Case Report

Successful treatment of hepatitis B virus (HBV)-associated membranoproliferative glomerulonephritis (MPGN) with alpha interferon

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Introduction

Adult-onset membranoproliferative glomerulonephritis (MPGN) has a poor prognosis with 50% mortality or development of end-stage renal failure (ESRF) at 10 years [1]. Spontaneous remission is seen in only 2–20% of patients (mean 6%). Nephrotic syndrome or renal impairment at presentation indicates a poor prognosis. Steroids or immunosuppressive therapy do not influence the rate of progression of renal failure. Anticoagulants, antiplatelet agents and plasma exchange have been shown to be of benefit in a few studies [2–4] but overall results are disappointing.

Although most cases of MPGN are idiopathic, it is associated with a variety of chronic infections and immune complex diseases. If a specific infection can be demonstrated, effective treatment may induce remission. For example interferon has been shown to be beneficial in hepatitis-C-associated disease [5]. There is much less evidence that treatment of hepatitis B virus (HBV)-related MPGN with interferon is effective and very few patients have been described [6,7].

We report a patient with HBV-associated MPGN who had a nephrotic syndrome and declining renal function. Treatment with alpha interferon was followed by remission with marked improvement in renal function, proteinuria and serum albumin.

Case

A 43-year-old man who was born in China and moved to the UK at the age of 23 years, presented with a 1-month history of generalized swelling, macular rash and hypertension. Nephrotic syndrome was diagnosed. He had been found to be a carrier of hepatitis B 7 years previously. There was no history of drug abuse, but he had received a number of vaccinations using reusable needles during the 1960s and 1970s. There was no past history of kidney disease, hypertension or diabetes mellitus.

Investigations

His 24-h urinary protein was 10.6 g/day, albumin 24 g/l, creatinine 157 μmol/l, urea 8.9 mmol/l, Hb 13.1 g/dl, white-cell count 6600, platelets 524 000, bilirubin 6 μmol/l, alkaline phosphatase 99 IU/l, AST 38 IU/l, gamma glutamyl transferase 202 IU/l, glucose 21.7 mmol/l, cholesterol 6.42 mmol/l, C-reactive protein <6.3 mg/l, chest X-ray was normal. Serum complement C3 was 0.73 g/l (0.75–1.65); C4 <0.06 g/l (0.20–0.65), C1 inhibitor 0.28 g/l (0.15–0.35); serum haemolytic complement (CH 50) <10 units (300–770); serum immune complexes were positive (C1q binding); rheumatoid latex test was positive; sheep cell agglutination test titre was negative; serum IgG 5.56 g/l (5.3–16.5), serum IgA 1.57 g/l (0.80–4.0) and serum IgM 7.62 g/l (0.50–2.0); serum electrophoresis, reduced gamma with no band detected; autoimmune screen, including nuclear antibodies, ANCA, anti-GBM antibodies, smooth muscle antibody and mitochondrial antibody were all negative. Cryoglobulins were weak positive.

HBsAg, HBeAg and HBeAg were detected. Hepatitis A IgM, HBc IgM and hepatitis C antibody were not detected.

Management and progress

He was started on enalapril 10 mg twice daily, frusemide 80 mg daily and tolbutamide 500 mg twice daily. On renal biopsy 11 of the 54 glomeruli were sclerosed. The glomeruli had diffuse hypercellularity with a marked increase in mesangial cells and matrix (Figure 1). The glomerular capillary loops were thickened.
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Over the next few weeks, his oedema increased and renal function deteriorated (creatinine 230 μmol/l). He was started on interferon alpha (Intron A, by Schering-Plough), 5 MU three times a week, in June 1996. He had some 'flu-like symptoms initially but otherwise tolerated the treatment well. There was a transient decrease in his white-cell count (to just under 3000) and a decrease in his platelet count (to around 100 000). His oedema improved and HepBeAg became negative in August 1996. HBV DNA, which was 1.7 pg/ml before starting the treatment, was no longer detectable. Renal function improved, proteinuria diminished and his serum creatinine and 24-h urinary protein were normal by November 1996. Serum albumin also increased back to normal (Figure 3). He had two of episodes of haematemesis in August and September 1996 and melaena in November 1996 requiring a blood transfusion. Endoscopy showed gastric varices. Interferon was stopped in November 1996 after 5 months of therapy because of poor diabetic control and persistent low platelet count. In December 1996 his HBsAg, HBcAg and HBeAg became positive again, and HBV DNA was detected using nested PCR. There was a transient increase in gamma glutamyl transferase (398 iu/l in August 1996) and AST (108 iu/l in August 1996) but they improved over subsequent months and were down to 45 iu/l and 81 iu/l respectively, in September 1997. His nephrotic syndrome remained in remission when he was last seen in September 1997, at which time his creatinine was 99 μmol/l, creatinine clearance was 92 ml/min and 24-h urinary protein was 0.1 g.

Discussion

The association between HBsAg and nephrotic syndrome was first reported by Coombes et al. in 1975 [8]. This is usually due to membranous GN but several studies report that patients with MPGN have a significant carrier rate of HBsAg [9]. The pathogenesis is thought to be immune complex mediated [10]. The renal lesion is similar to idiopathic type I disease with subendothelial deposits and mild cellular proliferation. Subepithelial and mesangial deposits can be seen, resembling MPGN type III. Immunofluorescence shows IgM and IgG deposition in most, and IgA and C3 deposits in some, patients. Although most patients are HBsAg positive, glomerular deposits of HBsAg may not be detectable. Serum complements C3 and C4 are often depressed and circulating immune complexes may be detected [9].

Patients commonly present with a nephrotic syndrome and microscopic haematuria. Almost half have hypertension and 20% have renal impairment. Many have abnormal liver function tests without a history of clinical hepatitis. Liver biopsy usually shows chronic hepatitis. Treatment such as steroid or immunosuppressive therapy is not effective and prognosis is
similar to idiopathic MPGN; for example, no difference in cumulative survival was found between steroid or immunosuppressive therapy treated and untreated patients in a retrospective study of 46 patients in Hong Kong [11], 20% of whom were HBsAg positive.

Alpha interferon has been shown to terminate viral replication and eradicate the carrier state in some patients with chronic hepatitis B infection. Loss of HBsAg occurred 6% more often and loss of HBeAg (indicating cessation of viral replication) 20% more often in interferon-treated patients as compared with controls in a meta-analysis of 15 controlled studies [12]. However, the value of interferon in HBV-related glomerulonephritis is not known. Chung et al. [6] treated eight patients with HBV-associated GN with alpha interferon for 6 months. Four of these patients had MPGN on renal biopsy; in all four serum HBsAg became transiently or persistently undetectable, but the proteinuria persisted. Two of these patients showed a transient decrease in proteinuria to less than the nephrotic range with seroconversion, but the other two did not. Serum creatinine levels did not change significantly during treatment. Lisker-Melman et al. [7] gave recombinant human alpha interferon to five patients with HBV-related GN for at least 6 months (four with membranous GN and one with MPGN). The four patients with membranous GN responded well and became negative for HB viral markers within 4–16 weeks, and 24-h urinary protein fell to less than 2 g/day at 1 year. However the patient with MPGN did not seroconvert. His 24-h urinary protein decreased during therapy but increased again after interferon was discontinued; he failed to respond to a second course of interferon.

Our patient was remarkable because there was almost complete remission of the nephrotic syndrome and this persisted despite the reappearance of viral markers in the serum when the interferon was withdrawn. Immune complexes were detected by C1q-binding assay before treatment, and the sustained remission may have been due to a change in their number or character such that they were no longer nephritogenic. It is not possible to prove this because they were not measured sequentially or characterized in detail.

The weak titre cryoglobulin and reduction of C3 and C4 are also consistent with immune complex disease, but several features are not typical of essential mixed cryoglobulinaemia: (i) only rheumatoid latex test was positive and sheep cell agglutination test titres were negative; (ii) no monoclonal band was detected on serum electrophoresis although total serum IgM was high; (iii) there were no other clinical features of cryoglobulinaemia; and (iv) electron-microscopy of the renal biopsy did not show any crystalline deposits.

Although it is not possible to exclude an inherited complement defect, there was no extra-renal manifestation to suggest connective tissue disease or systemic lupus erythematosus. Consumption of complements by immune complexes is much more likely.

In conclusion, there are few available data on the role of interferon alpha in the treatment of HBV-related MPGN. Our patient had a severe nephrotic syndrome with oedema, hypertension and deteriorating

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Fig. 3. Effect of interferon on plasma creatinine, plasma albumin and 24-h urinary protein.
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renal function suggesting a poor prognosis. Treatment with interferon alpha was followed within a few months by improvement in all these parameters and eventual complete remission of the nephrotic syndrome. The role of alpha interferon in the treatment of HBV-related MPGN requires further study. Meanwhile its use in HBV-related MPGN should still be considered experimental and it should be used with caution in view of a number of potential side-effects.

References


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