

SUCCESSFUL TREATMENT OF NEPHROTIC SYNDROME AND SEVERE RENAL FAILURE DUE TO HEPATITIS B VIRUS RELATED DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS, WITH IMMUNOSUPPRESSIVE DRUGS

HEPATİT B VİRÜSÜ İLE İLİŞKİLİ DİFFÜZ PROLİFERATİF GLOMERÜLONEFRİTİN OLUŞTURDUĞU NEFROTİK SENDROM VE CİDDİ BÖBREK YETMEZLİĞİNİN İMMÜNSUPRESİF İLAÇLARLA BAŞARILI TEDAVİSİ

Mustafa Balal, Neslihan Seyrek, İbrahim Karayaylalı, Saime Paydaş
Çukurova Üniversitesi, Tıp Fakültesi Nefroloji Bilim Dalı

SUMMARY

Chronic hepatitis B virus (HBV) associated glomerular disease are mainly membranous glomerulonephritis, membranoproliferative glomerulonephritis, essential mixed cryoglobulinemia, IgA nephropathy and diffuse proliferative glomerulonephritis. The pathogenesis of HBV related GN has been defined as chronic antigenemia and passive deposition of immune complex in glomeruli. We reported here a patient with liver cirrhosis and proliferative GN related with HBV.

A forty-one year old man, with history of hepatitis a 20 years ago was admitted to hospital due to generalized edema. Physical examination showed that ascites, pretibial edema and diminished pulmonary sounds. Laboratory investigations were as follows: BUN 86 mg/dl, creatinin 2.2 mg/dl, total protein 5 g/dl, serum albumin 2.3 g/dl, daily proteinuria 4g. and HbsAg positive. Liver and renal biopsy showed that cirrhosis, and diffuse proliferative glomerulonephritis. In this patient, nephrotic syndrome and dialysis requiring acute renal failure regressed with corticosteroid and cyclophosphamide treatment. In follow-up period after 12 months, his renal function was within normal limits and proteinuria was negative.

Key Words: Hepatitis B virus (HBV), nephrotic syndrome, acute renal failure

ÖZET

Kronik hepatit B virus(HBV) enfeksiyonu ile ilişkili glomerular hastalıklar arasında membranöz glomerulonefrit (GN), membranoproliferatif GN, esansiyel *mixt* kryoglobulinemi, IgA nefropatisi ve diffüzproliferatif GN sayılmaktadır.HBV ilişkili glomerulonefritlerin patogeneğinde, kronik antijenemi ve glomerulde immün komplekslerin pasif birikimi suçlanmaktadır. Burada HBV ilişkili karaciğer sirozu ve diffüzproliferatif glomerulonefriti olan bir olgu sunulmuştur.

Yirmi yıl önce sarılık hikayesi olan 41 yaşında erkek hasta ödem nedeni ile kabul edildi. Fizik incelemede asit, pretibial ödem ve akciğer seslerinde azalma saptandı. Laboratuvar incelemede; BUN 86 mg/dl, kreatinin 2.2 mg/dl, total protein 5 g/dl, serum albumin 2.3 mg/dl, günlük proteinüri 4 g idi. HbsAg pozitif olarak bulundu. Karaciğer ve böbrek biyopsisinde, siroz ve diffüzproliferatif glomerulonefrit saptandı. Bu hastada, nefrotik sendrom ve diyaliz gerektiren akut böbrek yetersizliği kortikosteroid ve siklofosfamid tedavisi ile geriledi. Oniki aylık takibinde böbrek fonksiyonları normaldi ve proteinürisi negatifti.

Anahtar Kelimeler: Hepatit B virüs, Kronik karaciğer hastalığı, nefrotik sendrom.

INTRODUCTION

Chronic hepatitis B virus (HBV) associated glomerular diseases are mainly membranous glomerulonephritis (GN) and membranoproliferative GN, essential mixed cryoglobulinemia, IgA nephropathy, diffuse proliferative GN(1). The pathogenesis of HBV related GN has been defined as chronic antigenemia and passive deposition of immune complex in glomeruli. Immune complexes are cleared from circulation by binding of C3b receptors on erythrocytes and the

erythrocytes are degraded in liver and spleen. In chronic liver disease, clearance of complexes is impaired and immune complexes with Fc receptors bind to mesangial cells and deposit in glomerulus(2). This mechanism may also explain the pathogenesis of hepatitis related GN. In children, hepatitis related GN is a benign disease and spontaneous remissions can be seen. Liver biopsies show chronic persistent hepatitis in majority of the patients. In adults, hepatitis related GN can be seen with chronic liver disease and

cirrhosis(3). We reported here a patient with liver cirrhosis and proliferative GN related with HBV. In this patient, nephrotic syndrome and dialysis requiring renal failure regressed with corticosteroid and cyclophosphamide treatment. In follow-up period after 12 months, his renal function was within normal limits and negative proteinuria

CASE

A forty-one year-old-man, with history of hepatitis 20 years ago, was admitted to hospital due to generalized edema since one-month. Physical examination revealed blood pressure of 140/90 mmHg, body temperature 36°C, heart rate 65 beats/min. Bilaterally pulmonary sounds diminished. Systolic ejection murmur, ascites and pretibial edema were detected. Laboratory investigation showed white blood count 4.800/mm³, hemoglobin 7.5 g/dL, hematocrit 22%, trombocyte 133.000/mm³, glucose 86 mg/dL, total cholesterol 213 mg/dL, HDL 44 mg/dL, LDL 142 mg/dL, triglyceride 136 mg/dL, total protein 5 g/dL, serum albumin 2.3 g/dL, AST 44 IU/L, ALT 46 IU/L, BUN 86 mg/dL, creatinine 2.2 mg/dL, Daily proteinuria was 4g. A serum protein electrophoresis revealed 34% albumin, 5.2% alpha-1 globulin, 15.7% alpha-2 globulin, 14.6% beta globulin and 30.3% gama globulin. Protrombin time was 18.2 sn. Serum complement levels were normal, ANA and anti DNA were negative. Hepatitis markers were negative for Anti Hbs and anti HCV, positive for HbsAg and titer of HBV DNA was 29 pg/mL. Peritoneal fluid culture was negative for bacteria, fungus and tuberculosis. Abdominal and thorax tomography showed pleural fluid, ascites and decrease in renal function. Inferior vena cava and renal arteriovenous Doppler ultrasonographies (US) were normal. Portosplenic Doppler US was significant for chronic liver failure and showed portal hypertension. Upper endoscopic examination did not reveal esophageal varices but antral gastritis was detected. Cirrhosis and diffuse proliferative GN were found in biopsies of liver and renal, respectively. Immunohistological staining for hepatitis B antigen was negative throughout the glomeruli.

With supportive therapy (ACEI, salt free diet, dipiridamol) his clinical status did not improve, hemodialysis was began. Due to severe renal disfunction and proteinuria, intravenous (IV) steroid (1 g/day) was started. IV pulse cyclophosphamide (500 mg/m²) was added to his treatment. After 6 weeks of immunosuppressive therapy serum BUN and creatinine decreased to 54 mg/dL and 1.4 mg/dL, respectively. His generalized edema resolved. Although renal function regained with immunosuppressive drugs, serum ALT levels incersed **and titer of HBV DNA**

rose to 83 pg/mL. An antiviral agent, Lamivudine, (100 mg/day) was given in addition to steroid and cyclophosphamide. In the third month of treatment, his blood pressure was normal, ascites and edema were not observed. Laboratory evaluation revealed BUN 16 mg/dL, creatinine 1.1 mg/dL, AST 26 IU/L, ALT 25 IU/L, total protein 5.8 g/dL, albumin 3.1 g/dL, hemoglobin 9 g/dL, white blood count 6400/mm³. Proteinuria disappeared and HBV titration was negative

DISCUSSION

The diagnostic criteria of HBV related GN has not been determined yet. Detection of serologic markers of HBV infection, immune-complex demonstration of GN with renal biopsy are supportive findings of HBV associated GN. Additionally, decline in complement levels may be seen approximately in 20-50 % of the patients(1). In our case, we did not demonstrate HBV antigens in renal biopsy specimen and his complement levels were within normal limits. Although serological marker of HBV infection could be seen in patients with HBV related GN, HBV antigens in the glomeruli are sometimes not detected. At autopsy studies, glomerular deposit of immune complex in hepatitis B carrier with symptom free individuals were found (1). This situation may be explained by temporary renal involvement of HBV. On the other hand, nonexistence of HBV antigen in glomeruli in patients with positive HBV markers suggests that these immune complex GN may be related to antigenemia other than HBV. Hepatitis related GN progresses more severe in adults and the possibility of serious liver failure may be explained with antigenic stimulus at porto-splenic shunts.

HBV-related GN may respond to high dose interferon therapy. In literature, it has been shown that treatment with interferon resulted in dramatic improvement of renal function. In a study of 40 patients, interferon treatment provided decline in proteinuria within 3 months and, disappearances of HbeAg and HbsAg from serum within 4-6 months and 10-12 months, respectively (4). But relapses were reported after cessation of interferon therapy (5,6). For this reason, it is necessary to define the exact dose and duration of interferon treatment. In patients with HBV related GN, interferon related nephrotic syndrome has been also reported. The patient with chronic active hepatitis due to HBV and HCV infection, had nonnephrotic proteinuria and microscopic hematuria. Nephrotic syndrome occurred 11 months after completion of interferon treatment and liver function tests were, normal at that time (5).

The use of corticosteroids in treatment of virus-related hepatitis infection has not been accepted. Since steroids may enhance virus replication and by this

manner they can cause severe liver failure. A short period of steroid treatment may be in cryoglobulinemia associated with chronic hepatitis infection.

In literature the improvement of renal function with corticosteroid therapy in a patient with HCV related membranous GN has been reported and his liver function had been kept within normal limits with steroid (7). Our case received steroid and cyclophosphamide and his renal function and his proteinuria became normal. But his liver function tests got worse and titer of HBV DNA increased. The addition of Lamuvidine decreased AST and ALT levels and changed positivity of HBV DNA to negative. The effect of Lamuvidine on renal function has not been observed in literature. We demonstrated corticosteroid induced virus replication could be treated with Lamuvidine. At last visit 12 months later his proteinuria and titer of HBV DNA were negative and his liver function tests were within normal limits. We did not use interferon because of good response to Lamuvidine.

In summary, HBV related GN presenting with renal failure and nephrotic syndrome could be treated with corticosteroid and immunosuppressive drugs even if those patients have diagnosis of cirrhosis. The monitoring of HBV DNA is necessary because if the titer of HBV DNA increases, antiviral drugs (Lamuvidine, etc) might be started.

REFERENCES

1. Willson RA. Intrahepatic manifestations of chronic viral hepatitis. *AJG* 1997; 92: 4-15.
2. Johnson RJ, Feehally J. Introduction to glomerular disease: Pathogenesis and classification. In: Johnson RJ, Feehally J (eds), *Comprehensive clinical nephrology*, 1st Ed. MOSBY Barcelona 2000, pp 20.
3. Johnson RJ, Burdmann EA, Ophascharoensuk V et al. Glomerular disease associated with infection. Johnson RJ, Feehally J (eds), *Comprehensive clinical nephrology*. 1st Ed. MOSBY Barcelona 2000, pp 30.
4. Lin CY. Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon. *Kidney Int* 1995; 47: 225-230.
5. Endo M, Ohi H, Fujita T et al. Appearance of nephrotic syndrome following interferon-alpha therapy in a patient with hepatitis B virus and hepatitis C virus co infection. *Am J Nephrol* 1998; 18:439-43.
6. Wong SN, Yu EC, Chan KW. Hepatitis B virus associated membranous glomerulonephritis in children-experience in Hong Kong. *Clin Nephrol* 1993; 40: 142-7.
7. Kurihara I, Saito T, Kakayama K et al. A case of hepatitis C virus associated membranous glomerulonephritis ameliorated by corticosteroid therapy. *Nippon Jinzo Gakkai Shi* 1998; 40: 290-4.