Reactivation of hepatitis B e antigen-negative chronic hepatitis B in a bone marrow transplant recipient following lamivudine withdrawal

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RP Myers, MG Swain, SJ Urbanski, SS Lee. Reactivation of hepatitis B e antigen-negative chronic hepatitis B in a bone marrow transplant recipient following lamivudine withdrawal. Can J Gastroenterol 2001;15(9):599-603. Reactivation of hepatitis B virus (HBV) is a recognized complication of bone marrow transplantation (BMT). Lamivudine is a nucleoside analogue with potent antiviral activity that has been used in the prophylaxis of HBV reactivation in at-risk BMT recipients. Currently, no data exist regarding the safety of nucleoside analogue withdrawal in these patients. A 32-year-old BMT recipient with hepatitis B e antigen (HBeAg)-negative, chronic HBV who developed a serious flare of hepatic inflammation due to a rebound in viral replication within 12 weeks of discontinuing lamivudine therapy is described. The patient remained HBeAg-negative despite high level viremia, suggesting the emergence of a mutant viral strain. The patient's acute hepatitis resolved promptly with the reinstitution of lamivudine therapy. Further studies are necessary to define the safety and efficacy of nucleoside analogues in the prevention of HBV reactivation in at-risk BMT recipients. Clinicians should consider the risk of inducing serious flares of hepatic inflammation due to abrupt nucleoside analogue withdrawal in these patients.

Key Words: *Adverse effects; Antiviral agents; Bone marrow transplantation; Hepatitis B virus; Lamivudine; Precore mutant*

Réactivation de l'hépatite HBeAg-négative chronique chez un receveur de transplantation de moelle osseuse après l'arrêt de la lamivudine

RÉSUMÉ : La réactivation du virus de l'hépatite B (HBV) est une complication reconnue de la transplantation de moelle osseuse (TMO). La lamivudine est un analogue nucléosidique doté d'une activité antivirale puissante qui a été utilisée en prophylaxie contre la réactivation du HBV chez des receveurs de TMO à risque. À l'heure actuelle, il n'existe

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aucune donnée quant à l'innocuité de l'arrêt des analogues nucléosidiques chez ces patients. On décrit ici le cas d'un receveur de TMO de 32 ans souffrant d'une hépatite B (HBeAg-négative) chronique et d'une poussée grave d'inflammation hépatique attribuable à un rebond de la réplication virale dans les 12 semaines suivant l'arrêt du traitement à la lamivudine. Le patient est resté HBeAg-négatif, malgré une virémie élevée. Ce qui suggère l'émergence d'une souche virale mutante. L'hépatite aiguë du patient est rapidement rentrée dans l'ordre avec le rétablissement du traitement à la lamivudine. D'autres études seront nécessaires pour préciser l'innocuité et l'efficacité des analogues nucléosidiques dans la prévention de la réactivation du HBV chez les receveurs de TMO à risque. Les médecins doivent tenir compte du risque de provoquer de graves recrudescences de l'hépatite lors de l'arrêt soudain des analogues nucléosidiques chez ces patients.

Reactivation of the hepatitis B virus (HBV) is a well recognized complication of immunosuppression, including that due to cytotoxic chemotherapy (1,2), corticosteroid administration (3) and organ transplantation (4). Bone marrow transplantation (BMT) is one such situation in which serious, occasionally fatal, flares of HBV have been reported (5-7). The recognition that HBV-infected patients are at risk of serious liver dysfunction in the post-BMT period, as well as the availability of potent antiviral agents, including lamivudine, have led to the widespread use of these agents as prophylaxis against HBV reactivation in this setting (8). The appropriate use, including the safety of withdrawal of these agents, however, has not been systematically investigated.

We describe the first reported case of a serious flare of hepatic inflammation in a patient with hepatitis B e antigen (HBeAg)-negative, chronic HBV infection following the withdrawal of lamivudine therapy used as prophylaxis against HBV reactivation in the peri-BMT setting.

CASE PRESENTATION

A 32-year-old Somalian man was evaluated in January 2000 for HBeAg-negative, anti-HBe-positive, chronic HBV infection. The patient had a history of idiopathic hypereosinophilic syndrome, which had responded suboptimally to corticosteroids, hydroxyurea and interferon-alpha; he was being considered for BMT. He denied symptoms suggestive of liver disease, additional medical problems and hepatotoxin exposure. The patient had massive splenomegaly; the remainder of the physical examination was unremarkable. Laboratory investigations revealed a marked peripheral eosinophilia, but the patient's liver enzymes, albumin and coagulation profile were normal. The patient's HBV DNA was negative (Digene assay; Digene Corporation, USA) as were serological tests for hepatitis C and the human immunodeficiency virus. A percutaneous liver biopsy revealed a mild eosinophilic infiltrate in the portal triads and hepatic parenchyma consistent with idiopathic hypereosinophilic syndrome. The interlobular bile ducts were normal, and there was no fibrosis. The patient had grade I/IV hemosiderosis. He was prescribed lamivudine 100 mg daily and ursodeoxycholic acid 500 mg twice daily for prophylaxis against reactivation of HBV and graft-versus-host disease, respectively.

The patient's 40-year-old brother, the prospective bone marrow donor, also had HBeAg-negative, anti-HBe-positive, chronic HBV infection with normal liver enzymes. He received lamivudine 100 mg daily for two weeks before the bone marrow donation. Both the patient and donor were positive for cytomegalovirus immunoglobulin (Ig) G antibodies.

In February 2000, the patient received a human leukocyte antigen (HLA)-matched bone marrow transplant from his brother, with fludarabine, busulphan and antithymocyte globulin preconditioning. Both the donor's and recipient's serum HBV DNA were negative on the day of the donation. Post-transplantation immunosuppression consisted of cyclosporine and prednisone, and lamivudine and ursodeoxycholic acid were continued. The post-transplantation course was uncomplicated, although engraftment was suboptimal, necessitating supportive erythropoeitin and granulocyte colony-stimulating factor injections, as well as intermittent platelet and red blood cell transfusions. By August 2000, the patient's blood counts were adequate, and his bone marrow eosinophilia (originally 55%) had resolved.

The patient's cyclosporine and prednisone doses were gradually tapered. He was re-evaluated in April 2000, at which point he was off all immunosuppression, but continued lamivudine and ursodeoxycholic acid therapy. Although he denied symptoms suggestive of liver disease, the patient had a stable, mildly cholestatic liver profile (alkaline phosphatase [ALP] concentration 193 U/L, normal less than 130 U/L; alanine aminotransferase [ALT] concentration 22 U/L, normal less than 60 U/L) and unconjugated hyperbilirubinemia (total bilirubin concentration 25 µmol/L, normal less than 20 µmol/L). The serum HBV DNA remained negative. In September 2000, the patient remained HBeAg-negative and anti-HBe-positive. The liver enzymes were also stable. As a result, after eight months of therapy, lamivudine was discontinued.

Twelve weeks later, in mid-December, the patient was reassessed due to complaints of jaundice, fatigue, diffuse upper abdominal discomfort and tea-coloured urine. The patient was jaundiced but had no organomegaly, ascites or edema. The patient's ALT level had risen to 2703 U/L; bilirubin level to 101 µmol/L and ALP level to 314 U/L (Figure 1). The international normalized ratio was mildly elevated at 1.3 (normal less than 1.1). Antibodies to hepatitis A (IgM) and hepatitis D were negative, and the patient remained HBeAg-negative and anti-HBe-positive. The HBV DNA level, however, had risen dramatically to 285.1 pg/mL (Digene assay). A transjugular liver biopsy revealed a marked lymphocytic infiltrate in the portal tracts and hepatic parenchyma with ground glass and necrotic hepatocytes. The findings were characteristic of acute HBV

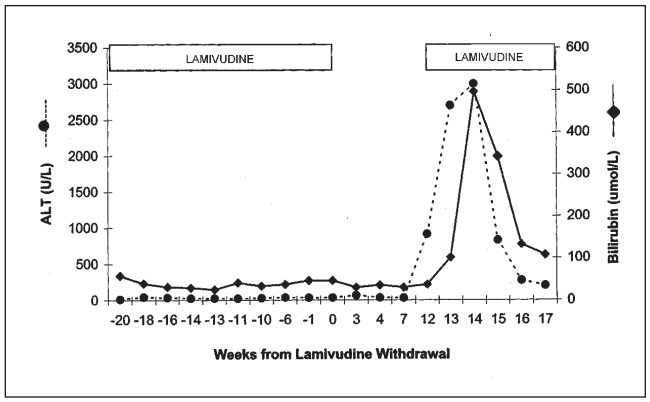

Figure 1) *Changes in serum alanine aminotransferase (ALT) and bilirubin levels in the case patient during and after lamivudine therapy. The patient's exacerbation occurred within 12 weeks of the discontinuation of lamivudine but responded prompty to the reinstitution of therapy. The patient remained hepatitis B e antigen-negative throughout the course, despite high level viremia associated with his clinical flare of hepatitis*

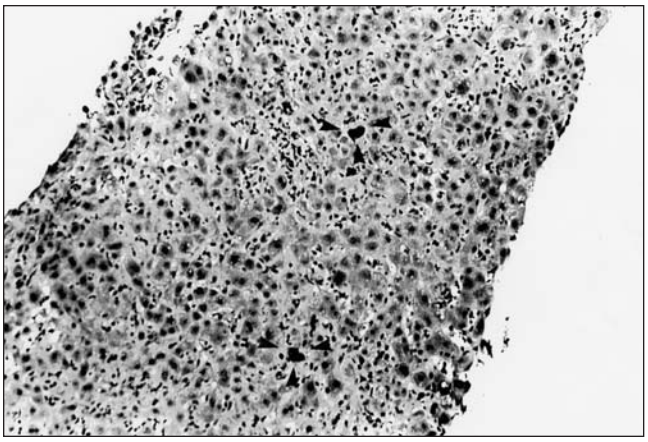

Figure 2) *Photomicrograph of liver biopsy specimen showing dense parenchymal lymphocytic infiltration, ballooning hepatocytes and apoptotic bodies (arrowheads) characteristic of acute hepatitis due to reactivation of hepatitis B virus (hematoxylin and eosin stain, original magnification ×200)*

infection (Figure 2). The patient also had mild portal fibrosis and grade III/IV hemosiderosis, but there were no features of graft-versus-host disease (Figure 3).

Lamivudine therapy 100 mg daily was reinstituted for the treatment of HBV reactivation. Within one week, the patient's ALT level peaked at over 3000 U/L and the bilirubin level rose to 496 µmol/L, although he did not demonstrate any clinical features of hepatic decompensation. Over the ensuing three weeks on lamivudine therapy, the patient's symptoms resolved, and the liver profile gradually improved (Figure 1). He remains well on continuing lamivudine therapy.

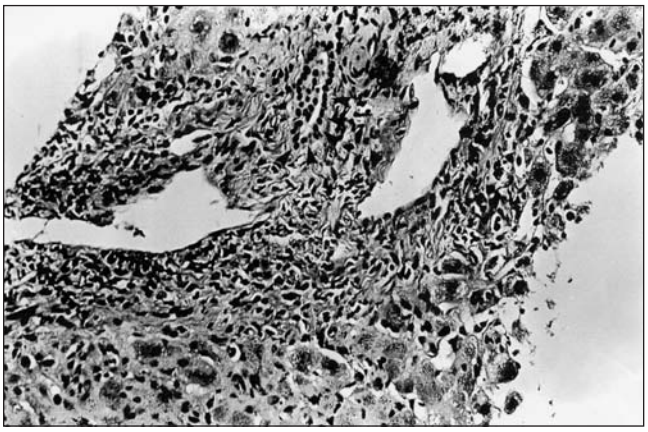

Figure 3) *Photomicrograph of liver biopsy specimen showing lymphocytic infiltration of the portal triad. The interlobular bile duct is normal (arrowheads), suggesting the absence of graft-versus-host disease. Hemosiderin is visible as dark cytoplasmic granules in periportal hepatocytes (hematoxylin and eosin stain, original magnification ×200)*

DISCUSSION

The development of the nucleoside analogue lamivudine has revolutionized the management of chronic HBV infection (9). Large, randomized trials have confirmed its efficacy in the treatment of both HBeAg-positive (10) and HBeAg-negative (11) HBV-infected patients, as well as in the prophylaxis of HBV recurrence following liver transplantation (12). Due to its efficacy, favourable side effect profile and ease of administration, the use of lamivudine has become widespread in a variety of clinical situations. For example, lamivudine is frequently prescribed to HBV-infected patients undergoing cytotoxic chemotherapy or BMT due to the recognition that the immununosuppression inherent in these situations can result in HBV reactivation and serious, even fatal, flares of hepatic inflammation (13). Unfortunately, the appropriate use of lamivudine in these situations has not been systematically investigated, and questions remain about this practice. In particular, the safety of lamivudine withdrawal with respect to the precipitation of reactivation flares has yet to be reported in these populations, although several reports have highlighted this problem in immunocompetent HBV-infected patients (14, 15). In one study of 41 patients treated with lamivudine, 17% of patients developed flares of hepatitis (29% of these with liver failure) after the discontinuation of lamivudine (15). As illustrated by the patient described herein, the discontinuation of nucleoside analogue therapy can also result in serious flares of hepatic inflammation in the post-BMT setting.

In this case, we believe that there was a causal relationship between the withdrawal of lamivudine therapy and the patient's acute hepatitis. Most striking is the temporal relationship between the patient's clinical deterioration and the discontinuation of lamivudine. Within 12 weeks of stopping therapy, the patient presented with a serious flare of hepatitis, which was associated with a dramatic rise in HBV DNA from previously undetectable levels to over 285 pg/mL. The consistent liver histology, absence of a likely alternative explanation and prompt response to reinstitution of lamivudine lend further support to the hypoth-

esis that lamivudine withdrawal led to a rebound in viral replication and, ultimately, the patient's deterioration.

The patient described remained persistently HBeAg-negative and anti-HBe-positive before and during therapy with lamivudine. During this time, he had normal aminotransferase levels and negative HBV DNA. Because this profile traditionally signifies the absence of viral replication and represents the end point for successful treatment with antivirals (10), we elected to discontinue lamivudine after eight months of therapy. The results were potentially disastrous, although the patient did respond to reinstitution of lamivudine. This highlights the importance of further investigations of antiviral therapy in these patients to define more accurately the appropriate end points for treatment. More sensitive polymerase chain reaction-based assays may be necessary to detect very low levels of viral replication that may lead to reactivation hepatitis on withdrawal of antiviral therapy.

The majority of HBeAg-negative, anti-HBe-positive patients with chronic HBV harbour mutations in the precore region of the viral genome – specifically an inframe TAG stop codon mutation at nucleotide 1896 (A1896) (16,17). These so-called 'precore mutants' are unable to produce HBeAg; however, they typically have high level viremia and abnormal aminotransferases (16,17), characteristics that were lacking in our patient. In the absence of viral nucleotide sequencing, we can only speculate on the predominant viral strain in the case patient. One possibility is that he had wild-type virus at low levels of replication – levels low enough to evade detection by the Digene HBV DNA assay, and requiring more sensitive polymerase chain reaction-based assays for detection. It is plausible that lamivudine therapy led to the emergence of a mutant strain of virus, such as a precore variant, with enhanced replication fitness under the selective pressure of antiviral therapy, that only became detectable on withdrawal of lamivudine. This would explain why the virus failed to produce HBeAg during the viremic period associated with the patient's flare of hepatitis. An alternative explanation is that the patient had wild-type HBV that remained at low levels of replication until lamivudine therapy was discontinued. Although wild-type viremia is typically associated with high circulating levels of HBeAg, recent reports suggest that this is not always the case (16,17). Mutations in the core promoter region (at nucleotides 1762 and 1764) have been associated with absent or low level HBe-antigenemia, despite high level viremia (16,17). Alternatively, detection of HBeAg could be overcome by complexing with excess circulating anti-HBe in some patients (18).

It is intriguing to speculate on the role that the patient's immunosuppression therapy, which was discontinued approximately seven months before his HBV reactivation, played in his clinical course. A wealth of literature suggests that immunosuppressant medications such as cyclosporine, corticosteroids and chemotherapeutic agents can result in reactivation of HBV and have grave clinical consequences (1,3,19). The incidence of HBV-related hepatitis in recipients of hepatitis B surface antigen (HBsAg)-positive bone marrow has been reported to range from 12% to 44% (6,8). Lamivudine therapy may have transiently protected our patient against this immunosuppressant-induced, uncontrolled viral replication (8), but the efficacy of lamivudine in this situation needs to be assessed in controlled trials.

Alternatively, the discontinuation of immunosuppression may have contributed to our patient's reactivation hepatitis. It is conceivable that the withdrawal of immunosuppression, in association with the cessation of antiviral therapy, led to the restoration of immunocompetence followed by immune-mediated cytolysis of HBV-infected hepatocytes. This concept forms the basis for the practice of prednisone withdrawal before antiviral therapy of chronic HBV (20,21). Although previously investigated in the setting of interferon therapy (20), 'prednisone priming' may be effective in the context of lamivudine therapy (21).

The case patient received an HLA-matched BMT from his brother who was also an HBeAg-negative, anti-HBe-positive, chronic HBV carrier with normal aminotransferase levels. In an attempt to minimize the risk of HBV transmission, the donor was treated with lamivudine before bone marrow harvesting. Recent evidence suggests that recipients of bone marrow from HBsAg-positive donors with high viral loads are more likely to develop HBV-related hepatitis (6), but the role of lamivudine therapy in reducing this risk has yet to be investigated. The presence of precore (A1896) and/or core promoter (1762, 1764) variants in the donor also appears to enhance the risk of HBV-related hepatitis in the recipient (6). This is intriguing considering the serological profile of the donor who may have transmitted one of these variant strains of HBV to his brother via the donated bone marrow.

The patient described in this case developed a serious flare of hepatic inflammation due to a rebound in viral replication shortly following the discontinuation of lamivudine therapy, despite serology, biochemistry and HBV DNA assays, suggesting an absence of viral replication. Our findings suggest that further studies are needed to examine the role of nucleoside analogues in HBV-infected BMT recipients. In particular, the efficacy of these agents in reducing the risk of HBV reactivation in at-risk patients, their role in reducing the risk of HBV transmission from HBV-infected bone marrow donors, and the safety and appropriate timing of their withdrawal, must be defined before their broad dissemination in clinical practice.

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