Complete Remission of Nephrotic Syndrome of Hepatitis B Virus-associated Membranous Glomerulopathy After Lamivudine Monotherapy

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We present the case of a 22-year-old male with chronic hepatitis B virus (HBV) infection, who developed nephrotic syndrome and had complete remission after lamivudine monotherapy. Renal biopsy showed membranous glomerulopathy, and the serum titer of HBV DNA increased to 1,130,000 copies/mL. As symptomatic therapy with angiotensin converting enzyme inhibitors did not improve the nephrotic syndrome, lamivudine 100 mg per day was started. His alanine aminotransferase level normalized 2 months after treatment, then hepatitis B e antigen seroconversion developed and serum HBV DNA became undetectable. His proteinuria improved subsequently and his leg edema disappeared completely 6 months after treatment. Neither hepatitis nor nephrotic syndrome had relapsed by month 13 when he came for follow-up. This suggests that lamivudine monotherapy may induce and maintain complete remission of membranous glomerulopathy associated with hepatitis B. [J Formos Med Assoc 2007;106(10):869–873]

Key Words: hepatitis B virus, lamivudine, membranous glomerulonephritis, nephrotic syndrome

According to clinical, epidemiologic and immunologic evidence, chronic hepatitis B virus (HBV) infection is strongly associated with the occurrence of membranous glomerulopathy (MN), particularly in children.1 The majority of pediatric patients with HBV-related MN have a good prognosis in terms of the preservation of renal function, and there is a high rate of spontaneous remission.2 In contrast, the clinical course of HBV-related MN in adults is not benign. Regardless of treatment, this disease has a slow but relentlessly progressive course in approximately one third of adult patients.3 Steroids and other immunosuppressive therapies that are the mainstay of treatment for idiopathic forms of MN may cause more harm than good by enhancing viral replication and precipitating hepatitis flares in HBV-related MN. Interferon (IFN)-α, while reported to be useful in children, has produced disappointing results in Chinese adult subjects.3 Recently, lamivudine, a nucleoside analog inhibitor of HBV DNA polymerase, has been shown to have advantages over IFN for HBV treatment because of its having fewer side effects and an oral route of administration.

Here, we report the case of an adult patient with chronic hepatitis B who developed MN with nephrotic syndrome and who experienced complete remission after lamivudine monotherapy.

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A 22-year-old Taiwanese male patient who had a history of chronic HBV infection lasting for several years was regularly followed-up at the local medical clinic. He was found to be positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antibody (anti-HBe Ab), and negative for hepatitis B e antigen (HBeAg). He had an increased serum level of aspartate aminotransferase (AST) of 268 U/L and alanine aminotransferase (ALT) of 239 U/L in May 2003. Three months later, due to progressive edematous changes in bilateral legs, he was referred to our outpatient department. Laboratory analyses showed the following: serum AST of 99 U/L, ALT of 119 U/L, creatinine of 0.9 mg/dL, and decreased albumin level of 1.6 g/dL. Serologically, his anti-HBe Ab was positive. His HBeAg, immunoglobulin (Ig) M antibody to hepatitis B core, IgM antibody to hepatitis A virus, and antibody to hepatitis C virus were all negative. His serum HBV DNA as determined by sensitive polymerase chain reaction assay (COBAS Amplicor HBV Monitor; Roche Diagnostics, Branchburg, NJ, USA) was 1,130,000 copies/mL. Urinalysis showed proteinuria 500 mg/dL by dipstick. His renal and abdominal ultrasound examinations were normal.

He was admitted to our hospital for a renal biopsy in September 2003. Physical examination was unremarkable except for the extremities which showed severe pitting edema. A repeat data collection showed decreased albumin level of 1.1 g/dL, high cholesterol level of 370 mg/dL and urine total protein loss of 6.0 g/day. His renal biopsy displayed diffusely thickened and rigid capillary walls. Spikes were identified in a few segments by silver stain. On immunofluorescence study, IgG, C3 and C4 were positive along the capillary loops in a granular pattern. IgM was also present, but to a lesser intensity. On electron microscopy, the glomeruli showed diffuse foot process effacement of the epithelial cells. The capillary loops were irregularly thickened by many small and large electron-dense deposits on the subepithelial side of the basement membrane, compatible with membranous nephropathy stage II to III (Figure 1). Fosinopril 10 mg/day was given initially, which was then changed to valsartan 40 mg/day and albumin infusion combined with diuretic therapy (25 mg spironolactone, three times daily) for the edema in his legs.

In October 2003, his bilateral leg edema persisted without any clinical improvement. Repeat data collection showed that his AST and ALT levels were still elevated (128 U/L and 84 U/L, respectively), and HBeAg was positive. Serum albumin had decreased to 0.7 g/dL. He began treatment with lamivudine 100 mg/day after giving informed consent. His ALT levels gradually decreased and normalized 2 months after the start of treatment, in which HBeAg seroconversion developed and his serum HBV DNA became negative (<200 copies/mL). His serum albumin level gradually increased and was >3.0 g/dL after 9 months of therapy. The pitting edema in both legs disappeared completely 6 months after lamivudine treatment, and diuretics were not necessary thereafter. Lamivudine was discontinued after 18 months of therapy. By month 13 after lamivudine treatment had been stopped, the patient remained free of edema, with normal ALT, albumin and cholesterol levels and no detectable HBV DNA in his serum. His daily urine protein loss had decreased to 0.6 g/day and 0.02 g/day at the end of treatment and at follow-up, respectively (Figure 2).

Discussion

A variety of extrahepatic manifestations is observed in patients with both acute and chronic viral hepatitis. A previous study has shown that approximately 16% of chronic hepatitis B patients have clinical extrahepatic manifestations, mainly sensorimotor deficiency (5%), sicca syndrome (3%), myalgia (3%), glomerulonephritis (3%), and arthralgia-arthritis (3%).4 MN is an uncommon but well-documented extrahepatic manifestation of HBV infection. The diagnosis of HBV-associated MN is usually established by serologic evidence of persistent HBV infection, the
Lamivudine for HBV nephrotic syndrome

Figure 1. (A) Glomeruli show diffusely thickened and rigid capillary walls (hematoxylin & eosin, 66×). (B) Silver stain shows spikes in a few segments (periodic acid methenamine silver stain, 330×). (C) Electron microscopy shows irregularly thickened capillary walls with many small and large electron-dense deposits on the subepithelial side of the basement membrane (4000×). (D) Viral-like particles (arrows) appearing as clusters of round to ovoid structures, 10–30 nm in diameter and of varying density, were seen in some electron-dense deposits.

Figure 2. Serial results of alanine aminotransferase (ALT), albumin and total daily protein loss (TDPL) with lamivudine treatment.
presence of immune complex deposits on kidney biopsy, and by the demonstration of glomerular deposits containing one or more HBV-related antigens (HBsAg and hepatitis B core antigen) on immunohistochemical study. In our patient, although special stains of HBV antigen was not performed, we used electron microscopy and found viral-like particles appearing as clusters of round to ovoid structures of 10–30 nm in diameter and varying density distributed within the glomerular capillary basement membrane. In addition, active HBV infection during the course of disease progression and evidence of the reversibility of the renal disease concomitant with a decrease in viral load suggested a direct link between MN and HBV infection.

The clinical manifestations of HBV-associated MN in pediatric and adult patients tend to be different. Pediatric chronic HBV carriers are not infrequently asymptomatic and HBV-associated nephropathy is detected by routine urine and serologic screening. Unlike childhood disease in which there is a high rate of spontaneous remission, adults with HBV-associated MN typically develop a progressive disease. Therefore, there is a pressing need to develop an effective treatment for the latter. To date, the most experience with antiviral treatment for HBV-associated MN in adults has been limited to trials with IFN, and the results have been disappointing in Chinese subjects. Furthermore, some disadvantages of IFN include its expense, the requirement for subcutaneous injection, and frequent side effects such as fever, headache, malaise, myalgia, as well as blood dyscrasias and neuropsychiatric disturbance. In contrast, the incidence of adverse effects with lamivudine is considered to be similar to that of placebo.

Lamivudine therapy is safe and effective in chronic hepatitis B patients in terms of HBV DNA suppression, ALT normalization and improvement in histology. Lamivudine treatment has been successful in adults with HBV-associated polyarteritis nodosa and other immune complex diseases. Recently, a few case reports and only one cohort study with small case numbers have shown that lamivudine treatment might remit HBV-associated MN successfully. In our patient, normalization of ALT levels and HBeAg seroconversion developed 2 months after the start of treatment, and nephrotic symptoms such as leg edema disappeared after 6 months of therapy. His daily urine protein excretion decreased from 6 g at baseline to 0.6 g by the end of treatment, and this continued to improve to the end of the follow-up period (0.02 g/day). The response in our patient is comparable to that seen in other previously reported cases, suggesting that recovery of nephrosis takes a longer time than hepatitis activity in HBV-associated MN. On the other hand, in contrast to childhood disease in which there is a rapid remission of proteinuria, adults with HBV-associated MN recover slowly.

Although lamivudine therapy successfully remitted the HBV-related membrane nephropathy, several issues need to be further clarified. First, the duration of lamivudine therapy remains unresolved. It is reasonable to maintain patients on long-term lamivudine treatment because of the high relapse rate on a short course. Second, a potential limitation of prolonged treatment with lamivudine is the emergence of drug-resistant strains due to the induction and selection of HBV variants with mutations at the tyrosine-methionine-aspartate-aspartate (YMDD) motif of DNA polymerase. One agent that might be considered in case of lamivudine resistance is adefovir dipivoxil, which is effective against both lamivudine-resistant HBV mutants as well as wild-type HBV. However, this agent is potentially nephrotoxic and there are no data on its efficacy in HBV-related MN. Third, whether lamivudine therapy is helpful in HBV-related MN cases in which ALT levels are normal and there is no hepatitis activity or hepatitis B viremia remains unclear. Further studies in a larger cohort of patients are needed to clarify these important issues.

References