Fulminant hepatitis subsequent to reactivation of precore mutant hepatitis b virus in a patient with lymphoma treated with chemotherapy and rituximab

We report a case of a precore mutant hepatitis B virus (HBV) reactivation in a patient with follicular lymphoma who was treated simultaneously with chemotherapy (cyclophosphamide, vincristine and prednisone) and rituximab, occurred five months after the end of therapy. Despite lamivudine therapy, she died because of fulminant hepatitis. This case illustrates the possibility of late reactivations of HBV after immunosuppressive or cytotoxic therapies, including rituximab. In these patients, prophylaxis with lamivudine seems justified.

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Reactivation of hepatitis B virus (HBV) is a severe and potentially fatal complication in chronic carriers of hepatitis B virus surface antigen (HbsAg) treated with cytotoxic or immunosuppresive drugs. The incidence ranges from 20 % to 50 %, and is associated with 10% to 40 % mortality; varying degrees of liver involvement can be found, from mild and asymptomatic cases to death due to massive hepatic necrosis.[1] When cytotoxic or immunosuppresive therapy is stopped and the immune function is restored, liver damage can occur. Rituximab therapy results in impaired immune responsiveness and recovery of B-cell counts starts several months after treatment is completed.[2] Recently, four cases of HBV reactivation after chemotherapy schedules containing rituximab have been described.[2-5] Herein, we report an additional case with a fatal course despite administration of antiviral therapy with lamivudine. A 66-year-old woman with multiple lymphadenopathy was diagnosed with follicular lymphoma including involvement of peripheral blood. The patient referred positivity of HbsAg, but no clinical or biological signs of liver damage had been observed. Pretreatment screening test for HBV showed the following serology: HBsAg positive, anti-HBs negative, anti-HBc positive, HBeAg negative, anti-HBe positive. HBV-DNA quantitative was lower than 5 pg/mL (detection limit, 5 pg/mL). She had no HIV, hepatitis C virus (HCV) or hepatitis delta virus markers, and liver and coagulation tests were normal. Between May 2001 to September 2001, she received 6 cycles of CVP (cyclophosphamide, vincristine and prednisone) with a partial response. In November 2001, salvage chemotherapy including the same cytotoxic drugs plus rituximab was iniciated, for a total of 6 cycles. The last infusion of rituximab was in May 2002. Tolerance to therapy was excellent and a complete clinical and molecular remission was obtained. Five months later, the patient presented with asymptomatic elevated levels of AST (6.4 μkat/L [n < 0.52]), ALT (12.3 μkat/L [n < 0.52]) and LDH (19.5 μkat/L [n < 7.7]). Coagulation tests were normal and reactivation of HBV was confirmed by high levels of HBV-DNA in the serum (6446 pg/mL). No antiviral therapy was iniciated because of a progressive improvement in liver function tests (in October 2002, AST 3.24 μkat/L, ALT 5.9 μkat/L, and in November 2002, AST 1.5 μkat/L, ALT 2.5 μkat/L). In January 2003, HBV-DNA levels were 4446 pg/mL and the patient developed fatigue, jaundice, ascites and hepatosplenomegaly. Acute hepatitis was documented (AST 28 μkat/L, ALT 18.3 μkat/L), with severe liver failure (bilirrubin 111 μmol/L [n < 17]), and prothrombin time of 24.8 seconds [control 11.8]). No infection of peritoneal effusion was observed, and an ultrasound study of the hepatobiliary system did not show focal lesions. HBV serology did not change regarding initial tests and HBV-PCR revealed the presence of a point mutation of precore region from G to A at nucleotide (nt) 1896, as much in the actual sample as in frozen specimen corresponding to asymptomatic hepatitis diagnosis (HBV level 6446 pg/mL). The patient was treated with lamivudine 100 mg daily p.o. The HBV-DNA levels were 37 pg/mL and < 5 pg/mL, 10 and 30 days later, respectively, but the patient presented progressive hepatic encephalopathy and she died 33 days after the onset of antiviral therapy. Reconstitution of immune response after cytotoxic or immunosuppressive therapy have been associated with destruction of hepatocytes in HBV carriers, but only rarely in HCV-infected patients.[6] In the former, activated T cells may produce the damage of the infected hepatocytes and subsequently their destruction. The role of rituximab for the reactivation of HBV remains uncertain, but several cases have been described after the administration of cytotoxic therapy plus rituximab in patients with lymphoproliferative disorders (Table 1.).[2-5] After withdrawal of the immunosuppressive drugs and recovery of immune response, delayed in patients treated with rituximab, activated CD8 cytotoxic T cells may attack the infected hepatocytes resulting in acute or even fulminant hepatitis. In HBV-infected patients, monitoring of the DNA level should be advised because of the severity of hepatocyte

Table 1. Clinical cases reported of hepatitis B virus reactivation after the treatment of lymphoproliferative syndromes with schedules containing rituximab

Clinical case	Disease **HBV serology**	Previous therapy	Reactivation of HBV **Therapy** Evolution
Cuzzubbo et al[2]	Low grade lymphoma **HBV status unknown**	5 cycles of CHOP and 4 cycles of rituximab	After 5th CHOP cycle **Non lamivudine** Death
Dervite et al[3]	Follicular lymphoma **HbsAg negative** **Anti-Hbs positive** **Anti-Hbe positive**	4 weekly courses of rituximab 7 months before reactivation, plus prednisone until one month before	Seven months after rituximab **Non lamivudine** Recovery
Ng et al[4]	B-prolymphocytic leukemia **HbsAg positive** **HbsAg negative** **Anti-Hbs positive**	4 weekly courses of rituximab two months before reactivation. Fludarabine and cyclophosphamide, previously	Two months after rituximab **Non lamivudine** Death
Sklots et al[5]*	Follicular lymphoma **HbsAg positive** **Anti-Hbs positive** **HbsAg negative** **Anti-Hbs positive**	6 cycles of rituximab plus CHOP	After 5th cycle **Lamivudine 100 mg daily p.o.** Recovery
Hernández et al, this case*	Follicular lymphoma **HbsAg positive** **Anti-Hbs positive** **HbsAg negative** **Anti-Hbs positive**	6 cycles of CCP plus rituximab, five months before reactivation	Five months after rituximab **Lamivudine 100 mg daily p.o.** Death

*In both cases, a HBV nt 1896 precore mutant was present.

destruction seems to be proportional to the viral replication, despite the possibility of viral reactivation in patients HBsAg negative with anti-HB positive and/or naturally acquired anti-HBs as well. Moreover, in patients with a HBeAg negative, anti-HBe positive profile, like the case reported herein, can be tested the assay to determine the presence of the mutant strain in the precore region because of a great risk of fulminant hepatitis.[7] Reactivations of HBV can be successfully treated with lamivudine, a reverse-transcriptase inhibitor of viral DNA polymerase. In most cases, lamivudine suppresses HBV DNA values in 1 month, leading to improvement of biological and histological lesions and HBeAg seroconversion.[8] In our case, lamivudine resulted in suppression of HBV DNA copies, but, unfortunately, the clinical course was fatal, probably due to a late onset of antiviral therapy. Recently, lamivudine has been used prophylactically in HbsAg positive patients who are candidates for chemotherapy or immunosuppressive therapy with a good response.[8,9] In these cases, the optimal duration of therapy is unknown, but it is possible that it should continue up to 6 months following the last cytotoxic or immunosuppressive treatment.[8] In cases of lamivudine-resistant HBV reactivation, tenofovir disopropil fumarate therapy is an option to cope with this problem.[10] In conclusion, prophylaxis with lamivudine should be offered to HBV carriers treated with chemotherapy or immunosuppressive therapy to avoid viral reactivation.

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References

1. Lok ASF, Liang RHS, Chiu EKW, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100:182-188.
2. Czuczman MS, Grillo-López AJ, White CA, Saleh M, Gordon L, LoBuglio AF, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17:268-276.
3. Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. N Engl J Med 2001;344:68-69.
4. Ng HJ, Lim LC. Fulminant hepatitis B virus reactivation with concomitant listeriosis after fludarabine and rituximab therapy: case report. Ann Hematol 2001;80:549-552
5. Skrabs C, Müller C, Agis H, Mannhalter C, Jäger U. Treatment of HBV-carrying lymphoma patiets with rituximab and CHOP: a diagnostic and therapeutic challenge. Leukemia 2002;16:1884-1886.
6. Persico M, De Marino F, Di Giacomo Russo G, Severino A, Palmentieri B, Picardi M, et al. Efficacy of lamivudine to prevent hepatitis reactivation in hepatitis B virus-infected patients treated for non-Hodgkin's lymphoma. Blood 2002;99:724-725.
7. Dai MS, Lu JJ, Chen YC, Perng CL, Chao TY. Reactivation of precore mutant hepatitis B virus in chemotherapy-treated patients. Cancer 2001;92:2927-2932.
8. Shibolet O, Ilan Y, Gillis S, Hubert A, Shouval D, Safadi R. Lamivudine therapy for prevention of immunosupresive-induced hepatitis B virus reactivation in hepatitis B surface antigen carriers. Blood 2002;100:391-396.
9. Liao CA, Lee CM, Wu HC, Wang MC, Lu SN, Eng HL. Lamivudine for the treatment of hepatitis B virus reactivation following chemotherapy for non-Hodgkin´s lymphoma. Br J Haematol 2002;116:166-169.
10. Van Bömmel F, Schernick A, Hopf U, Berg T. Tenofovir disoproxil fumarate exhibits strong antiviral effect in a patient with lamivudine-resistant severe hepatitis B reactivation. Gastroenterology 2003;124:586-587.