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. Following chemotherapy, the patient was treated with lamivudine and interferon-alfa. 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 immunosuppressive 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. When cytotoxic or immunosuppressive 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. Recently, four cases of HBV reactivation after chemotherapy schedules containing rituximab have been described. 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 refused 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, HBcAg 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) 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.

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 | Resolution of Symptoms | Mortality
|--------------|--------|--------------|-----------------|---------------------------|-----------------------|---------|
| González et al. | Folliculare lymphoma HbsAg positive | 5 cycles of CHOP and 4 cycles of Rituximab | After 6 months of CHOP, lamivudine was started | CHOP cycle | Lambda 1 mg daily p.o. | Non-lamivudine mortality | 4 months after CHOP | Non-lamivudine mortality
| Danet et al. | Folliculare lymphoma HbsAg negative | 3 months of CHOP before chemotherapy | Rituximab | 4 months of CHOP before chemotherapy | Non-lamivudine mortality | 8 months after CHOP | Non-lamivudine mortality
| Sig et al. | Folliculare lymphoma HbsAg positive | 2 cycles of CHOP | CHOP | Non-lamivudine mortality | 3 months | Non-lamivudine mortality | 6 months | Non-lamivudine mortality
| Skow et al. | Folliculare lymphoma HbsAg negative | 5 cycles of CHOP | CHOP | 6 months of CHOP | Non-lamivudine mortality | 6 months | Non-lamivudine mortality | 6 months | Non-lamivudine mortality
| Hernández et al. | Folliculare lymphoma HbsAg negative | 5 cycles of CHOP | CHOP | 6 months | Non-lamivudine mortality | 6 months | Non-lamivudine mortality | 6 months | Non-lamivudine mortality

*In both cases, a HBV viral 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. 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. 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 immuno-suppressive therapy with a good response. 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 immuno-suppressive treatment. In cases of lamivudine-resistant HBV reactivation, tenofovir disoproxil fumarate therapy is an option to cope with this problem. In conclusion, prophylaxis with lamivudine should be offered to HBV carriers treated with chemotherapy or immuno-suppressive therapy to avoid viral reactivation.

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References