Precore mutant hepatitis B reactivation after treatment with CHOP–rituximab

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A patient with stage IV non-Hodgkin's lymphoma and chronic hepatitis who was treated with chemotherapy and rituximab developed fatal reactivation of hepatitis B. High viral load titers of hepatitis B DNA were demonstrated. DNA sequencing analysis revealed the presence of the precore mutant strain. Hepatitis B reactivation in patients receiving rituxmab-based chemotherapy is reviewed and the role of precore mutant virus strains resulting in fatal complications is discussed. ***Anti-Cancer Drugs*** **16:83–85**

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Introduction

Fulminant liver failure due to hepatitis B reactivation in patients receiving myelosuppressive chemotherapy is a severe complication. Hepatitis B reactivation has been observed in patients treated with the anti-CD20 chimeric antibody, rituximab [1–7]. This report describes a patient who developed fatal fulminant hepatic failure from reactivation of a precore 1896 mutant hepatitis virus while receiving rituximab and chemotherapy for non-Hodgkin's lymphoma (NHL).

Case history

A 34-year-old Vietnamese man diagnosed as a hepatitis B carrier for 10 years presented to UC Irvine Medical Center with fatigue, abdominal pain and a palpable abdominal mass. His hepatitis B serologies revealed: $HepBsAg^+$, $HepBsAb^-$, HepB core IgM $antibody^-$, $HepBeAg^-$ and $HepBeAb^+$. Liver enzymes and total bilirubin were normal. Hepatitis B viral load was 3600 copies/ml. Resection of a large hepatic mass revealed extensive infiltration with $CD20^+$ diffuse large B cell-type NHL, thus his lymphoma was stage IV. Chemotherapy was initiated with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and rituximab (R) every 3 weeks. Liver enzymes and hepatitis B viral load were closely monitored. The fifth cycle of CHOP-R was held due to elevated liver enzymes (Fig. 1). Three days later he presented to the emergency room with severe nausea and vomiting.

Admission examination showed a jaundiced, ill appearing man, with marked scleral icterus and right upper quadrant abdominal tenderness. Aspartate aminotransferase (AST) was 1090 IU/l, alanine aminotransferase (ALT) 1013 IU/l and total bilirubin 5.9 mg%. Prothrombin time was 36.7 s (normal 12–16 s) with an INR of 3.67 and activated partial thromboplastin time was 52 s (normal 26–38 s).

The presumptive diagnosis of acute hepatic failure from reactivation of hepatitis B was suspected. Lamivudine 100 mg daily was started, but the total bilirubin continued to rise and on hospital day 6 adefovir was added to cover for possible resistant strains of hepatitis B virus (HBV). Despite continued antiviral therapy and supportive care, the liver enzymes increased and total bilirubin reached 48 mg%. On hospital day 30, the patient developed hematemesis and respiratory failure followed, requiring ventilatory support. He expired on hospital day 39.

On admission the patient's HBV viral load was greater than 200×10^9 copies/ml of blood (Fig. 1). DNA sequence analysis detected a single G to A transition at the 1896 nucleotide position of the hepatitis B viral genome, which is commonly referred to as the precore 1896 mutant. Flow cytometric analysis of the patient's blood revealed the presence of lymphocytes but a complete depletion of $CD20^+$ lymphocytes.

Discussion

Our patient had precore mutant type HBV reactivation without demonstrable CD20 lymphocytes in the circulating blood pool following treatment with CHOP-R. The lack of circulating $CD20^+$ lymphocytes supports the hypothesis that rituximab-induced immunosuppression

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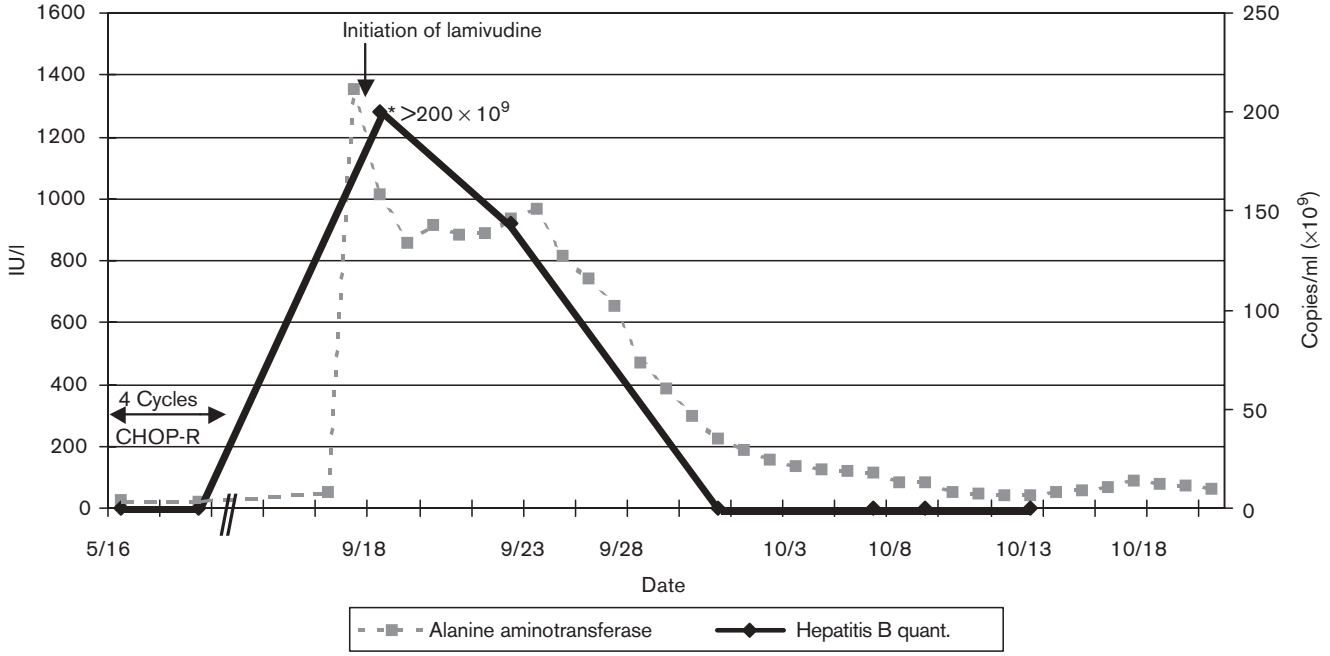
Fig. 1



Rapid proliferation of HBV and hepatocellular injury.

contributed to hepatitis B reactivation, but does not exclude the role of CHOP chemotherapy, since this regimen has also been implicated. However, review of the eight published cases (including the present case) of rituximab-associated hepatitis B reactivation in NHL illuminates several important findings. Five of the eight cases (including the present case) were $HepBsAg^+$, $HepBeAg^-$, $HepBeAb^+$, and with normal AST and ALT prior to the initiation of chemotherapy [3,4,5,7]. Our case and four others reported on the level of HBV DNA prior to therapy and in all instances the levels were low or negative [3–6]. In this case and two others the presence of a precore mutant virus genotype was investigated after hepatitis activation, and a precore mutant was identified in all three patients (Table 1) [4,5]. In our case, mutant status prior to activation was unknown.

Reactivation of the HBV during cytotoxic chemotherapy is a well-documented complication in cancer patients. The incidence of severe hepatitis in these patients has been reported as high as 52.7% with a mortality rate of 23.6% in chronic HBV carriers in Japan [8]. Certain tumor types have been associated with hepatitis reactivation, with lymphoma having the highest prevalence (27%) [9]. Other risk factors for reactivation have been mentioned in previous studies, such as male gender, younger age and being $HBeAg^+$ [10]. The 1896 precore mutation leads to a truncated HepBeAg, which is infective despite the presence of HepBe antibody. Its presence is not detected by conventional HepBeAg serology.

Given the rapid decline in hepatic function in the setting of a markedly accelerated rate of viral replication, we suspect that this patient also was suffering from fibrosing cholestatic hepatitis (FCH). This rare and usually fatal condition, with or without lamivudine treatment, has been observed in patients with HBV reactivation after liver transplantation [11]. There is one case report of FCH from HBV reactivation after conventional-dose chemotherapy in the non-transplant setting [12]. The precise mechanism of this condition remains to be elucidated; however, it is postulated that FCH results from direct hepatocytolysis in the absence of significant T lymphocyte activity, rather than the typical immune destruction of hepatocytes [12]. Pathologic characteristics include balloon degeneration of hepatocytes, periportal fibrosis, striking cholestasis with minimal inflammatory cell infiltration with the resultant clinical presentation of severe hepatic dysfunction.

The natural history of FCH remains extremely bleak, with or without treatment and even with marked decrease in HBV viral load during therapy (as seen in this patient). Furthermore, prophylactic treatment with lamivudine prior to the initiation of cytotoxic chemotherapy has been shown to be beneficial in patients with

Table 1 Existing published case reports of HBV reactivation in NHL patients treated with rituximab

Individual case reports	Pre-chemotherapy HBV serology	Chemotherapy	Mutant status during reactivation	Reactivation therapy/result
Low-grade lymphoma [1]	not reported	CHOP × 5 cycles and rituximab × 4 cycles; reactivation after 5th cycle CHOP	not described	no treatment/death
Follicular lymphoma [2]	$HepBsAg^-$, $HepBsAb^+$, $HepBeAb^+$	weekly rituximab × 4 weeks, 7 months prior to reactivation; prednisone until 1 month prior to reactivation	not described	no treatment/survival
Diffuse large-cell lymphoma [6]	$HepBsAg^-$, $HepBsAb^+$	CHOP × 5 followed by rituximab for 3 months	L110R, R122K, Y/F134S, P142L and D144A (HBV escape mutants)	lamivudine/death
B-prolymphocytic leukemia [3]	$HepBsAg^+$, $HepBeAg^-$, $HepBeAb^+$	weekly rituximab × 4 weeks, 2 months prior to reactivation	not described	no treatment/death
Follicular lymphoma [4]	$HepBsAg^+$, $HepBeAg^-$, $HepBeAb^+$	CHOP-R × 5 cycles, reactivation after 5th cycle	1896 bp precore mutant	lamivudine/survival
Follicular lymphoma [5]	$HepBsAg^+$, $HepBeAg^-$, $HepBeAb^+$	COP-R × 6 cycles, 5 months prior to reactivation	1896-bp precore mutant	lamivudine/death
Diffuse large B cell lymphoma [7]	$HepBsAg^+$, $HepBsAb^-$, $HepBeAg^-$, $HepBeAb^+$	CHO-R × 3 cycles	not described	lamivudine/death
Diffuse large B cell lymphoma [present case]	$HepBsAg^+$, $HepBeAg^-$, $HepBeAb^+$	CHOP-R × 4 cycles; 5th cycle held due to reactivation	1896-bp precore mutant	lamivudine + adefovir/death

chronic HBV infection by preventing uncontrolled replication [10]. Additionally, the use of lamivudine in patients infected with precore variant HBV has been shown to control proliferation and improve histology [13]. Therefore, concomitant treatment using antivirals with chemotherapy and rituximab may prevent inception of HBV reactivation, and, consequently, the potential for fulminant hepatic failure.

The extremely high HBV viral load in our patient might have been a consequence of rapid replication of the precore mutant HBV due to immunosuppression from rituximab and chemotherapy. Short-term use of lamivudine is safe and relatively inexpensive. In light of our experience, lamivudine or adefovir prophylaxis is recommended in patients who have chronic hepatitis B (i.e. $HBsAg^+$) and especially for those infected with the precore mutant virus, prior to rituximab-containing chemotherapy.

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