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Case Report

A Case of Rapidly Progressive Glomerulonephritis in a Hepatitis B Virus Carrier Successfully Treated with High dose Immunosuppressive Therapy and Prophylactic Lamivudine

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A 35-year-old man, previously hepatitis B surface antigen (HBsAg) carrier, presented with gross hematuria and heavy proteinuria that he had been suffering from for 1 month. Serum creatinine was 4.4 mg/dL. Renal biopsy showed pauci-immune crescentic glomerulonephritis. He received plasmapheresis and was treated with high-dose steroids and cyclophosphamide. Lamivudine was started for the prevention of hepatitis B virus (HBV) activation. Serum creatinine and proteinuria were ameliorated one week after the treatment. There was no sign of HBV activation after six months of treatment. We report a case of rapidly progressive glomerulonephritis in a HBV carrier successfully treated with high dose immunosuppressive therapy and prophylactic lamivudine.

Key Words : Lamivudine, Hepatitis B virus, Rapidly progressive glomerulonephritis

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) histologically shows extensive crescent formation and is a clinical situation in which glomerular injury is so acute and severe that renal function deteriorates over days or weeks. RPGN is mostly treated with immunosuppressive agents, such as steroids or cyclophosphamides, both of which frequently aggravate underlying infections and heightens the chances of opportunistic infections. Chronic hepatitis B surface antigen (HBsAg) carriers are known to have a higher risk of hepatitis-related mortality and morbidity when undergoing immunosuppressive therapy. We report a case of RPGN in a hepatitis B virus (HBV) carrier that was treated successfully by plasmapheresis, immunosuppressive agents, and prophylactic lamivudine without aggravation of HBV hepatitis.

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CASE REPORT

A 35-year-old man who was a HBsAg carrier from adolescence was admitted with a 1-month history of recurrent gross hematuria. On admission, he looked ill and his blood pressure was 130/80 mmHg. Physical examinations were otherwise unremarkable. Laboratory tests showed a high blood urea nitrogen level of 52.2 mg/dL, and a serum creatinine level of 4.4 mg/dL. The levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were normal. C3 and

C4 levels remained within the normal range. Cytoplasmic antineutrophil cytoplasmic antibody (cANCA) or perinuclear antineutrophil cytoplasmic antibody (pANCA) was not detected. HBsAg was positive, while hepatitis B e antigen (HBeAg) and anti-HBe antibodies were negative. HBV-DNA quantitation was negative. Urinalysis revealed heavy proteinuria (4.5 g/day) and hematuria. Creatinine clearance was 21.8 mL/min/1.73m^2. Ultrasonograpahic findings showed increased size and enhanced echogenecity with papillary swelling in both kidneys, without evidence of hydronephrosis. On the third day of admission, plasmapheresis was performed using albumin solution for six sessions. Renal biopsy was performed on the fifth day of admission. Fibrocellular crescents were present in three glomeruli of total ten glomeruli. The glomerular basement membrane was not thickened. The tubules showed focal degeneration, necrosis, and mild atrophy. The interstitium was widened by moderate fibrosis and mild mononuclear infiltrate. Immunofluorescence microscopy showed minimal granular deposits of fibrinogen in the mesangium (Fig. 1). Microscopic examination showed linear IgG (+) and fibrinogen (+) staining along the peripheral capillary wall. Granular deposits of IgA (specks), C3 (specks), and fibrinogen (+) were present in the mesangium. Electron microscopy showed a relatively even glomerular basement membrane without electron densities. The mesangium was expanded with increased mesangial cells and contained some electron densities in mesangial matrix. In light of these findings, the patient was diagnosed with pauci-immune focal proliferative crescentic glomerulonephritis.

Steroid pulse therapy was started on the 14th day of admission with concomitant oral steroid therapy (methylprednisolone 1 g/day intravenously for 3 days, then prednisone 1 mg/kg/day), and pulse cyclophosphamide treatment (1 g intravenously for 1 day). Lamivudine (50 mg/day) was given prophylactically in order to suppress the activation of HBV infection. The serum creatinine level dropped to 1.3 mg/dL, and proteinuria decreased to 1.55 g/day by the 21st day. The patient was discharged with oral steroids and lamivudine. After discharge, the patient underwent five more consecutive cyclophosphamide pulse treatments, and his renal function steadily improved (Fig. 2). The patient is currently well without any evidence of activation of chronic hepatitis B.

DISCUSSION

The course of RPGN is often life threatening and requires high dose corticosteroids and cyclophosphamide as a first-line treatment. However, infections caused by immunosuppression, not vasculitis itself, is the most common cause of death in RPGN patients,

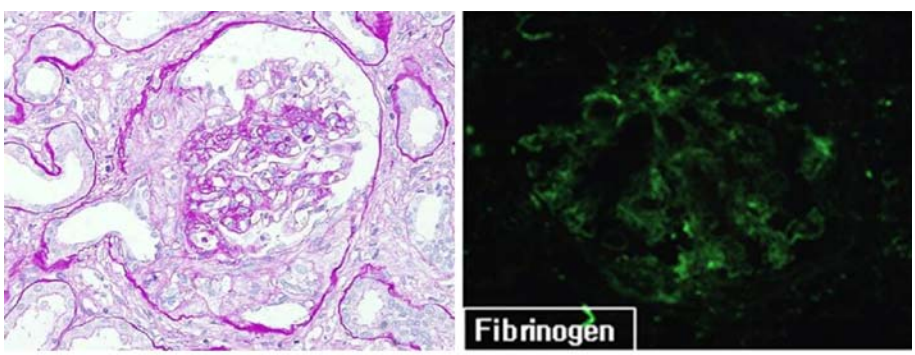

Fig. 1. (A) A glomerulus shows mild endocapillary proliferation and a fibrocellular crescent obstructiong the tubular pole (H&E, ×400). **(B)** Immunofluorescence microscopy showed minimal nonspecific granular deposits of fibrinogen in the mesangium.

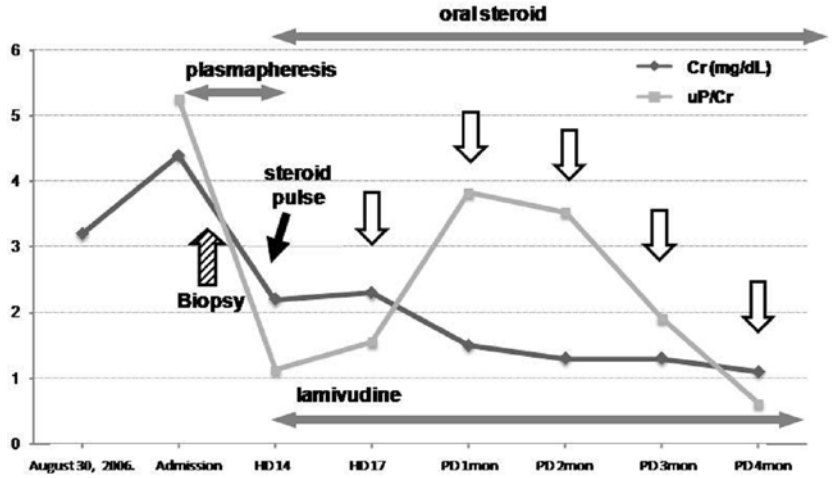

Fig. 2. Clinical course of a patient. Abbreviations : HD, hospital day; PD, postdischarge.

especially in chronic viral carrier patients. Reactivation of HBV after cytotoxic or immunosuppressive therapy in patients who are seropositive for HBsAg has been well documented[1-4]. Additionally, HBV reactivation can cause fatal fulminant hepatitis[5, 6].

The mechanism of acute hepatic injury by HBV reactivation after immunosuppressive treatment or chemotherapy has not been fully elucidated. It has been suggested that immunosuppression increases HBV replication and ultimately results in viral infection of hepatocytes. Withdrawal of immunosuppressive agents results in the destruction of infected hepatocytes due to immune function restoration. In cases of HBV reactivation, immunosuppressive therapy is often delayed or discontinued, leading to suboptimal treatment of nephropathy.

Lamivudine is an oral synthetic nucleoside analog that inhibits reverse transcription by causing chain termination of nascent viral DNA in HBV infected cells. Several studies have shown that prophylactic lamivudine treatment prevents HBV replication in HBsAg-positive patients with hematological malignancies or solid tumors who have received cytotoxic chemotherapy[7, 8]. Tang et al.[9] reported that lamivudine improves renal outcomes in patients with HBV infection and membranous nephropathy. In the case reported by Marco et al.[10], renal and hepatic functions were improved, and HBsAg was negatively conversed with lamivudine and steroids in a patient with acute hepatitis B and RPGN. To our knowledge, our case is the first to be reported with successful improvement of renal function as a result of treatment with high dose steroids, cyclophosphamide and prophylactic lamivudine in a patient with RPGN and chronic hepatitis B infection. The optimum duration of lamivudine therapy is not yet determined. Previous reports suggest that maintenance of lamivudine is recommended for at least four to six months following chemotherapy[7, 11, 12]. Others advocate that lamivudine should be maintained for one to two years because HBV has been seen to reactive even after 12 months following chemotherapy [13]. In the present case, since the patient was taking monthly cyclophsphamide treatments, lamivudine has been continued for over six months. Although lamivudine treatment in immunosuppressed patients is helpful, there is still a limit due to the emergence of lamivudine-resistant mutants. The cause of the resistance is due to a point mutation in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the virus′ reverse transcriptase, leading to the replacement of methionine (M) by valine (V) or isolencine (I) (M204V/I) within the polymerase domain. Previous studies reported that

20-40% of post-organ transplantation patients who were HBV carriers developed YMDD mutants in the first year of their transplantation[14, 15]. Chang et al.[16] also reported that YMDD mutation was present in 67% of patients with B viral hepatitis, following four years of lamivudine therapy. The present case did not show any signs of mutant formation up to the sixth month of lamivudine treatment. A long-term follow-up monitoring of mutant emergence may be necessary.

In conclusion, we report a case of RPGN with latent HBV infection treated successfully with high-dose steroids, cyclophosphamide, and prophylactic lamivudine. Prophylactic lamivudine can be effective in preventing the activation of HBV carrier with RPGN and should be considered whenever treatment with high-dose steroids or immunosuppressive therapy is initiated.

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