Case Report

Hepatitis B associated Membranoproliferative Glomerulonephritis successfully treated with Entecavir with brief review of literature

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Abstract
Membranoproliferative Glomerulonephritis (MPGN) associated with Hepatitis B virus has been treated by Interferon and Lamivudine in the past. With Interferon alfa there was no sustained improvement in fall of protienuria and resistance has been found in many series with Lamivudine on long term use. We are reporting a case of Membranoproliferative glomerulonephritis due to Hepatitis B virus successfully treated with Entecavir, and being a first case of its kind to be reported will help in creating further guidelines.

Introduction
Membranoproliferative Glomerulonephritis (MPGN) in adults have poor prognosis with half of patient developing end stage renal disease at 10 years. In various studies about 2-20% of patients have shown spontaneous remission. Most cases of MPGN are idiopathic; however it is also associated with a number of chronic infections like hepatitis B and C virus and a number of immune complex diseases. Source directed treatment has found to be effective in various studies. However any patient of MPGN associated with hepatitis B virus, treated with Entecavir has not been described yet.

We report a case of MPGN associated with hepatitis B successfully treated with Entecavir and patient has shown marked improvement in renal function and protienuria.

Case Report
A 40 years old female presented in OPD with complaints of pedal edema off and since one month, fever mild grade, not associated with chills and rigor with no diurnal variation since one month. Her blood pressure was 156/90 mm of Hg in right arm and pulse rate was 88 beats/min. On her routine examination total white cell counts were 6300/mm³ with Neutrophill 55% and Lymphocyte 45%. Her hemoglobin was 9.2gm/dl. Her platelet count was 2.8 lakhs/mm³. Her serum albumin was 2.9g/L, serum creatinine 1.4g/dl, urea 49mg/dl. Serum glucose, serum
cholesterol, SGOT, SGPT, Alkaline phosphatase, Gamma Glutamyl Transferase were within normal limits. C-reactive protein was 20.2 mg/L, chest X-ray PA view was normal. On urine routine examination 70-80 RBCs/high power field with no pus cells were present. On repeated urine examination RBCs were present persistantly. On ultrasonography bilateral renal parenchymal disease Grade I was present. Her spot urine albumin/creatinine ratio was 963 mcg/mg of creatinine and 24 hour urinary protien was 1259 mg/24 hrs. A provisional diagnosis of glomerulonephritis was suspected and she was planned for renal biopsy. Serum complement C3 was 0.72g/L (0.75-1.65); C4 <0.09g/L (0.20-0.65). C1-inhibitor-0.26g/L, (0.15-0.35) serum haemolytic complement (CH-100) < 26 units (300-770). Serum IgG-5.9 g/L, serum IgA-1.54 g/L (0.80-4.0) and serum-IgM was 7.81 g/L (0.50-2.0). Serum electrophoresis, ANA, ANCA, Anti GBM antibody, smooth muscle antibody (anti-Sm) and mitochondrial antibody were negative. On serological examination she was found to be HBsAg positive and was negative for HIV and HCV. On renal biopsy glomeruli were enlarged and capillary membrane thickening and increased cellularity in the mesangium was seen. Focal synechiae and occasional intermesangial hypercellular nodule were present. Presence of RBC cast and proteins was also noted in the tubules. Lymphocytes were present in the interstitium, all suggestive of Membranoproliferative glomerulonephritis. Figure 1 shows the histopathology of the renal biopsy. She was found to HBeAg positive and her viral load was 4610 IU/ml with a conversion factor of 1 IU equivalent to 5.82 copies/ml. She was started on Ramipril 10 mg daily and Furosemide 40 mg twice daily and Entecavir 0.5mg OD and patient showed gradual improvement clinically and became seronegative by the end of 9 months.

Discussion

MPGN especially in adults have poor prognosis with half of patient developing end stage renal disease at 10 years. Association between glomerular disease and Hepatitis B virus was first described by Coombes et al in 1975. The most common glomerular lesion is membranous nephropathy leading to nephrotic syndrome. However other lesions like minimal change nephropathy, IgA nephropathy, mesangial proliferative glomerulonephritis and Membranoproliferative glomerulonephritis have been reported. The pathogenesis is supposed to be immune complex mediated. The pathology is similar to type 1 MPGN demonstrating subendothelial deposits and mild grade of cellular proliferation. Immunoflorescence study shows deposition of IgM and IgG and may also show deposition of IgA and C3 deposits and HBsAg deposits may or may not be detectable. Complements level (C3 and C4) may be depressed.
Patients usually present with proteinuria that could be in nephrotic range and haematuria. 50% of the patients have hypertension at presentation and 20% have raised urea levels. Liver involvement in these patients may or may not be present. Immunosuppressive agents and steroids have not shown any improvement and prognosis is similar to MPGN due to other causes. The use of corticosteroid use has actually lead to the evolution of chronic active hepatitis. Furthermore, the appearance of virus-like particles have also been found histopathologically in the glomeruli after corticosteroid therapy which supports the serological evidence of viral replication. Chung et al have treated MPGN patients with interferon and found out that treatment lead to transient or persistent clearance of HBsAg but there was no improvement in proteinuria. A metaanalysis by Fabrizi et al showed that sustained remission of proteinuria could be seen only in 50 % of the patients suffering from membranous nephropathy who were successfully treated with antiviral therapy however no patient suffering from MPGN has shown any persistent improvement.

Lamivudine has advantages over interferon for HBV treatment, by having lesser side effects and ease of oral administration however prolonged lamivudine treatment has shown the emergence of drug resistance. Specific mutations (Val 552 Met and Met 528 Val) of the tyrosine, methionine, aspartate, aspartate (YMDD), nucleotide-binding locus of HBV polymerase result in significant resistance to lamivudine treatment. Though it was not possible to exclude connective tissue disorder or system lupus erythematosus, our patient did not show any extrarenal manifestation pertaining to the disease. Our patient had MPGN with pedal edema, hypertension and abnormal renal function suggestive of poor prognosis. We used one of the latest antiviral drug Entecavir and the results were extremely significant. Patient became seronegative by the end of 9 months. Her proteinuria decreased to 280 mg / day and there were no RBCs or RBC cast in the urine after the end of nine months of treatment.

Nephrotic syndrome due to Membranous nephropathy has been treated successfully by antiviral treatments in the past whereas treatment of Membranoproliferative glomerulonephritis has rarely been reported.

**Conclusion**

Hepatitis B virus (HBV) infection has been shown to induce several extra-hepatic lesions, especially through immune complex deposition in different organs, and renal involvement is one of the most important. The association between chronic HBV infection and glomerular diseases was first described by Combes et al. in 1971, and since then, vast observations have been reported by authors from all over the world. HBV associated nephropathy is one of the HBV infection manifestations that has provoked high sensitivities around the world, especially in terms of the management and treatment of the infection and the renal involvement. Treatment of HBV associated renal diseases is based on the treatment of underlying diseases and Membranoproliferative glomerulonephritis has been treated by Interferon and Lamivudine in the past. However no cases have been reported with Entecavir yet. We are reporting a case of Membranoproliferative glomerulonephritis due to Hepatitis B virus successfully treated with Entecavir.

**References**

1. Schmitt H, Bohle A, Reineke T, Mayer-Eichberger D, Vogl W. Long-term prognosis of Membranoproliferative Glomerulonephritis type 1. Nephron 1990; 55: 242-250
2. Combes B, Shorey J, Barrera A, et al. Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. Lancet. 1971;2(7718):234-7.
3. Lee HS, Choi Y, Yu SH, Koh HI, Kim MJ, Ko KW. A renal biopsy study of hepatitis B
virus-associated nephropathy in Korea. Kidney Int 1988; 34:537-543

4. Lai KN. Hepatitis B virus associated Glomerulonephritis in adults. Nephrology. 1996;2(Suppl. 1):S72-S9

5. Chan MK, Chan KW, Chan PCK, Fang GX, Cheng IKP. Adult-onset mesangiocapillary Glomerulonephritis: a disease with a poor prognosis. Q J Med 1989; 40(Suppl.35): 40-45

6. Lai KN, Tam JS, Lin HJ, Lai FM. The therapeutic dilemma of the usage of corticosteroid in patients with membranous nephropathy and persistent hepatitis B virus surface antigenaemia. Nephron 1990;54:12-7.

7. Lai FM, Tam JS, Li PK, Lai KN. Replication of hepatitis B virus with corticosteroid therapy in hepatitis B virus related membranous nephropathy. Virchows Arch A Pathol Anat Histopathol 1989;414:279-84.

8. Chung DR, Yang WS, Kim SB, Yu E, Chung YH, Lee Y, Park JS. Treatment of Hepatitis B virus associated Glomerulonephritis with recombinant human alpha interferon. Am J Nephrol 1997; 17: 112-117

9. Lisker-Melman M, Webb D, Di Biscegli AM, Kassianides C, Martin P, Rustgi V, Waggoner JG, Park Y, Hoofnagle JH. Glomerulonephritis caused by chronic hepatitis B virus infection: Treatment with recombinant human alpha interferon. Ann Intern Med 1989; 111: 479-483

10. Fabrizi F, Dixit V, Martin P. Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis. Aliment Pharmacol Ther 2006;24:781-8.

11. Lai CL, Ching CK, Tung AK, et al. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers: a placebo-controlled trial. Hepatology 1997; 25:241-4.