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SHORT REPORT

Fatal Liver Failure Secondary to Chemotherapy Induced Hepatitis-B Virus Reactivation in a Patient with Acute Myeloid Leukemia*

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Cancer chemotherapy in chronic carriers of hepatitis B virus surface antigen (HBsAg) is known to promote viral replication, and when immunosuppressive treatment is stopped the return of immunocompetence can be followed by liver damage of varying degrees of severity, including fulminant hepatitis. Hepatitis B virus (HBV) reactivation of various degrees may develop in 20-50% of HBsAg positive patients undergoing immunosuppressive or cytostatic treatment (1). We report a patient with acute myeloid leukemia (M1) who developed fatal liver failure from reactivation of HBV after chemotherapy.

Case

The patient was a 45-year-old man with acute myeloid leukemia (M1) who received chemotherapy and was an asymptomatic HBV carrier previously (pre-chemotherapy serology was HBsAg, anti-HBc, and anti-HBe were positive). Two months after chemotherapy, he was admitted to hospital with the complaints of malaise, anorexia, vomiting, dark urine and jaundice, and he was hospitalized. According to his history, he had not received a transfusion or transmission. On physical examination, jaundice and hepatomegaly were noted. Laboratory findings revealed elevated liver enzymes, high levels of bilirubin, and coagulopathy. On admission, total bilirubin was 13.8 mg/dl; AST, 2340 U/l; ALT, 964 U/l, and LDH 1270, U/l; prothrombin time, 20 s; and albumin and other parameters were normal. The results of the serologic tests were as follows: HBsAg, anti-HBc and anti-HBe, positive; anti-HDV and anti-HCV, negative; and HBV DNA by PCR, 1.4 x 10^5 copy/ml. The patient was diagnosed with HBV reactivation after cancer chemotherapy. In addition to supportive therapy, lamivudine (100 mg/day) was initiated.

In 3 months, fatal liver failure developed; ascites and personality changes were added to the clinical picture despite the lamuvidine therapy. Final laboratory findings were as follows: erythrocyte sedimentation rate (ESR), 25 mm/h; WBC, 14,000/mm^3; PLT, 162,000/mm^3; AST, 4300 U l^{-1}; ALT, 4995 U l^{-1}; total bilirubin, 40 mg dl^{-1}; direct bilirubin, 25 mg/dl; prothrombin time, 45 s; partial thromboplastin time, 72.2 s; INR, 2.4; ammonia, 130 ng/dl; and albumin, 1.9 mg/dl. Despite lamuvidine and intensive supportive therapy, the patient unfortunately died in the fourth month.

Reactivation of HBV is a well-described complication among cancer patients undergoing cytotoxic chemotherapy. The prevalence of chronic carriers of HbsAg in cancer patients varies among different

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geographic areas and may be as high as 12% in endemic areas (2). Careful prospective serological testing has shown that hepatitis B virus reactivation is a 2-staged process. The initial stage occurs during intense cytotoxic or immunosuppressive therapy and is characterized by enhanced viral replication, as reflected by increases in the serum levels of HBV DNA, HbeAg, and HBV DNA polymerase, and infection of naive hepatocytes with hepatitis B virus. The second stage is related to the restoration of immune function following withdrawal of cytotoxic or immunosuppressive therapy, which causes rapid immune-mediated destruction of infected hepatocytes. Clinically, this can lead to hepatitis, hepatic failure, and even death (3). The mortality rate of acute liver failure ranges from 4% to 41% of affected patients (1).

It is not possible to predict the occurrence or clinical severity of HBV reactivation in a patient. Yeo et al. (2) investigated frequency and risk factors in 626 patients, and they identified male gender, younger age, HbeAg positivity, and the diagnosis of lymphoma as risk factors for HBV reactivation in HBV carrier cancer patients. In our patient, only gender was a risk factor. In another study, the presence of corticosteroids among the protocol drugs was considered the most important predisposing factor for treatment-induced HBV reactivation (4). As observed by Cheng et al. (5), the frequency of reactivation after chemotherapy cycles that did or did not include corticosteroids was 47% and 8%, respectively.

There are many cases of HBV reactivation after chemotherapy in patients with AML or other hematologic malignancies (6-17).

Lamivudine is a nucleoside analogue that can directly suppress HBV replication. It has been used extensively and has proven effective both as a treatment and prophylaxis of chemotherapy-induced HBV reactivation (1,6-17). Lamivudine was initiated in our patient after HBV reactivation, and, despite therapy, fatal liver failure developed, and the patient died. Waiting for HBV reactivation before starting antiviral treatment does not avoid the significant risk of fulminant hepatitis, particularly in HbeAg negative patients (1). Controlled studies are needed to define the incidence and risk factors of hepatitis B reactivation so that pre-emptive treatment with lamivudine can be administered to those patients at high risk of disease (3).

DNA mutations may develop in HBV during lamivudine therapy (18). Adefovir dipivoxil is an alternative drug in such cases (18,19). Recently, it was reported that adefovir dipivoxil was successfully used in prevention of recurrence of lamivudin-resistant hepatitis B infection in a patient with liver transplantation and in another patient, who had received chemotherapy for non-Hodgkin's lymphoma (20,21).

This case indicates the importance of HBsAg screening before chemotherapy, and the need for lamivudine prophylaxis for the prevention of HBV reactivation in HBsAg positive cases. After reactivation of HBV, despite lamivudine therapy, the prognosis may be poor.

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