 U/L	15-40 U/L
	Total Bilirubin	15.2 μmol/L	3.4-20.5 μmol/L
	Albumin	38 g/L	35-55 g/L

**Note:* HBV serology was performed using chemiluminescence immunoassay (CLIA, Abbott Architect i2000SR). HBV DNA was quantified using the Roche COBAS TaqMan HBV DNA Test, v2.0. This profile (HBsAg-/anti-HBs+/anti-HBe+/anti-HBc+) with detectable HBV DNA is diagnostic for occult hepatitis B infection (OBI).*

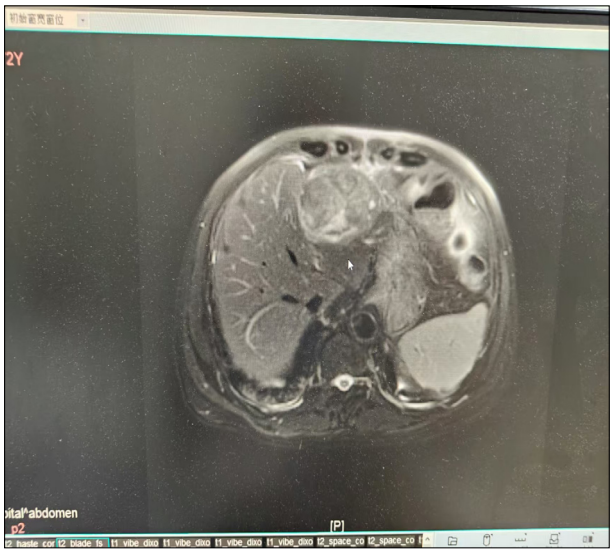

Fig.1: Upper Abdominal MRI: Plain Scan + Contrast-Enhanced Scan + MRCT.
Multiparametric liver MRI including plain scan, contrast-enhanced phases, and MR cholangiopancreatography (MRCP). The study characterizes the heterogeneous mass in the left hepatic lobe, which was later pathologically confirmed as hepatocellular carcinoma.

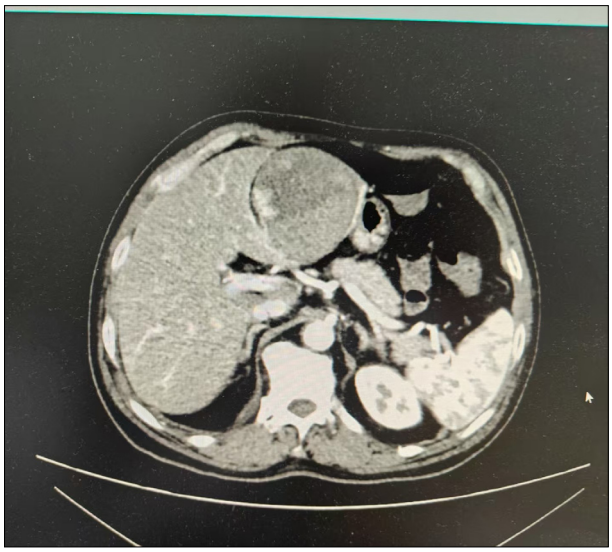

Fig.2: Abdominal CT Angiography.
Triple-phase contrast-enhanced CT (hepatic arterial, portal venous, and hepatic venous phases) used for preoperative evaluation of the liver mass and its vascular relationship, crucial for surgical planning.

highlighting three major deficiencies in clinical management:

Underestimation of the risk of viral reactivation: The rate of viral reactivation reaches 30%–50% in elderly OBI patients with impaired immunity.[7] In the present case, regular HBV DNA monitoring was not conducted, resulting in missed opportunities for intervention.

Inadequate HCC screening: Intrahepatic covalently closed circular DNA (cccDNA) persists within OBI patients, driving liver fibrosis and carcinogenesis. Studies have demonstrated that the risk of HCC in anti-HBc-positive individuals is 4.6-fold higher than that in anti-HBc-negative counterparts.[8]

Notably, tumor marker profiling revealed an elevated CEA (5.50 ng/mL) in the absence of significant AFP or CA19-9 elevation, which, while atypical for HCC, may reflect the heterogeneous nature of tumor biomarker expression in HBV-associated liver masses. This highlights the importance of integrating imaging, histopathology, and a panel of tumor markers in the diagnostic evaluation of hepatic space-occupying lesions.

Flaws in treatment decision-making: screening solely for HBsAg prior to immunosuppressive therapy misses OBI patients, leading to reactivation-induced hepatitis.[9] Guidelines recommend that all anti-HBc-positive individuals undergo HBV DNA testing before initiating treatment.

The accurate diagnosis of this case depends on a multi-platform integrated diagnostic strategy, including:

- Combined serological and virological assays, which mandates supplementary HBV DNA testing for individuals with the "245-positive" serological pattern;
- Cross-validation using dual reagents, employing reagents targeting different epitopes to minimize the risk of missed detection of mutant strains. In particular, this diagnostic workflow can be implemented for screening in scenarios including unexplained liver damage, populations at high risk of HCC, and patients prior to immunosuppressive therapy.

Among approximately 254 million individuals with chronic HBV infection worldwide, the actual burden of OBI is severely underestimated, and OBI-positive blood donors pose a risk of transfusion-transmitted infections.[10] A Japanese study has reported that HBsAg-negative/HBV DNA-positive blood donors constitute 0.03% of all blood donors.[11] While nucleic acid amplification testing (NAT) alongside HBsAg is increasingly used in many high-prevalence regions to enhance blood safety, the potential inclusion of universal anti-HBc screening remains a topic of discussion. This is because such a policy, while ideal for intercepting some OBI donations, could also lead to the exclusion of a substantial number of non-infectious blood units from individuals who are anti-HBc positive due to past, resolved infection. The studies conducted in China have shown that infections with these mutant strains account for 12.7% of post-vaccination HBV infections.[12]

Limitations: preoperative quantitative measurement of HBV cccDNA in liver tissue samples—the gold standard for OBI diagnosis—was not available, and although our diagnosis was supported by a multi-platform approach including serum HBV DNA positivity, the absence of

histological confirmation remains a constraint; deep sequencing was not conducted to assess the complexity of viral quasispecies, and it may not have captured low-frequency variants or the full spectrum of viral populations; the S-region sequencing results compared with the wild-type sequence were not provided, limiting a comprehensive understanding of the mutational landscape; and in vitro neutralization assays for the mutant strains were not performed to validate their capacity for immune escape, with the conclusion that high-titer anti-HBs failed to neutralize the virus being inferred from published functional data on known mutations rather than direct experimental evidence from this isolate. As a retrospective single-case report, practical and sample-related constraints prevented the performance of some experimental validations, and future studies on similar cases should incorporate functional assays and deep sequencing to provide more comprehensive mechanistic insights.

CONCLUSION

This case highlights the complex nature of OBI. The failure of high anti-HBs titer (714.2-mIU/ml) to clear the virus fundamentally challenges the conventional conceptual framework. Furthermore, this serological paradox may be partly explained by the formation of immune complexes between anti-HBs antibodies and circulating HBV virions or subviral HBsAg particles, which could both mask HBsAg from detection and permit low-level viral persistence. Clinical management is therefore recommended to adhere to the following principles:

1. HBV DNA testing should be performed in all anti-HBc-positive individuals, regardless of their anti-HBs titer;
2. Genetic sequencing should be initiated in cases of contradictory serological findings;
3. OBI patients should undergo lifelong monitoring of HBV DNA and HCC biomarkers every six to 12 months;
4. Nucleic acid amplification testing (NAAT) should be implemented prior to high-risk medical procedures (e.g., blood transfusion and organ transplantation).

Recommendations: Additionally, it is recommended to integrate OBI into HCC monitoring pathways, define clear screening criteria prior to immunosuppressive therapy, and facilitate the clinical translation of technologies for detecting mutant strains.

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Authors' contributions:

LD: Writing– original draft, Investigation, Conceptualization, review & editing, is responsible and accountable for the accuracy and integrity of the work.
YL& SX: Resources, Writing– original draft, Methodology, Supervision.
ML & XL: Writing– review & editing, Conceptualization, Supervision, Investigation.