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CASE REPORT

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HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb

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Abstract A 51-year-old man who was hepatitis B surface antigen (HBsAg)-negative and positive for anti-hepatitis B surface antigen (anti-HBs) and anti-hepatitis B core antigen (anti-HBc), during rituximab therapy for chronic Lymphocytic leukemia, developed reactivation of hepatitis B virus (HBV) infection with hepatitis that proceeded towards hepatic failure and death in spite of lamivudine therapy. HBsAg remained persistently negative, notwithstanding a high HBV-DNA titer. Our observation, following other cases of fatal reactivation of HBV infection in patients receiving rituximab, suggests that, in all patients with previous markers of HBV infection, lamivudine prophylaxis should be considered during rituximab therapy.

Key words Rituximab · Lamivudine · Hepatitis B virus · Leukemia

Introduction

It is well known that a previous hepatitis B virus (HBV) infection may be reactivated during chemotherapy or immunosuppressive therapy.[1–3] These reactivations have been observed, especially in hepatitis B surface antigen (HBsAg)-positive subjects[4] and they occur in 20%–50% of cases, with a mortality rate of 10%–40%. Consequently, lamivudine prophylaxis is strongly recommended in HBsAg-positive subjects receiving chemotherapy or immunosuppressive therapy,[5–7] although there are no clear guidelines for HBsAg-negative subjects.

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Recently, fatal fulminating hepatitis has been observed in patients treated with rituximab. This caused the FDA, in October 2004, to alert physicians about the possible relationship between fulminating hepatitis and rituximab use.[8] The majority of cases have been reported in HBsAg-positive patients, but also, in few instances, in HBsAg-negative and anti-hetpatitis B surface antigen (anti-HBs)-positive subjects.[9,10]

Here, we report a fatal case of HBV fulminating hepatitis that occurred despite the administration of antiviral therapy with lamivudine, in a man treated with rituximab for B-chronic lymphocytic leukemia, who was HBsAg-negative and positive for anti-hepatitis B core antigen (anti-HBc) and anti-HBs, suggestive of previous exposure to HBV, with recovery.

Case report

A 53-year-old Caucasian man with B-chronic lymphocytic leukemia was treated in 2002, with six courses of fludarabine chemotherapy, with complete remission. In June 2004, he began treatment with rituximab, because of leukemia reactivation, given at a dosage of 300 mg/monthly. Pretreatment screening for hepatitis displayed the following pattern: HBsAg-negative, anti-HBs- and anti-HBc-positive, and negativity for hepatitis C virus (HCV)-antibodies (Abs). Aminotransferases were normal. He was not treated with steroids or other immunosuppressive drugs, nor did he receive blood or blood product transfusions. He has been treated with amlodipine and candesartan for blood hypertension.

At the end of September 2004, he was admitted to hospital with jaundice and increasing serum aminotransferases (Fig. 1).

On admission he appeared to be in good health. Bilirubin was 17 mg/dl and alanine aminotransferase (ALT), 2120 U/l. An ultrasound study and computed tomography (CT) scan of the abdomen were negative for neoplasia or obstruction. Serum screening for hepatitis B (Architect; Abbott, Abbott

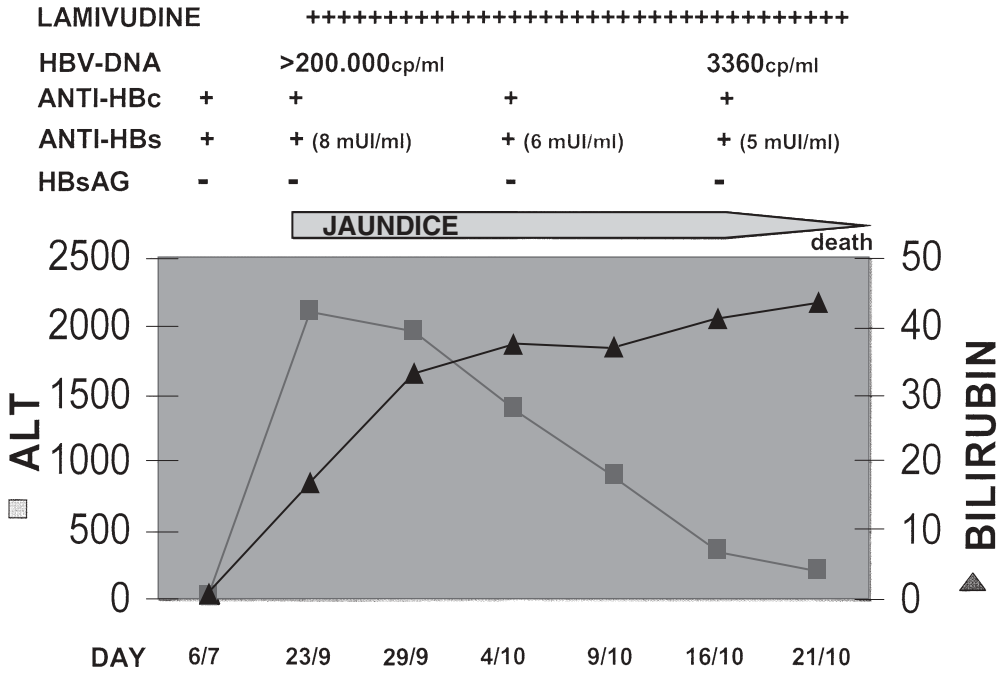

Fig. 1. Patient's clinical course. *Anti-HBc*, anti-hepatitis B core antigen; *anti-HBs*, anti-hepatitis B surface antigen; *HBsAG*, hepatitis B surface antigen; *ALT*, alanine aminotransferase

Park, IL, USA) revealed that he was HBsAg-negative, anti-HBc-positive, and had a low titer of anti-HBs (8 mUI/ml); however, HBV-DNA (Amplicor Roche quantitative assay; Hoffmann-La Roche, Basel, Switzerland) was positive, at more than 200 000 cp/ml. HCV Ab and HCV-RNA (Amplicor Roche) were negative. HDV Ag and HDV Ab were absent, and HDV polymerase chain reaction (PCR) was negative. Cytomegalovirus (CMV) IgG, HAV IgG, rubella IgG, and Epstein Barr virus (EBV) IgG were present.

After 1 day, the patient received lamivudine; in spite of this, his condition worsened and he developed hepatic insufficiency. On day 20, his HBV-DNA was 3360 cp/ml, the HBsAg negativity persisted, and both anti-HBs and anti-HBc remained positive.

On day 27, the patient died of hepatic failure with hepatorenal syndrome.

Comment

It has been shown that HBV replication may persist after the resolution of acute hepatitis B, and HBV-DNA has been detected by PCR in the livers of patients with resolved chronic HBV infection and sustained clearance of HBsAg from serum.[11]

Detection of HBV-DNA despite HBsAg negativity, with or without the presence of HBV antibodies, defines an occult HBV infection. This pattern can derive from recovered infection with persistence of HBsAb, low levels of viral replication, or the presence of viral mutants not revealed in biochemical tests for HBsAg.[12–14]

There are clearly documented cases of the reactivation of latent viral infections following chemotherapy or immunosuppressive therapy and, more recently, some cases have been reported during rituximab therapy.

In our case, the HBV reactivation developed during rituximab therapy for chronic lymphocytic leukemia in a subject with post-hepatitis B status (negative for HBsAg and positive for HBsAb and HBcAb); but, nevertheless, it is clinically unusual to observe HBV reactivation with a high HBV DNA concentration, with persistent HBsAg negativity, as observed in this patient. This could be due to HBV with an escape mutation in a determinant region of the HBV genome that does not express HBsAg, even though, in the absence of viral sequencing, it could not be demonstrated. In fact, cases of active viral replication in the presence of anti-HBs have been described, and are usually caused by surface mutations. Indeed, Westhoff and colleagues[10] decribed a case characterized by a mutation in the S region of the *HBsAg* gene that did not allow the expression of HBsAg.

It is also clinically remarkable, in our case, that, in spite of antiviral therapy with lamivudine that was started opportunely, with a resulting decrease in viremia within 3 weeks, hepatic function did not recover, and the patient died of hepatic failure.

Our observation, following other cases of fatal reactivation of HBV infection in patients receiving rituximab, in both HBsAg-negative and HBsAb-positive subjects, suggests that, in all patients with previous markers of HBV infection, lamivudine prophylaxis, to prevent HBV reactivation, should be considered during rituximab therapy.

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