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Immune mediated crescentic MPGN secondary to HBV infection: A rare presentation for a common infection

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CASE STUDY

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ABSTRACT

Hepatitis B virus (HBV) infection presenting as crescentic glomerulonephritis in the absence of cryoglobulinemia is an extremely rare phenomenon. We report a case of a 44-year-old male with HBV infection, who underwent kidney biopsy for rapidly progressive renal failure and nephrotic range proteinuria. Histopathological evaluation of the kidney biopsy was consistent with immune complex mediated crescentic membranoproliferative glomerulonephritis (MPGN). The patient achieved complete renal and virological remission with steroids, plasmapheresis and antiviral therapy. This case report summarises the importance of early initiation of immunosuppression and plasmapheresis under antiviral coverage for improved clinical outcomes.

Key Words
Hepatitis B Virus, crescentic glomerulonephritis, crescentic membranoproliferative glomerulonephritis, MPGN

Implications for Practice:

1. What is known about this subject?
HBV infection presenting as crescentic glomerulonephritis in the absence of cryoglobulinemia is extremely rare. Presence of crescents and renal failure can influence the outcomes.

2. What new information is offered in this case study?
This case emphasises the need for a multidisciplinary approach (plasmapheresis and immunosuppression along with anti-viral therapy) for improved clinical outcomes with reduced morbidity and mortality.

3. What are the implications for research, policy, or practice?
Immunosuppressants along with antiviral agents may prevent the disease progression of crescentic glomerulonephritis associated with Hepatitis B virus infection.

Background

Hepatitis B virus (HBV) infection is a global public health problem. Approximately 240 million people are infected with HBV worldwide and roughly 600,000 die annually from HBV-related liver disease.[1,2] A variety of renal abnormalities like membranous nephropathy (MN), mesangial proliferative glomerulonephritis (MPGN), Immunoglobulin A (IgA) nephropathy, focal segmental glomerulosclerosis, and polyarteritis nodosa are associated with HBV infection.[3] Renal injury caused by HBV may be related to the glomerular deposition of immune complexes or virus-induced immune effectors.

Membranous nephropathy is the most common HBV-associated nephropathy and liver function may be normal or be mildly deranged.[4] In HBV-associated glomerulonephritis, though focal crescents may be seen, the presence of >50

per cent crescents is rare in the absence of cryoglobulinemia.

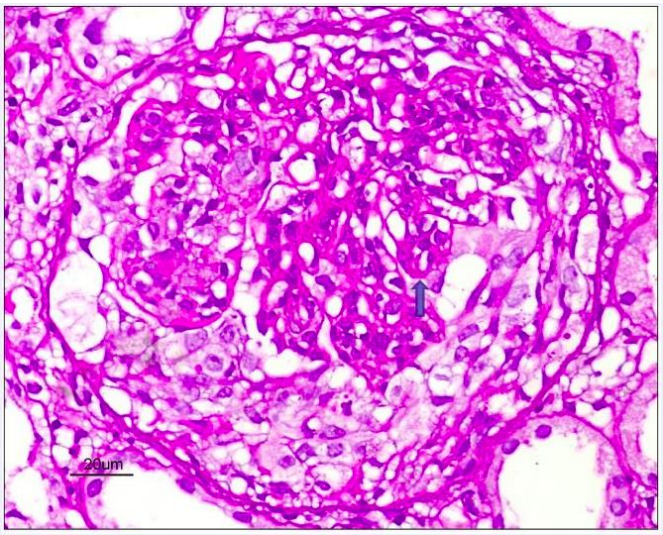
Case details

A 44-year-old male presented with facial puffiness and swelling in the lower limbs of one-week duration. On initial examination, his blood pressure was elevated (160/90mmHg). His investigation showed nephrotic range proteinuria (3,820mg), hypoalbuminemia (2.0g/dl), with active urinary sediment (urine RBC 40–45 cells/hpf and RBC casts), moderate renal dysfunction (serum creatinine–2.2mg/dl), normal serum bilirubin and elevated liver enzymes [AST–96IU/L (range 15–40 IU/L) and ALT–132IU/L(range 17–63IU/L)]. He had low serum C3 [34mg/dl (range 90–150mg/dl)], and C4 [2mg/dl (range 15–50 mg/dl)]. Anti-nuclear antibodies, Rheumatoid factor (RF), ANCA serology, anti-GBM, serum protein electrophoresis, and serum cryoglobulins were negative. Ultrasonography of abdomen showed normal-sized kidneys, normal liver echo texture, and portal vein diameter. Viral serology was positive for hepatitis B surface antigen (HBsAg) and hepatitis B envelope antigen (HBeAg) with high HBV DNA titres (9,97,94,782 copies/ml).

Antibodies to hepatitis B core antigen (Anti-HBc IgM) were negative. His renal function deteriorated and the patient had progressed to oliguria over the next 72 hours. A provisional diagnosis of rapidly progressive glomerulonephritis secondary to HBV was proposed. A percutaneous renal biopsy was performed, which demonstrated circumferential cellular crescents in (10 out of 11 glomeruli) with light microscopy (PAS stain) showing endocapillary proliferation and capillary wall showed double contoured basement membrane with no evidence of interstitial fibrosis or tubular atrophy (Figure 1). Immunofluorescence (IF) showed diffuse granular deposits of C3 (3+) and IgG (2+) along the capillaries and mesangium (Figures 2 and 3).

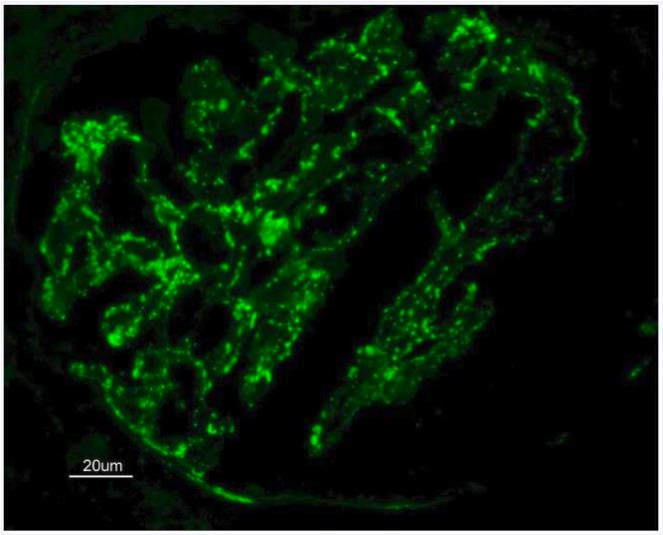
He was initiated on treatment (on fifth day after admission) with three doses of intravenous pulse methylprednisolone (500mg/day) and five sessions of plasmapheresis (over a period of 10 days) followed by oral steroids at 1g/kg under the cover of entecavir (0.5mg) modified according to his GFR. He was discharged on maintenance dose of steroids and entecavir. He was discharged after two weeks with stable serum creatinine of 2.8mg/dl, non-oliguric and blood pressure controlled (120/80mmHg). On follow up, his serum creatinine normalised to 1.2mg/dl at three months with complete remission in proteinuria by the end of six months. Steroids were tapered and stopped at six months. HBeAg seroconversion was negative at 10 months after initiation of anti-viral therapy. However, HBV DNA was undetectable by quantitative PCR and patient is still in complete remission with normal renal function (serum creatinine-1.2mg/dl) after eight months after stopping steroids. He is currently on entecavir (0.5mg once daily) therapy.

Figure 1: Light microscopy picture of renal tissue



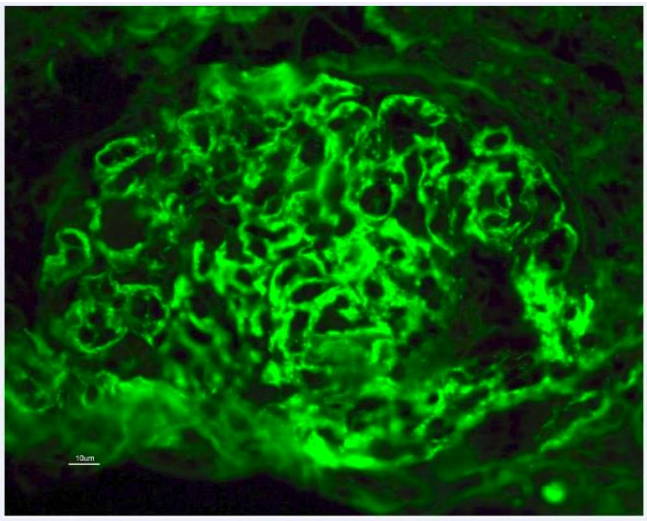
Circumferential active cellular crescent covering proliferative tufts with double contoured (arrow) basement membranes

Figure 2: Immunofluorescence picture of renal tissue for C3



Coarser granular deposits with C3 (3+) along the capillary walls and mesangium (x40)

Figure 3: Immunofluorescence picture of renal tissue for IgG



Coarser granular deposits with IgG (3+) along the capillary walls and mesangium (x40). Deposits in the capillary wall show smooth outer contours suggesting sub-endothelial location.

Discussion

The association between glomerulonephritis and chronic hepatitis B virus infection was first described in 1971 by Combes et al.[5] In a prospective study including patients with chronic HBV infection, an abnormal serum creatinine at baseline was significantly associated with increased mortality at six months with a hazard ratio (HR) for death of 5.23.[6] Hepatitis B virus-associated glomerulonephritis (HBVGN) is a typical immune complex glomerulonephritis mediated by deposition of hepatitis B antigen (HBsAg) and HBV antibody in the glomeruli. Various morphological patterns like MN, MPGN, mesangial proliferative glomerulonephritis, minimal change disease, and IgA nephropathy have been reported.[3] Among these, MN is the most common pattern of glomerular abnormality detected.

Several studies have reported a significantly higher carrier rate of HBsAg for both children and adults with MPGN. An 80 per cent and 87.5 per cent carrier state for HBV has been reported in children from Poland and in adults from South Korea, respectively.[7,8] Common clinical manifestations are nephrotic syndrome, microhematuria, and hypertension. Renal insufficiency was present in 20 per cent of the cases.[8] As in HBV-MN, patients with MPGN often do not have a history of clinical hepatitis despite having abnormal liver function tests.[8] Serum complement levels (C3, C4) are often depressed. Though we could not do the staining for HBsAg or HBeAg on our biopsy specimen (due to lack of availability of HBV antigen stains in our lab), the clinical scenario with which the patient presented and prompt response to antiviral therapy with renal remission correlating with virological remission (in the background of well-established relation between HBV infection and MPGN), a possibility of MPGN secondary to HBV infection has been considered in our case.

HBVGN rarely presents as rapidly progressive glomerulonephritis (RPGN). On renal biopsy, though focal crescents may be seen, histological evidence of >50 per cent crescents (crescentic MN) is an infrequent presentation and very few cases have been reported in literature.[9,10] Lai et al. reported two cases of chronic hepatitis B carrier state presenting with nephrotic syndrome and acute renal failure. One of them was diagnosed with crescentic glomerulonephritis with endocapillary proliferation who had a spontaneous remission despite persisting viraemia. The second patient, who was diagnosed with membranous nephropathy on first biopsy and responded to symptomatic therapy, later presented with recurrence of proteinuria and renal failure.

A second biopsy was done which showed crescentic transformation with mixed membranous and membranoproliferative glomerulonephritis.[9] There are no controlled studies regarding the efficacy of steroid or cytotoxic therapy in HBVGN. However, spontaneous remission rates in children with HBV-MN were similar to idiopathic MGN in uncontrolled studies.[11,12] Few patients with HBV-MN have been treated with interferon-alpha with suppression of HBV load and clearance of the HBeAg that resulted in either a complete or partial remission of nephrotic syndrome.[13–15] Hepatitis B is rarely associated with cryoglobulinemia, with prevalence ranging from 0–15 per cent.[16]

Enriquez et al. reported a case of cryoglobulinemic glomerulonephritis in a case of chronic hepatitis B infection. The patient presented with nephrotic syndrome and acute renal failure with MPGN type 3 pattern on renal biopsy. He was treated with lamivudine (100mg/day) for 48 weeks, three doses of intravenous pulse methylprednisolone (500mg) daily followed by oral prednisolone starting at 1mg/kg/day, seven sessions of plasma exchange, and mycophenolate mofetil (2gm/day) for a duration of six months. The patient achieved complete renal and virological remission.[17] No studies have been reported regarding the treatment of HBV-MPGN. Both interferon alpha and interferon beta have been tried in two patients HBV-MPGN and the one who received interferon beta achieved partial remission of proteinuria.[13]

Nasri et al.[18] reported a case of crescentic transformation of MPGN and HBV infection with high HBV DNA load. Patient achieved remission with steroids and lamivudine treatment. In our case, because the patient developed rapidly progressive renal failure with biopsy showing crescentic MPGN, he was given IV methyl prednisolone under the cover of entecavir followed by oral steroids and plasma exchange to decrease the immune complex burden. He was not treated with other cytotoxic drugs like cyclophosphamide in view of high viral load, fearing an acceleration of viral replication and increase in viral load with possible deleterious effects on liver and the kidney.

Conclusion

This case highlights the unique renal manifestations of HBV infection that can manifest and the need for a high degree of suspicion and low threshold for early renal biopsy which can deliver prompt diagnosis. It also emphasises the need for a multidisciplinary approach (plasmapheresis and immunosuppression along with anti-viral therapy) for improved clinical outcomes with reduced morbidity and mortality. This case encourages clinicians to treat crescentic glomerulonephritis aggressively, but with a balanced approach of combination of immunosuppression with antiviral agents even with high viral loads to prevent the progression to end-stage renal disease.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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PATIENT CONSENT

The authors, *Mareddy AS, Rangaswamy D, Vankalakunti M, Attur RP, Nagaraju SP, Koti N*, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.