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Fatal HBV-related liver failure during lamivudine therapy in a patient with non-Hodgkin's lymphoma

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Reactivation of hepatitis B virus (HBV) infection in patients undergoing chemotherapy or immunosuppressive therapy for non-Hodgkin's lymphomas is a well-known complication[1-3] and may result in liver damage of varying degrees of severity, from mild alteration of aminotransferases to fatal fulminant hepatitis[4]. It has been hypothesized that immunosuppression prompts enhanced HBV DNA replication that results in increased and diffuse hepatocyte necrosis.

Lamivudine, a nucleoside analogue and a potent inhibitor of HBV reverse transcriptase, has been demonstrated to suppress HBV DNA replication[5] and is routinely adopted in patients with HBV infection undergoing chemotherapy[6-10].

We report the case of a 59-year-old man admitted to our department on 2 August 2006 with fever, fatigue and jaundice. In December 2005 the patient was first diagnosed with stage IIB bulky diffuse large B cell lymphoma, CD20+ with an aa IPI of 1. At the time of diagnosis, he had splenomegaly and hepatomegaly; laparoscopic spleen and liver biopsy resulted in a histological diagnosis of splenic infiltration of non-Hodgkin's lymphoma (NHL) in a context of chronic hepatitis (with mild activity, grade G2), suggestive of viral infection. Staging was completed with thoracic and abdominal CT that evidenced a splenic lesion of 13 x 14 x 16 cm along with liver involvement with small nodules in the fourth segment and several mesenteric, hepatic hilum and paraaortic involved lymph nodes. Serology revealed the patient to be a chronic HBV carrier (HbsAg positive). The patient was HbeAg negative and anti-HBc positive with a high HBV DNA titer of 5,017,954 IU/mL. Coexisting hepatitis C or hepatitis D virus was excluded before chemotherapy. The level of aspartate aminotransferase (AST) was 60 U/L (normal 10-45 U/L), alanine aminotransferase (ALT) was 50 U/L (normal 10-50 U/L), while the remaining routine biochemical examinations including bilirubin, albumin, platelet and WBC counts were within normal ranges. Viral sequencing of the HBV strain did not reveal the presence of mutations associated with resistance to lamivudine. Lamivudine treatment 100 mg/day was started together with a chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (CHOP-R) given for 8 cycles. PET CT after chemotherapy showed remission of the neoplastic disease but a splenic residual, so the patient was given additional radiotherapy to the splenic area (last course on 7 July 2006).

At his admission to our department, the patient's hematological panel was normal but liver biochemistry revealed serum AST to be 3,878 U/L, ALT 4,364 U/L, total bilirubin 137.1 mol/L, alkaline phosphatase 138 U/L, and albumin 35.5 g/L. Other nonviral causes of acute hepatitis were excluded. HBV DNA was 95,528 IU/mL. The patient was still on lamivudine treatment. Viral sequencing of the HBV strain revealed the presence of a combined L180M and M204I mutation, which is associated with resistance to lamivudine[11,12]. During hospitalization the patient's neurological status gradually worsened, he developed significant ascites and diffuse edema, and became comatose. He died on the 15th day after admission due to respiratory failure.

The present case report confirms that all patients with NHL must undergo determination of hepatitis serology and, if seropositive, preemptive lamivudine treatment must be administered in patients undergoing chemotherapy, especially when ritux-

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imab is included in the regimen[6-10]. As lamivudine may be less effective in immunocompromised patients due to the emergence of resistant mutant strains[13], liver enzymes and HBV DNA viral load have to be monitored to detect DNA mutations, so that a timely switch to other antiviral treatment such as adefovir or tenofovir can be made[14,15]. This report also shows that the appearance of liver complications is not always heralded by an increase in the HBV DNA titer. Moreover, it suggests – in this setting and increasingly in other situations of chronic HBV-related damage – the opportuneness of combined treatment with lamivudine and adefovir or with other combinations of the available antivirals.

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