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Fatal Postlymphoma Chemotherapy Hepatitis B Reactivation Secondary to the Emergence of a YMDD Mutant Strain With Lamivudine Resistance in a Noncirrhotic Patient

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Hepatitis B reactivation is a well-known complication during or after chemotherapy in chronic hepatitis B (HBV) carriers. The current practice guidelines in Canada and the United States recommends patients receive antiviral prophylaxis prior to the onset of chemotherapy in chronic HBV carriers with lamivudine. We report a case of a 57-year-old man with follicular lymphoma on lamivudine prophylaxis and no clinical evidence of cirrhosis, and developed fatal HBV reactivation after the emergence of a YMDD mutant strain of HBV that confers lamivudine resistance. Fatal reactivation secondary to the development of lamivudine resistance has not, to date, been well- reported. Our experience indicates the need to carefully monitor patients for suspected drug- resistant HBV mutants with the addition of antiviral agents effective against the YMDD mutational strain, when lamivudine resistance emerges. Am. J. Hematol. 81:969–972, 2006. © 2006 Wiley-Liss, Inc.

Key words: hepatitis B; YMDD mutation; lamivudine; resistance; chemotherapy

INTRODUCTION

Hepatitis B reactivation is a well known complication during or after chemotherapy in chronic hepatitis B (HBV) carriers. In the absence of specific prophylaxis, the incidence of reactivation HBV in lymphoma patients is high with studies reporting rates between 32%–78% [1–5]. Lamivudine is efficacious in the prophylaxis of HBV reactivation before or at the initiation of chemotherapy. However, the emergence of the YMDD mutant strain of HBV, conferring lamivudine resistance is a function of the duration of therapy, with current practice recommending that patients be maintained on lamivudine therapy upon emergence of virus mutation to prevent return of wild type and to decrease the frequency of flare-ups [6]. The current belief is that the emergence of the YMDD mutation in isolation without cirrhosis or return of wild type virus is not fatal in the post-chemotherapy setting as a recent study [7], concluded that the emergence of lamivudine resistant strains "was of little clinical relevance." We report a case of a 57-year-old man with follicular lymphoma and hepatitis B who developed YMDD mutation during chemotherapy while on lamivudine prophylaxis with fatal reactivation hepatitis upon withdrawal of chemotherapy.

CASE

A 57-year-old Chinese man was brought to the emergency department (ER) confused and jaundiced having been in a normal state of health 5 days previ-

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ously. The patient's medical history dated back 9 months prior to presentation when he was first diagnosed with stage 3A, grade 3A follicular lymphoma. The diagnosis followed a parotidectomy that on hematopathological review revealed a high density of nodules composed of small and large typical cells that were B cells expressing BCL2 and BCL6 but negative CD10. Polymerase chain reaction was negative, and there was no BCL2 rearrangement found. A CT scan of the abdomen revealed a normal liver without splenomegaly At presentation, he had widespread adenopathy with splenic lesions and no hepatic involvement. Because of the splenic lesions, rapid decline in his performance status, and elevated LDH, he most likely clinically transformed to a more aggressive subtype, although this was not proven histologically. At the time, routine bloodwork ordered in anticipation of chemotherapy revealed the patient to be a chronic hepatitis B (HBV) carrier (HBsAg positive). His baseline liver biochemistry revealed a serum AST of 34 U/l (normal I10-38 U/l), alkaline phosphatase 72 U/l (normal 30–105), total bilirubin 7 μmol/l (normal < 26 μmol/l), serum albumin 40.6 g/l (normal 35–45 g/l). His platelet count was 259,000/ml. His prechemotherapy hepatitis B investigations revealed that the patient was hepatitis B e antigen negative (HBeAg), anti-HBeAg positive, with a HBV DNA of 2,037,459 copies/ml by branched DNA assay (Versant HBV 3.0; Bayer Healthcare, Tarrytown NY; lower limit of detection 3,300 copies/ml). Prophylactic lamivudine 100 mg/daily (Hepatovir, GlaxoKlineSmith, Mississauga, ON) was initiated 2 months before the chemotherapy regimen of CHOPR (cyclophosphamide, adriamycin, vincristine, prednisone, and rituximab (CHOP-R)). A HBV DNA revealed his viral load to be 782,246 copies/ml at the initiation of chemotherapy and prednisone was held. Vincristine was omitted because of a history of familial spastic paresis.

The patient was seen and evaluated 3 months after initiation of chemotherapy and found to have no signs or symptoms suggestive of hepatitis B or of chronic liver disease. At the time, the patient's bloodwork, including liver biochemistry, was entirely within normal limits except for the elevated viral load. In light of the high viral load after 2 months of lamivudine therapy, the initiation of an alternate antiviral agent was discussed with the patient. The patient refused additional therapy and a repeat viral load was ordered with clear instructions to continue on lamivudine. The repeat bloodwork in 2 months before presentation to the ER revealed a viral load of 140,637 copies/ml and liver enzymes within normal range (i.e., serum ALT 38 U/l, serum AST 33 U/l). The patient continued on his modified chemotherapy regimen along with lamivudine prophylaxis and repeat viral load was performed the following month. The repeat viral load 1 month before ER presentation now revealed his HBV DNA to be 749,361 copies/ml with stable liver enzymes. Again, the issue of lamivudine-resistance with the recommendation of additional antiviral agents was discussed and declined by the patient. The patient completed only 6 courses of chemotherapy and had an excellent response to treatment with a near complete remission.

Upon presentation to the ER, the patient was noted to be significantly jaundiced with complaints of pruritus. He was confused to person, place and time; rousable but not obeying any commands. Physical examination revealed tender left cervical lymphadenopathy. Abdominal exam revealed a diffusely tender abdomen with significant ascites, an enlarged but nontender liver and no palpable spleen.

Hematology panel was remarkable in this patient for a leukocytosis at 18,400 cells/ml and thrombocytopenia with a platelet count of 61,000/ml. The patient had a significant coagulopathy with the INR greater than 11.9 and fibrinogen of 0.4 mg/l (normal values 1.9–4.7 mg/l). Other laboratory investigations were remarkable for an ALT of 1574 U/l (normal 20–65 U/l), AST of 1175 U/l (normal 10–38 U/l), GGT at 37 U/l (normal 15–80 U/l), Alkaline phosphatase of 117 U/l (normal 30–105 U/l) and total bilirubin of 218 μmol/l (normal < 26 μmol/l). An ultrasound revealed moderate amounts of ascites with a small, coarse liver without any focal lesions. In light of the normal liver size and echotexture on CT scan 9 months previously, the findings were compatible with acute massive necrosis. No evidence of intrahepatic or biliary dilation was noted but the anterior wall of the gallbladder was notably thickened with echogenic areas within the wall. The portal vein was patent. The patient was admitted to the general medicine service and started on tenofovir 300 mg/daily (Viread; Gilead-Sciences, Foster City, CA).

Throughout the course of hospitalization, the patient's neurological status continually declined. The patient was unable to tolerate any oral intake and developed progressive encephalopathy. He became comatose on the fifth day after admission and died on the sixth day from respiratory failure. Virologic sequencing of his HBV strain revealed the presence of a mutation in the YMDD motif conferring resistance to lamivudine and the absence of the original wild-type strain.

DISCUSSION

The risk of hepatitis B reactivation during or after chemotherapy in HBV carriers is well-reported with

the first case reports first appearing over 20 years ago [8]. Lamivudine, an oral nucleoside analogue, inhibits HBV replication and can significantly reduce serum HBV DNA levels and normalize ALT levels suggestive of decreased liver necroinflammation. One setback associated with long-term lamivudine monotherapy, however, is the development of resistance with mutation of the tyrosine-metheonine-aspartate-aspartate (YMDD) motif in the C domain of the HBV DNA polymerase gene [9,10]. Although resistance is a point mutation with substitution of metheonine with isoleucine or valine [11] that develops during lamivudine therapy with occasional genotypic progression to more than one point mutation [12], there is evidence suggesting that the development of resistance may also represent selection of pre-existing nests of resistant strains [13].

Lamivudine resistant virus has been demonstrated in 14%–32% of patients after 1 year of treatment [8,9]; however, despite this, patients have significantly lower HBV DNA and ALT levels compared to baseline values [14]. Additionally, with continuation of lamivudine therapy after the emergence of YMDD mutation, there is frequently clinical amelioration after acute exacerbation of hepatitis [15]. In one series of 51 nononcologic patients treated for chronic hepatitis B with lamivudine, patients were clinically followed after the development of YMDD mutation and either continued or discontinued lamivudine. In long-term followup of these patients, those who discontinued lamivudine therapy were found to have more frequent acute exacerbations and higher ALT peaks than those who continued lamivudine after 4 months from the development of the YMDD mutation [6]. All fatalities were noted in patients with previously documented cirrhosis and differences were not significant between the two groups. Little has been reported in the oncologic literature with regard to these mutations. In a recent study [7] from Italy, only one patient out of 31 patients given prophylactic lamivudine in association with chemotherapy, for hematologic maligancies, developed genotypically confirmed lamivudine resistance. The patient who developed lamivudine resistance did not develop abnormal liver biochemistry and the investigators concluded that the emergence of lamivudine resistance during hematologic chemotherapy was "of little clinical relevance."

Genotypically-characterized lamivudine resistance, in the absence of wild-type virus, however, is not commonly associated with fatal reactivation in either the nononcologic or postchemotherapy setting. We are aware of only two previously reported cases, not associated with chemotherapy, in the literature of lamivudine-resistant HBV mutant causing fatal reactivation in a noncirrhotic patient [16] and an HIV positive patient on high activity antiretroviral therapy (HAART) with recovery of the CD4 count [17]. In both cases, the lamivuidine resistance occurred after the methionine was replaced by isoleucine in the HBV YMDD motif (i.e., YMDD to YIDD where Y is tyrosine and D is aspartate) after chronic lamivudine therapy. Interestingly, the methionine to isoleucine substitution has been reported to produce recurring jaundice in the setting of prednisilone therapy for Still's disease [18]. To date, however, we are unaware of any reports of the YMDD motif mutation resulting in fatal postchemotherapy HBV reactivation. Although, in our patient's situation, we do not know if the use of antiviral agents effective against the YMDD mutation would have prevented his reactivation as he declined therapy. Treatment options in this setting include the use of adefovir [19] or tenofovir [20]. The use of adefovir dipivoxil, a nucleotide analogue, has been well described for the treatment of lamivudine-resistant hepatitis B mutants [19]. In one series of 135 patients with YMDD mutant HBV, patients were randomized to either continuation of lamivudine alone or with the addition of adefovir. This study showed that the addition of adefovir to lamivudine in compensated and decompensated liver disease due to YMDD mutant HBV is associated with virologic and biochemical improvement [21]. More recently, tenofovir has been reported to be markedly more efficacious in terms of HBV viral suppression in the setting of lamivudine resistance when compared with adefovir [20] suggesting that this may be the drug of choice. In Canada, at this current time, tenofovir is commercially available whereas adefovir is not. In the United States, both antiviral agents are available commercially.

Our experience demonstrates important clinical implications in oncologic patients with chronic hepatitis B undergoing chemotherapy on prophylaxis. First, the need to monitor oncology patients undergoing chemotherapy and immediately postchemotherapy for evidence of lamivudine resistance either biochemically (i.e., flare of liver biochemistry) or virologically (i.e., phenotypically with an increase in HBV viral load while on lamivudine or genotypically looking for the YMDD mutation). Second, with evidence of the emergence of lamivudine resistance, the need to add another antiviral such as adefovir or tenofovir should be considered. Although it is difficult to make strong recommendations on a single case report, we note that HBV reactivation with the YMDD mutant strain in our patient's case was associated with a fatal outcome. The ability to perform HBV genotyping will

become readily available and is not harmful. The information from such testing may impact upon therapy and treatment outcomes.

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