Hepatitis B reactivation in patients with pemphigus vulgaris after immunosuppressive therapy including rituximab

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Key words: Hepatitis B reactivation; pemphigus; rituximab.

INTRODUCTION

Pemphigus is a potentially fatal autoimmune blistering disease. Rituximab, a monoclonal antibody against CD20, has increasingly been used in pemphigus patients resistant to conventional therapies. Recently, rituximab therapy has been reported as the first-line treatment for moderate-to-severe pemphigus.[1] However, rituximab has potential complications because of its immunosuppressive effects, including reactivating chronic or latent infections.[2] We herein report 2 cases of hepatitis B reactivation in patients with pemphigus vulgaris (PV) after immunosuppressive therapy including rituximab.

Abbreviations used:

ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
anti-HBc:	antibody to HBV core antigen
ELISA:	enzyme-linked immunosorbent assay
HBV:	hepatitis B virus
HBsAg:	HBV surface antigen
PV:	pemphigus vulgaris

CASE REPORTS

The 2 patients with PV showed hepatitis B reactivation after injection of rituximab, 1 g twice at 2-week intervals. One patient suffered from acute hepatic failure necessitating a liver transplantation and the other patient successfully recovered with tenofovir (Table I).

Case 1

A 65-year-old woman was hospitalized for PV and treated with oral prednisolone (20 mg/d) and mycophenolate mofetil (1 g/d). Before treatment, her enzyme-linked immunosorbent assay (ELISA) testing of antidesmoglein 1 antibody titer was 231.8 U/mL and antidesmoglein 3 antibody titer was 194.4 U/mL. She was an inactive hepatitis B virus (HBV) carrier with HBV surface antigen (HBsAg) positive and antibody to HBV core antigen (anti-HBc) positive. Her initial liver function test found normal range of aspartate aminotransferase (AST) (18 IU/L) and alanine aminotransferase (ALT) (18 IU/L). Her skin lesions improved after 1 cycle of intravenous immunoglobulin (0.5 g/kg for 4 days) and injection of 1 g rituximab twice at 2-week intervals. Two months after rituximab therapy, she presented to the emergency room with general weakness and jaundice. Liver function test found elevation of AST (1,124 IU/L) and ALT (1,472 IU/L), and serum HBV DNA level was 21,400,000 IU/mL. Acute liver failure caused by hepatitis B reactivation was diagnosed, and an emergency liver transplantation was performed. Serum HBV DNA level dropped to 77 IU/L but the patient died of septicemia 5 months after liver transplantation.

Case 2

A 64-year-old woman with PV who was an inactive HBV carrier and was HBsAg-positive/anti-HBc-positive had been treated with oral methylprednisolone (20 mg/d) and mycophenolate mofetil (1 g/d). ELISA testing of antidesmoglein 1 antibody titer was 63.8 U/mL and antidesmoglein 3 antibody titer was 154.9 U/mL. Her initial liver function test revealed normal range of AST (23 IU/L) and ALT (16 IU/L), and serum HBV DNA was 643 IU/mL. Her

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Funding sources: None.
Conflicts of interest: None disclosed.
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JAAD Case Reports 2020;6:83-5.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.10.017

Table I. Details of 2 PV patients with hepatitis B reactivation after immunosuppressive therapy including rituximab

Patient no.	Gender/age	Dsg ELISA Dsg 1 / Dsg 3	GC dosage/duration of GC usage	Concurrent immunosuppressant	Duration of HBV reactivation from RTX therapy	Hepatitis type	Hepatitis viral tests	AST level ALT level HBV DNA level before RTX therapy	AST level ALT level HBV DNA level at diagnosis of HBV reactivation	Outcome
1	F/65	231.8 U/mL 194.4 U/mL	Prednisolone 20 mg - 5 mg/d/4-5 mo	Mycophenolate mofetil 1 g/day	2 mo	Inactive HBV carrier	HBsAg (+) HBeAg (-) Anti-HBs (-) Anti-HBe (+) Anti-HBc (+) Anti-HCV (-)	18 IU/L 18 IU/L Not done	1,124 IU/L 1,472 IU/L 21,400,000 IU/mL	Dead
2	F/64	63.8 U/mL 154.9 U/mL	Methylprednisolone 20 mg - 2 mg/d/ 5 mo	Mycophenolate mofetil 1 g/day	4 mo	Inactive HBV carrier	HBsAg (+) HBeAg (-) Anti-HBs (-) Anti-HBe (+) Anti-HBc (+) Anti-HCV (-)	23 IU/L 16 IU/L 643 IU/mL	1,499 IU/L 1,368 IU/L 75,500,000 IU/mL	Recovered with tenofovir

Dsg, Desmoglein; *GC*, glucocorticosteroid; *RTX*, rituximab; *HBeAg*, hepatitis B e antigen; *Anti-HBe*, antibody against hepatitis B envelop.

skin lesions improved after injection of 1 g rituximab twice at 2-week intervals. Three months after rituximab therapy, she achieved complete remission with methylprednisolone (2 mg/d). Four months after rituximab therapy, hepatitis B reactivation occurred with symptoms of general weakness. Liver function test revealed elevation of AST (1,499 IU/L) and ALT (1,368 IU/L), and serum HBV DNA was 75,500,000 IU/mL. The patient was hospitalized and recovered from HBV infection after treatment with tenofovir 25 mg daily.

DISCUSSION

Many reports warn about risk of hepatitis B reactivation during or after immunosuppressive treatment with corticosteroids and rituximab therapy.[3,4] The rate of hepatitis B reactivation during or after rituximab therapy has been reported as 20% to 55% when combined with chemotherapy.[4] Therefore, careful attention also should be paid to dermatologic patients who are already administered or plan to receive rituximab therapy. However, to the best of our knowledge, hepatitis B reactivation in patients with pemphigus after rituximab therapy has not been reported. Only few cases of hepatitis B reactivation in patients with PV after high-dose corticosteroid therapy have been reported.[5,6]

In the setting of immunosuppressive therapies, treatment with B-cell-depleting agents, including rituximab, is included in category of a high risk of hepatitis B reactivation in HBsAg-positive or HBsAg-negative/anti—HBc-positive patients.[3,7] Similarly, high-dose corticosteroid therapy indicates a high risk of reactivation in HBsAg-positive patients and a moderate risk of reactivation in HBsAg-negative/anti—HBc-positive patients.[3] Hence, screening tests for hepatitis B with AST, ALT, HBsAg, anti-HBs, and anti-HBc should be performed before initiation of rituximab therapy to help avoid potent reactivation of inactive HBV, especially in cases of using high-dose corticosteroid therapy together.[3]

Prophylactic treatment against hepatitis B reactivation during immunosuppressive agents or rituximab therapy has shown preventive effectiveness in high-risk patients for hepatitis B reactivation.[3,4,8] Prophylactic antiviral treatment was proposed to be continued until 12 months after rituximab therapy not only in HBsAg-positive patients but also in anti—HBc-positive patients with a high risk of hepatitis B reactivation.[3,4,7]

Besides rituximab therapy, corticosteroid and mycophenolate mofetil may have caused HBV reactivation in our patients, but it is relevant to consider that the main cause of HBV reactivation is rituximab therapy, because the patients received

relatively low doses of prednisolone and mycophenolate mofetil for a few months.

Our cases showed that rituximab may reactivate HBV in patients with pemphigus. Therefore, screening tests for hepatitis virus infection should be performed before starting rituximab therapy, and prophylactic or appropriate antiviral therapy should be administered to high-risk patients.

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