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Hepatitis B virus reactivation after cessation of prophylaxis with entecavir in a patient with Burkitt type acute lymphoblastic leukaemia treated with rituximab[☆]



Reactivación del virus de la hepatitis B tras el cese de la profilaxis con entecavir en un paciente con leucemia linfoblástica tipo Burkitt tratado con rituximab

Hepatitis B virus (HBV) reactivation has been reported in inactive carriers (50%) and, rarely, in patients with an HBV infection that has resolved (6–10%). Reactivation is considered to have occurred if an elevated HBV DNA level is detected in patients with elevated ALT and who previously had a negative result on the HBV DNA test.¹

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The severity of HBV reactivation ranges from an asymptomatic and transient increase in transaminases to fulminant hepatic failure. The mortality rate associated with reactivation varies from 5% to 40%.²

In inactive carriers of HBV, viral reactivation usually occurs in situations that involve significant immunosuppression, such as with antineoplastic or immunosuppressive treatment. Patients with past or resolved HBV infection have been reported to show traces of the virus in serum years after the infection was resolved, and the virus-host balance may be disrupted in cases of immunosuppression.^{3,4} In these cases, the recurrence of HBsAg and the detection of HBV DNA has been observed.

The risk of reactivation depends on several factors such as previous infection status (HBeAg-positive, elevated baseline viral load, ALT levels prior to starting immunosuppressive therapy), type of disease (increased risk in haematopoietic stem cell transplantation), type of immunosuppressive therapy (rituximab, corticosteroids, anti-TNF) and patient-related factors (men or young people).⁵

Here we report the case of a male patient diagnosed with B-ALL, who received treatment with rituximab and presented with HBV reactivation after stopping prophylaxis with entecavir.

42-year-old man with ALL. At diagnosis, he was positive for HBsAg, negative for HBeAg, positive for HBeAb and had an HBV DNA level of 372 IU/ml. He was considered an

inactive carrier, and prophylaxis was therefore started to treat the HBV reactivation with entecavir 0.5 mg/day.

Antineoplastic treatment was started with rituximab, cyclophosphamide, cytarabine, methotrexate, dexamethasone, ifosfamide, vincristine and etoposide (in total 8 doses of rituximab), and the haematological disease resolved completely. Viral load tests were performed every six months. After 36 months of chemotherapy, 2 consecutive negative viral load tests and an entirely normal liver function test, it was decided to stop treatment with entecavir. Five months later, the patient was admitted to hospital for abdominal pain and jaundice. The lab test showed a prothrombin time (PT) of 47%, bilirubin 10.35 mg/day, ALT 3768 IU/L, AST 999 IU/L, AP 128 U/L, GGT 174 U/L and albumin 34.8 g/L. An abdominal CT scan ruled out bile duct dilatation, space-occupying lesions and portal vein thrombosis. A liver biopsy showed changes compatible with acute hepatitis with moderate inflammation and periportal, lobular and central necrosis; but no fibrosis was observed.

The serological test showed HBV reactivation (positive for HBsAg and IgM-HBcAg and an HBV DNA level of 10,080 IU/ml). The patient was put on treatment with entecavir 0.5 mg/day and showed favourable clinical progress and lab test results, with the liver function test at discharge as follows: PT of 94%, bilirubin 2.85 mg/dl, ALT 540 U/L. Subsequently, the patient continued with antiviral treatment, and had undetectable HBV DNA levels and was negative for HBsAg 5 months after the reactivation.

The current guidelines recommend that patients who are positive for HBsAg or negative for HBsAg but positive for HBV DNA, and who are candidates for chemotherapy and immunosuppressive therapy, should receive preventive treatment with nucleotide analogues (NA) (regardless of HBV DNA), which should be started at least one week before starting immunosuppressive therapy and maintained for at least 12 months after stopping therapy, or indefinitely, depending on the baseline status of the HBV infection.⁶

At present, high-potency antiviral NAs and genetic barriers, such as entecavir and tenofovir, are considered as first-line treatment. Different studies have shown that these drugs significantly reduce the risk of HBV reactivation.⁷

By contrast, patients who are negative for HBsAg, positive for anti-HBc with undetectable serum levels of HBV DNA, and who are on chemotherapy and/or immunosuppression, should be closely monitored with tests for ALT and HBV DNA and treated with an NA if HBV reactivation is confirmed. Also, some experts recommend starting NA prophylaxis in all HBsAg-negative and anti-HBc-positive cases who are treated with rituximab, bone marrow or stem cell transplants.⁵

In our case, despite complying with the guidelines, 4 months after the prophylaxis was stopped, the patient presented with a spontaneous HBV reactivation in the form of acute hepatitis.

Until the publication of the first clinical guidelines on NA prophylaxis in patients at risk of reactivation (the 2009 EASL and AASLD),^{8,9} there have been numerous published

cases of HBV reactivation with immunosuppressive treatment. In addition, in 2005, 2 cases of fulminant hepatitis B were reported when lamivudine prophylaxis was stopped following a stem cell transplant.¹⁰ Our case reaffirms the risk of HBV reactivation after stopping prophylaxis, and it highlights the need to individualise prophylactic treatment according to patients' risk factors.

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