Rituximab administration in a patient with pemphigus vulgaris following reactivation of occult hepatitis B virus infection

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Abstract

Immunosuppressive drugs are the milestone of treatment of autoimmune diseases, but they can lead to serious complications, including hepatitis B virus reactivation in HBV carriers as well as in patients with occult HBV infection (OBI). A 36-year-old man with OBI was diagnosed with pemphigus vulgaris. He was prescribed prednisolone and his hepatitis B surface antigen turned positive. Viral replication was successfully controlled by lamivudine and adefovir. Mycophenolate mofetil and intravenous immunoglobulin were not effective in controlling the pemphigus vulgaris. The patient received rituximab 500 mg weekly for four weeks and went into remission without any adverse effect. He safely received another course of rituximab after a relapse one year later. In conclusion, testing for hepatitis B core antibody should be considered mandatory, in addition to HBsAg, for the screening of pemphigus patients to detect rare cases of OBI before starting therapy. Furthermore, rituximab may in some cases be safely used in HBV carriers using antivirals concomitantly.

Keywords: pemphigus vulgaris; hepatitis B virus reactivation; rituximab; occult HBV infection; HBsAg reappearance.

Introduction

Hepatitis B reactivation (HBVr) may occur during or after immunosuppressive-chemotherapy. This reactivation may depend on multiple factors, including host factors [1, 2], viral status [1-3], underlying disease [1, 2, 4], and potency of immunosuppressive drugs [2, 4]. In addition to HBV carriers, patients with occult HBV infection (OBI) or resolved HBV infection may experience HBVr [5]. Pemphigus vulgaris (PV) is a rare potentially fatal autoimmune bullous disease, usually treated with immunosuppressive therapy. Prednisolone is a mainstay in the treatment of PV. High doses of this drug for more than four weeks can be considered as a major risk factor for HBVr [6]. Herein we report a patient with PV showing HBVr upon treatment with prednisolone and successfully treated with antivirals and rituximab.

Case Synopsis

A 36-year-old man presented to Razi hospital in January, 2014 with a four-month history of oral erosions. He was receiving 15 mg of prednisolone daily for 2 months. Histopathology and direct immunofluorescence were suggestive of PV. Desmoglein 1 and 3 ELISA were 80 and >200 U/ml, respectively. Prednisolone dosage was increased to 70 mg daily after the PV diagnosis was confirmed. Routine tests revealed that hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) were negative, but hepatitis B core antibody (anti-HBc) was positive, compatible with OBI. Until late February, 2014, the negative HBsAg result was confirmed by three tests in two different laboratories. Prednisolone was increased to 100 mg in order to control the new skin lesions appearing on the scalp and face in late February, 2014. In late March, reappearance of HBsAg positivity was confirmed after a two-fold rise in alanine transaminase (ALT) levels. However, HBV DNA test indicated non-detectable viral load (Table1). With appearance of the positive HBsAg, the prednisolone dose was tapered

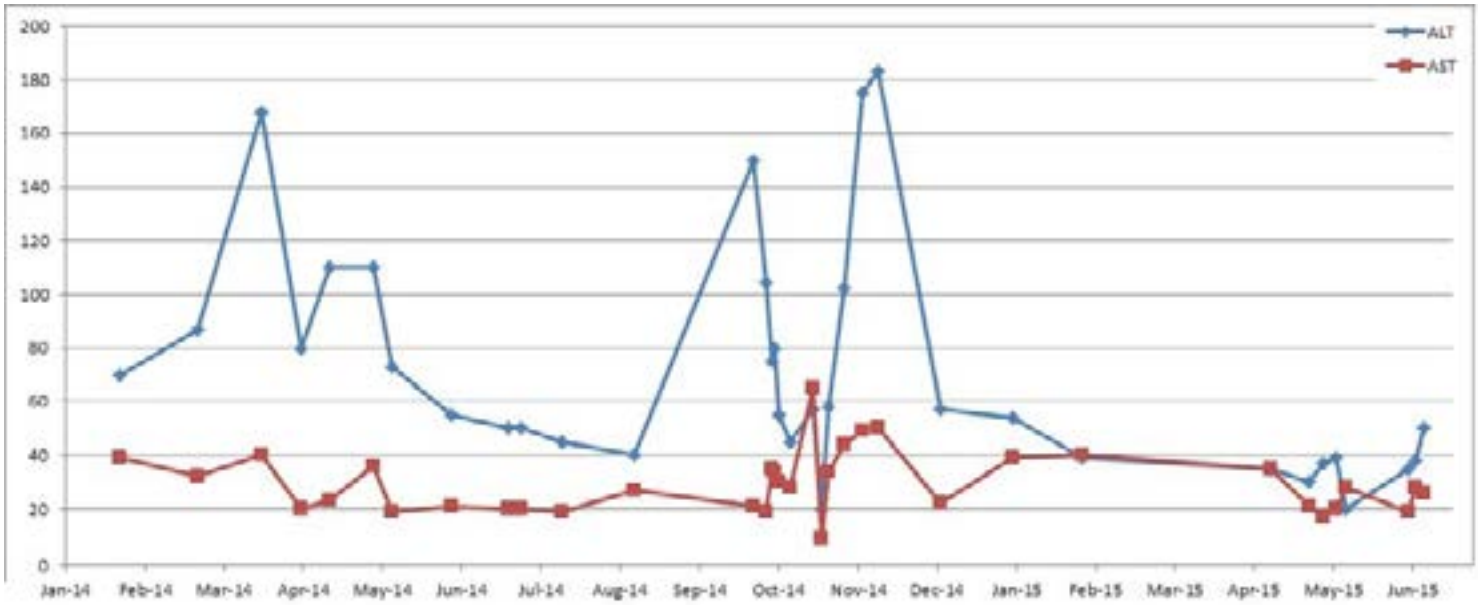

Figure 1. *Alanine transaminase and aspartate transaminase levels during the disease course. They were increased while the patient was receiving high-dose prednisolone and rituximab therapy. However, these elevations were successfully treated with lamivudine and adefovir in earlier and remaining treatment, respectively.*

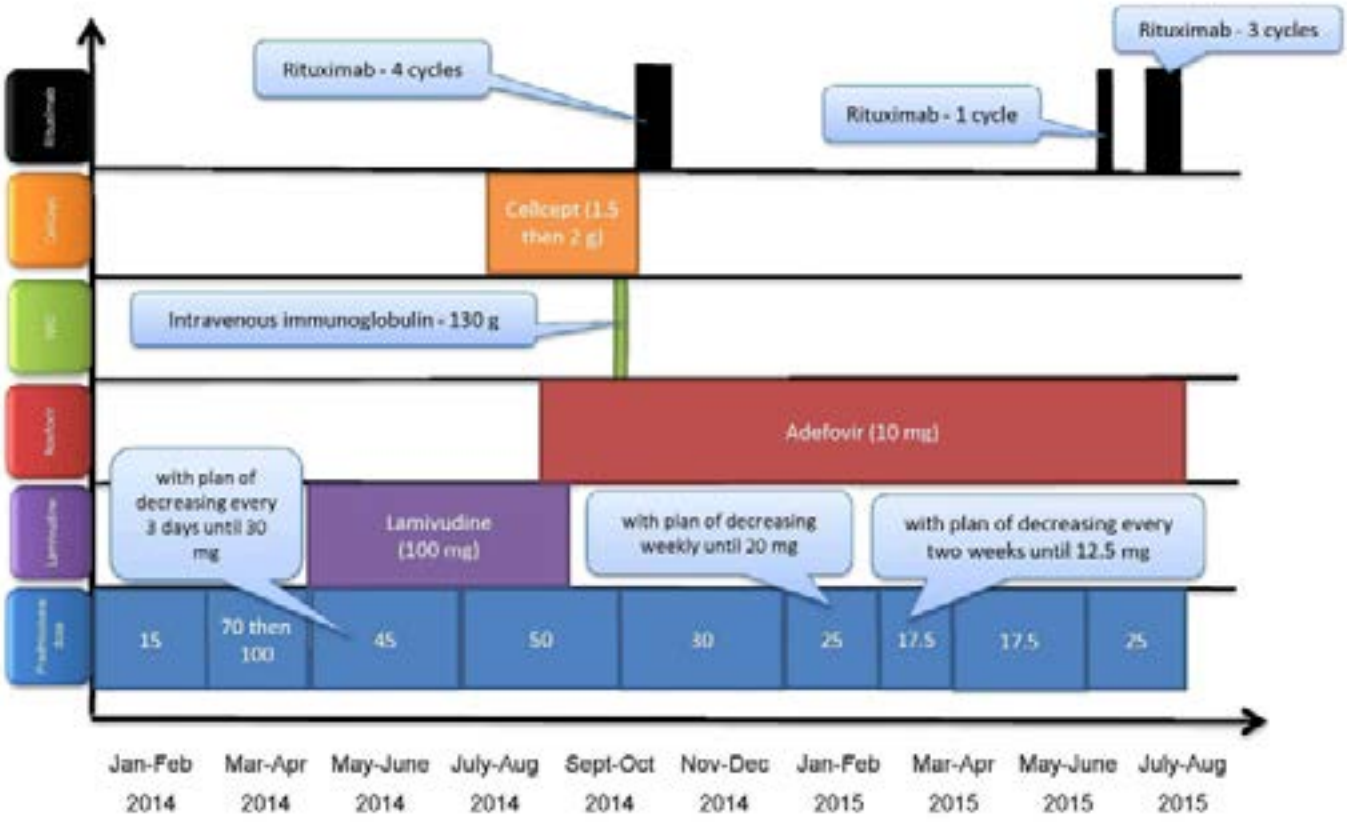

Figure 2. *Timeline of drugs used by the patient during treatment. Prednisolone dose fluctuated for accommodating viral replication versus pemphigus severity. Lamivudine was replaced by adefovir in order to reduce the risk of drug resistance. Meanwhile, it was maintained for another two weeks because of the delay in adefovir effects. IVIg and MMF were not effective and were stopped after confirming their ineffectiveness. Rituximab with prednisolone was the only effective treatment in this patient.*

to 45 mg and antiviral therapy with lamivudine was started in May 2014. ALT and aspartate transaminase (AST) decreased significantly in June, 2014. Lack of improvement of the mucocutaneous lesions, led to increasing prednisolone to 50 mg. Mycophenolate mofetil (MMF) was added at a dose of 1.5 and then 2g

Table 1. *Results of hepatitis B viral tests during follow-up period.*

Date	HBsAg*	anti-HBc*	HBsAb*	HBeAg*	HBeAb*	HBV DNA†
17/02/2014#	Negative	Positive	Negative	Not tested	Not tested	Not tested
25/02/2014	Negative	Positive	Negative	Not tested	Not tested	Not tested
25/03/2014	Positive	Not tested	Not tested	Not tested	Not tested	Non-detectable
30/03/2014	Positive	Not tested	Not tested	Not tested	Not tested	Not tested
06/04/2014	Positive	Not tested	Not tested	Negative	Positive	Not tested
17/06/2014	Positive	Not tested	Negative	Not tested	Not tested	Not tested
14/10/2014	Positive	Positive	Negative	Negative	Positive	Non-detectable
06/05/2015	Positive	Positive	Not tested	Not tested	Not tested	Non-detectable

 # This test was confirmed by two different laboratories.

*** Detected** *using enzyme-linked immunosorbent assay (ELISA) (Radim SpA, Rome, Italy)*

† Measured *by real-time PCR*

Abbreviations: HBsAg, *hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; HBsAb, antibody to hepatitis B surface antigen; HBeAg, Hepatitis B envelope antigen; HBeAb, Hepatitis B envelope antibody; HBV, hepatitis B virus.*

daily. Considering the high risk of drug resistance in long-term treatment with lamivudine, it was replaced by adefovir in late August, 2014. Prednisolone was kept at a dose of 50mg until October and then reduced to 30 mg. Prednisolone alone was not sufficient and MMF was not effective.

The patient received one cycle of intravenous immunoglobulin (IVIg) at a total dose of 130g during five consecutive days without any improvement. Mycophenolate mofetyl was stopped in October, 2014 and rituximab administration was considered. Quantitative HBV DNA test showed a non-detectable viral load. He received intravenous rituximab 500mg weekly for four consecutive weeks. The injection was followed by a considerable rise in ALT and AST levels, which returned to normal by the end of rituximab therapy and tapering of prednisolone. Clinically the patient improved dramatically with rituximab administration and went into remission. In March, 2015, he experienced a serious emotional shock, followed by a major mucocutaneous relapse. Because of the appearance of new lesions on the face and legs, prednisolone dosage was increased. Since disease continued with deterioration, and there appeared new bullous lesions, the second course of rituximab was planned. Quantitative HBV DNA test was again negative. In June, 2015, he received rituximab 500mg. Prednisolone was also kept at a dose of 25mg. After one month, no improvement was observed. Therefore, he received rituximab 500mg for another three weeks. He was lesion-free at his last follow-up visit in late July, 2015. The ALT and AST values from the first day of therapy until the last days of follow-up are shown (**Figure 1**). Summary of the main drugs used are presented (**Figure 2**).

Case Discussion

Corticosteroids with or without immunosuppressive agents are considered the mainstay of treatment for PV. However, systemic corticosteroids may lead to increasing viral replication in HBV carriers, patients with OBI, or resolved infection. Hepatitis B virus reactivation is not limited to positive HBsAg patients; actually it may occur in patients with negative HBsAg and positive anti-HBc. In patients with OBI or even resolved HBV infection, HBsAg may reappear during or after immunosuppression [7, 8]. Liver enzymes rise or increased level of HBV DNA may be observed during HBVr. Based on reports of the World Health Organization (WHO) in 2001 and Centers for Disease Control and Prevention (CDC) in 2005, Iran has an intermediate prevalence of chronic hepatitis B infection (2-7%), [9]. However, hepatitis B vaccination introduced within the National Immunization Program (NIP) in 1993, caused a significant reduction

in the rate of seropositivity. Not all guidelines recommend routine screening for OBI prior to the institution of immunosuppressive therapy in pemphigus [10]. Corticosteroid-induced HBVr and HBsAg conversion in our HBsAg-negative, anti-HBc-positive PV patient argues for caution, screening for risk factors of HBVr, and closer follow-up.

Our patient became HBsAg positive less than two months after receiving prednisolone. He was prescribed MMF with a concomitant rise of ALT with no clinical benefit. One cycle of IVIg was not beneficial, although liver function tests (LFT) remained stable. Rituximab seemed a high risk choice for the patient as an HBV carrier. Fortunately, despite a rise of LFTs, rituximab was very effective in controlling the disease activity. Rituximab could not be the sole reason for this rise, since the patient was also receiving high doses of prednisolone. It seems that rituximab was administered safely owing to the concurrent antiviral therapy. It is worth mentioning that the viral load was undetectable since antiviral therapy was prescribed as soon as HBVr was diagnosed.

Only a few cases of HBVr have been reported to date among pemphigus patients. Yang et al. [11] reported three cases of HBVr in PV patients. Their viral serology status at the beginning of treatment was unknown. One patient was HBeAg (hepatitis B envelope antigen)-positive and the other two had precore mutant strains of HBV that were HBeAg-negative /anti-HBeAb-positive. Lamivudine was initiated but the course of disease eventuated in one fatal and two severe reactivations following lamivudine-resistance. In another study, an HBV carrier (HBsAg-positive, IgG anti-HBc-positive, anti-HBs- negative, HBeAg-negative), who was diagnosed with PV, received azathioprine, leading to HBVr after 6 months with raised LFT, cirrhotic liver on computed tomography, and positive HBeAg. Lamivudine was started followed by rituximab. She received six cycles of rituximab with no complications and her HBV-DNA was undetectable [12]. There is no documented published report of HBVr in pemphigus patients with OBI in the literature, although similar cases were seen in rheumatologic, gastroenterologic, and oncologic cases [13].

Conclusion

Considering the lack of global awareness about HBV infection and the high risk of reactivation among HBV carriers and previously infected patients during immunosuppression, it is essential to check anti-HBc status, in addition to HBsAg, for pretreatment screening in pemphigus. These tests should be performed before initiation of immunosuppressive agents including corticosteroids, even at low doses. Preemptive therapy should be considered in all OBI patients diagnosed with pemphigus who are candidates for immunosuppressive therapy.

Finally, this report shows that rituximab, a potent anti-CD20 antibody used increasingly in the treatment of pemphigus, can, at least in some cases, be administered safely in HBVr in conjunction with antiviral treatment.

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