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BRIEF REPORT

Assessing Hepatitis B Reactivation Risk With Rituximab and Recent Intravenous Immunoglobulin Therapy

Claire Dysart,[1] Karine Rozenberg-Ben-Dror,[2] and Mariscelle Sales[3]

[1]Department of Veterans Affairs, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin, USA, [2]Department of Veterans Affairs, VISN 12 Great Lakes Healthcare System, Westchester, Illinois, USA, [3]Department of Veterans Affairs Pharmacy Benefits Management Services and Center for Medication Safety (VA MedSAFE), Hines, Illinois, USA

Hepatitis B reactivation (HBR) is a complication of immunosuppression associated with significant morbidity and mortality. To further complicate interpretation of hepatitis B serologies, false positivity can occur in patients with recent intravenous immunoglobulin exposure. This scenario is not well recognized and may lead to inappropriate prescribing of HBR prophylaxis.

Keywords. hepatitis B; immunoglobulin; reactivation; rituximab; serologies.

Hepatitis B reactivation (HBR) is an unintended consequence of systemic immunosuppression and can result in fulminant hepatitis, hepatic decompensation, and death. The American Society of Clinical Oncology and the American Gastroenterological Association have published guidelines to aid providers in the appropriate assessment of patients before prescribing treatments associated with HBR. High-risk agents include anti-CD20 monoclonal antibodies, chemotherapy, immunotherapy, high-dose corticosteroids, and direct-acting antivirals for hepatitis C [1–4].

Hepatitis B (HB) viral serologies are measured before starting certain immunosuppressive treatments due to risk of HBR. Hepatitis B virus (HBV) infection is characterized by serologic markers, heralded by HBV deoxyribonucleic acid (DNA), then followed by HB surface antigen (HBsAg). After exposure to the HBV core antigen, which is highly immunogenic, HB core antibodies (HBcAb) emerge (immunoglobulin [Ig]M, then IgG). Hepatitis B core antibodies persist indefinitely and signifies previous HBV infection. Patients with prior natural HBV exposure that do not develop chronic infection still have HBV DNA persisting in the host genome as covalently closed circular DNA, which can reactivate with immunosuppression or exposure to very high-risk agents such as anti-CD20 monoclonal antibodies (ie, rituximab) [5]. More than 1 marker may appear in acute and chronic infections. Presence of HBsAg signifies acute or chronic infection. Presence of HBcAb suggests acute, resolved, or chronic HBV infection (not present after immunization). Presence of hepatitis B surface antibodies (HBsAb) indicate resolved infections or immunity after immunization.

The correct interpretation of HB viral serology in the context of immunosuppression is important because positive results would indicate the need for prophylactic antiviral medication to minimize the risk of reactivation. False-positive HB serologies may occur because of transient, passive transfer of antibodies through administration of intravenous Ig (IVIG) [6–11]. This poses a concern for patients exposed to IVIG for treatment of immunologically mediated diseases who are in need of systemic immunosuppression that would require screening for previous HB infection to minimize reactivation.

The Department of Veterans Affairs (VA) identifies patients with potential risk for HBR for provider assessment/action through VA's web-based application called Medication Utilization Evaluation Tracker (MUET). The MUET is VA's risk-reduction tool used for national medication-related interventions overseen by the VA Pharmacy Benefits Management Services Center for Medication Safety (VA MedSAFE) [12]. The VA's closed system and ability to track medication use facilitates these risk-reduction efforts. Facility reporting of the following events informed the MUET program about potential false HB serologies temporally associated with recent IVIG treatment and promoted internal provider awareness and education regarding HBR risk-assessment across the VA system-wide.

We detail the events of 2 cases in which HB serologies were misinterpreted as a result of passive transfer of HBV antibodies after IVIG infusions before initiation of rituximab. In both cases, patients were given HBR prophylaxis until false positivity was confirmed and HB antivirals were discontinued. In addition, we offer guidance for providers to recognize these scenarios and a management approach to prevent misinterpretation of HB serologies that can lead to unnecessary HB antiviral prophylaxis.

Patient 1

A 69-year-old male received IVIG infusions for polymyositis for 11 months. Concurrently, he began methotrexate requiring screening for HBV exposure. The patient was positive for both HBsAb and HBcAb and negative for HBsAg. These results were consistent with immunity from previous natural infection. The patient was transitioned from IVIG to rituximab approximately

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Correspondence: Claire Dysart, PharmD, Department of Veterans Affairs, Clement J. Zablocki Veterans Affairs Medical Center, 5000 W. National Ave., Milwaukee, WI 53295 (claire.dysart@va.gov).

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1 month after his last IVIG infusion, which required prophylaxis with entecavir for known risk of HBR. However, absence of HB exposure suggested false seropositivity. Repeat serologies approximately 8 weeks later revealed negative HBcAb, which confirmed suspicions (Table 1), and entecavir was discontinued. Hepatitis B virus DNA and HBsAg were negative at baseline and repeat HBcAb remained negative at 12 weeks.

Patient 2

A 70-year-old male received IVIG infusions intermittently for 4 years for refractory idiopathic thrombocytopenic purpura and was transitioned to rituximab therapy. Assessment for HB exposure yielded a positive HBcAb, and additional laboratory tests including HBV DNA and liver function tests were completed. All laboratory tests returned negative and within normal limits, respectively. Repeated laboratory tests performed 9 weeks post-IVIG treatment, including a negative HBcAb, supported IVIG-associated passive transmission (Table 1).

Each clinical scenario showed lack of infection or exposure in patient history, no prior record of immunization, recent transfusion of Ig-containing products, presence of core antibodies without viral antigen or DNA, and degradation of antibody titers over time. Waning HBsAb titers observed after repeated serological testing for both patients suggested passive transfer by IVIG.

DISCUSSION

Hepatitis B reactivation with immunosuppressive drugs varies by patient and has implications for screening and treatment. Several published reports have shown that Ig therapy has confounded diagnostic test results due to passive transfer of antibodies and has occurred in patients with hematologic malignancies, autoimmune conditions, and infectious diseases [6–11]. When assessing a patient for HBR in the setting of IVIG treatment, false-positive HB serologies may persist for 12–16 weeks [9–11]. Patients who had repeat serological testing performed after IVIG therapy were found to have lower or negative antibody titers 4–8 weeks after cessation of IVIG [6, 10]. Despite growing evidence of spurious serologies, cases continue to occur that impact management of patients and infection risk, demonstrating a potential gap in translating this knowledge into practice. In addition, due to nuances in immunodeficient populations, careful assessment should consider not only the contribution of IVIG, but the underlying immunologic status of the patient as well. For example, patients with hypogammaglobulinemia may have insufficient immune response for appropriate HBV assessment. Patients with hypogammaglobulinemia and past HB infection may present with negative HBcAb, complicating the assessment for exposure or risk [9].

Serological tests should be interpreted cautiously to direct appropriate antiviral prophylaxis and/or immunosuppressive therapy. Clinical implications of misleading test results may include unnecessary antiviral administration, which can result in unintended consequences secondary to acute and/or long-term toxicities as well as unneeded monitoring. Delaying and/or withholding vital immunosuppressive therapy may also occur, leading to suboptimal treatment of the intended condition and exacerbation of existing comorbidities.

CONCLUSIONS

Our cases remind providers to anticipate passive antibody transfer with IVIG and false-positive HB serologies. Serological tests should be interpreted carefully especially when assessing for HBR in autoimmune and autoinflammatory comorbidities that may require concomitant IVIG and rituximab use. Routine screening for HBV pre-IVIG treatment can avert misleading serologies in the future. We urge providers to consider passive antibody transfer when there is a temporal relationship between recent IVIG and unexpected HB serologies in patients with a reported low risk for HBV exposure, particularly in the setting of positive HBcAb without viral antigen or DNA and degradation of antibody titers over time. Patients with positive HBcAb should be offered HBR prophylaxis until further confirmatory testing can be completed and false positivity is confirmed with repeat serological assessment at least 3–4 months after the last IVIG infusion.

Table 1. Diagnostic Tests for HBV for Patients 1 and 2

	Patient 1			Patient 2	
Serological test[a]	Day 2[b]	Day 55[b]	Day 83[b]	Day 35[b]	Day 62[b]
HBsAg	Nonreactive	Not obtained	Not obtained	Nonreactive	Nonreactive
Antibody to HBsAg HBsAb (mIU/mL)	>1000.00	215.73	114.57	312.28	152.53
Total antibody to HBcAb	Reactive	Nonreactive	Nonreactive	Reactive	Nonreactive

Abbreviations: HBcAb, hepatitis B core antibodies; HBsAb, hepatitis B surface antibodies; HBsAg, hepatitis B surface antigen; HBV hepatitis B virus.
[a]The pattern of seropositivity that includes the presence of HBcAb in patients 1 and 2 implies hepatitis infection. However, it has also been associated with the passive transfer of antibodies from use of certain intravenous immunoglobulin (IVIG) products.
[b]Number of days after last IVIG infusion.

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