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CASE REPORT

A Case of Intravenous IVIg Interfering with Serological Test Results of HBV

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SUMMARY

Background: **Since Imbach [1] first reported the use of high-dose intravenous immunoglobulin (IVIg) in the treatment of idiopathic thrombocytopenic purpura (ITP) in children, indications for IVIg therapy have been increaseing. At present, IVIg infusion has become an important means of clinical treatment. The phenomenon of anti-HBs and anti-HBc elevation caused by IVIg infusion in patients has been reported in journals, but similar reports in journals related to laboratory diagnosis are rare.**
Methods: **We reported a case of a patient with immune thrombocytopenia (ITP) which interfered with hepatitis B virus (HBV) serological detection after receiving intravenous IVIg. We used chemiluminescence immunoassay to detect serological markers of HBV. IU/mL was used to represent the detection data of HBsAg and HBsAb and cutoff value was used to represent the detection HBeAg, HBeAb, and HbcAb.**
Results: **The serological markers of HBV were all negative before IVIg infusion. One week after IVIG infusion, the item was tested again, and the results of HBsAb, HBeAb, and HBcAb were positive. As the time increased after infusion, HBsAb, HBeAb, and HBcAb in the patient gradually decreased.**
Conclusions: **After IVIg infusion, the sudden positive change of HBsAb, HBeAb, and HbcAb in the patient's body was not caused by HBV infection, but caused by the infusion of foreign antibody. This case study shows that physicians should be particularly careful when interpreting results in patients treated with intravenous IVIg involving viral hepatitis B.**
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KEYWORDS

IVIg treatment, HBV serological test; passive antibody transfer, immune thrombocytopenia (ITP)

INTRODUCTION

Intravenous human immunoglobulin (IVIg) therapy has become a relatively common treatment for autoimmune diseases [2]. IVIg is prepared from the plasma of healthy people and contains broad-spectrum immunoglobulin antibodies against viruses, bacteria or other pathogens. After intravenous infusion, it can rapidly increase the IgG level in the blood of the recipient, enhance the anti-infection ability, and immune regulation function of the body [3]. Now we found a case of abnormal HBV serological test results in a patient with

immune thrombocytopenia who received intravenous IVIg, as shown below.

CASE PRESENTATION

The patient, a 27-year-old female, was admitted to the emergency department of our hospital on June 23, 2023, due to "the discovery of hemorrhagic spots scattered throughout the body for 2 days". Blood count test on admission showed WBC 5.08 x 10^9/L, NEUT 2.81 x 10^9/L, Hb 144 g/L, PLT 4 x 10^9/L. The patient, diagnosed with “immune thrombocytopenia (ITP)”, was given an infusion of apheresis platelets 10 U to improve bleeding, and IVIg 22.5 g to resist autoimmune reactions. After admission, the serological test of HBV showed that HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb were negative. One week later (June 30, 2023), the patient retest for serological markers of HBV indicates that HBsAb, HBeAb, and HBcAb were positive. The complete inconsistency of the corresponding indexes of HBV in a short period of time immediately caused great concern to the laboratory physician. We immediately re-examined the specimen and also conducted liver function indicators and HBV-DNA test for this specimen. There was nothing suspicious about these test results. In addition, we checked the past results of the HBV serological test of this patient in the laboratory information system (LIS) (Table 1). The patient completed the transformation from HBV three antibodies negative to positive in just one week. We were full of doubts about this result. After communicating with the ward and consulting the patient's medical history, we ruled out the possibility of specimen collection error and the recovery period of recent HBV infection. However, the patient's medical history data “IVIg22.5g to resist autoimmune reactions” attracted our attention. We immediately tested HBV serum markers on the same batch of IVIg (JM20230138) injected by the patient (Table 1). From the data in the Table 1, we speculate that positive results for HbsAb, HbeAb, and HbcAb are transient in the patient's body and due to the passive transfer of antibodies after IVIg infusion. To further confirm the inference, we conducted 30-day, 90-day, and 180-day follow-up of patients with HBV serological markers (Table 2). On the 30th day after the infusion of large dose IVIG, HBsAb, HBeAb, and HBcAb in the patient's body decreased compared with June 30, 2023. On the 90th day, the HBeAb first turned negative, HBsAb and HBcAb also continued to decline. On the 180th day, HBsAb, HBeAb, and HbcAb in the body turned negative and returned to the state before IVIg infusion.

DISCUSSION

According to the guidelines on the preparation standards of IVIg issued by the World Health Organization, IVIg is a polyclonal product prepared from more than 1,000 healthy human plasma samples using a special separation and purification technology (low-temperature ethanol protein separation) [4]. During the production of blood products in Chinese blood products enterprises, the amount of plasma in a single batch is generally large (more than 5,000 people), and the plasma collection station generally carries out hepatitis B vaccination on plasma donors, and the plasma donors are not screened for anti-HBs and anti-HBc, so the titer of anti-HBs in mixed plasma is high, which will inevitably lead to IVIg products containing not only anti-HBs, but also anti-HBc. Therefore, it is possible that non-infectious but anti-HBc positive plasma may be mixed into the finished IVIg [5], which may result in transient positive test results due to passive transfer of anti-HBs and anti-HBc after IVIg treatment [6]. However, passive antibody transfer is still not routinely considered by doctors in the interpretation of viral serology results. When unexpected serological changes are found, we should first consider passive antibody transfer. After the passive transfer of antibodies is excluded, then further diagnosis is made to avoid causing misjudgment of serological results and poor management of the patient's condition. Moreover, false diagnosis can also cause psychological harm to patients, negatively affect their quality of life, and lead to a significant incidence of mental illness (mainly depression) [7].

It is worth noting that the patient cleared the three antibodies of passive metastasis over a period of 6 months, and the pattern of declining anti-HBs titers in the above cases is typical of passive metastasis antibody clearance. Studies have shown that the half-life of intravenous immunoglobulins, when given to healthy recipients, is 21 to 28 days, meaning that any passively acquired antibodies from IVIg are cleared in about 3 - 4 months. However, there is considerable variation between patients, with the half-life of patients receiving IVIg for both primary and secondary immunodeficiency may be extended up to 45 days [8]. Therefore, the metabolism of antibodies passively transferred by IVIg infusion is different in different patients, and corresponding attention should be paid to clinical detection. In addition, patients with autoimmune diseases (such as ITP) usually need to consider further immunomodulatory therapy with rituximab while receiving IVIg treatment. This anti-CD20 monoclonal antibody treatment can cause adverse reactions such as HBV reactivation in patients previously infected with HBV [9]. Therefore, previous hepatitis B infection and anti-HBc positivity are obstacles to anti-CD20 monoclonal antibody treatment. This emphasizes the necessity of virus screening before routine treatment and the importance of clinicians recognizing such potentially confounding results [10].

It can be seen from this case that the short-term positive HBV antibody after the patient was infused with IVIg was not caused by HBV infection, instead it is through passive transfer of foreign antibodies. As the time increases after infusion, the antibody titer of passive transfer in patients will gradually decrease. For patients

Table 1. Results of HBV serologic markers in different periods of patients and JM20230138 batch number IVIg.

Project	01-30-2023 (WANTAI)	06-23-2023 (WANTAI)	06-30-2023 (WANTAI)	06-30-2023 (ABBOTT)	IVIg (WANTAI)	Reference range
HBsAg	< 0.05 (-)	< 0.05 (-)	< 0.05 (-)	< 0.05 (-)	< 0.05 (-)	< 0.05 IU/mL
HBsAb	3.54 (-)	2.47 (-)	631.52 (+)	655.85 (+)	966.60 (+)	< 10.0 IU/mL
HBeAg	0.24 (-)	0.32 (-)	0.01 (-)	0.08 (-)	0.01 (-)	< 1.0 S/CO
HBeAb	1.76 (-)	1.94 (-)	0.46 (+)	0.37 (+)	0.23 (+)	> 1.0 S/CO
HBcAb	0.02 (-)	0.01 (-)	6.17 (+)	7.38 (+)	24.11 (+)	< 1.0 S/CO

Note: (1) WANTAI and ABBOTT instrument company name. (2) (-) indicate negative, (+) indicate positive.

Table 2. Results of HBsAb, HBeAb, and HBcAb at 30, 90, and 180 days after the infusion.

Project	30 days	90 days	180 days	Reference range
HBsAb	431.52 (+)	125.23 (+)	8.55 (-)	< 10.0 IU/mL
HBeAb	0.86 (+)	1.50 (-)	1.94 (-)	> 1.0 S/CO
HBcAb	3.17 (+)	1.48 (+)	0.32 (-)	< 1.0 S/CO

Note: HBeAb uses anti-competition testing principles, so the reference range > 1.0 S/CO is interpreted as negative.

treated with such intravenous IVIg, clinicians should be particularly cautious in interpreting and handling results involving viral hepatitis B.

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Declaration of Interest:
All authors declare that they have no competing interests.

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