Novel treatment (new drug/intervention; established drug/procedure in new situation)

Hepatitis B virus related membranous glomerulonephritis and proteinuria treated with lamivudine and tenofovir

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Summary

Membranous glomerulonephritis is the most common histological renal lesion associated with hepatitis B virus (HBV) infection. The authors describe here a case of a patient presenting with the nephrotic syndrome and HBV infection but without progressive liver disease. The use of lamivudine and tenofovir resulted in arrest of proteinuria and stabilisation of renal function.

BACKGROUND

Hepatitis B virus (HBV) infection is a well-recognised cause of membranous glomerulonephritis (GN). Antiviral drugs are available to treat HBV infection and there are reports of remission of nephrotic syndrome with successful treatment of HBV in patients with evidence of both liver and renal disease. We describe how the use of antivirals slowed progression and reduced proteinuria in a man with hepatitis B with membranous GN without evidence of progressive liver disease. Combination therapy with lamivudine and tenofovir was successful without obvious nephrotoxicity or development of escape mutations.

CASE PRESENTATION

A 24-year-old man was found to have dipstick proteinuria during routine examination by his general practitioner in 1989. He had been well previously and took no prescription drugs. He had noticed ankle swelling a few weeks prior to presentation. He was referred to a renal physician for further evaluation.

Physical examination revealed mild pedal oedema, hypertension (blood pressure 154/100) and 3+ proteinuria on dipstick testing. Investigations revealed a serum albumin of 24 g/l, urinary protein excretion of 5.8 g/day, serum creatinine of 79 µmol/l and normal sized kidneys on ultrasound scanning. Screening for autoimmune illnesses and paraproteinaemia was negative. He was commenced on antihypertensive drugs and underwent a percutaneous renal biopsy which revealed membranous GN.

He presented a few months later with worsening oedema necessitating intravenous diuretic therapy. He commenced a course of high dose steroids (prednisolone 0.5 mg/kg for 6 months) but his protein leak remained high at around 12 g/day. His hepatitis status was checked during the steroid course and he was found to be hepatitis B surface and e antigen positive. His liver function tests were normal at this time and did not worsen on stopping the steroids. He was reviewed by the local hepatology team who did not recommend any further treatment be added at that time.

Nearly 2 years later, he developed elevated serum transaminases and was further evaluated in the regional liver unit. He remained hepatitis B surface and e antigen positive with a low HBV viral load of 71 pg/ml. His liver appeared normal on ultrasound examination and his liver biopsy showed mild portal and focal lobular hepatitis. He was treated with interferon-α 10 M units three times a week for 16 weeks. His liver enzymes normalised and a year later he became hepatitis B e-antibody positive. He was given a second course of low dose interferon-α (5 M units 3× weekly for 6 months) with the aim of complete viral clearance and development of hepatitis B surface antibodies. However, this treatment was poorly tolerated due to severe flu-like symptoms and nausea. The treatment resulted in a transient rise in serum transaminases, but he remained persistently hepatitis B surface antigen positive and hepatitis B surface antibody negative.

Throughout both phases of his interferon-α treatment he continued to have nephrotic range proteinuria. His hypertension was managed with progressively increasing doses of ACE inhibitors. His serum creatinine was 115 µmol/l and creatinine clearance was 99 ml/min on 24 h collection. A year after completion of interferon treatment his hepatitis viral load remained at a low level of 42 pg/ml with normal liver function tests. However, he continued to have heavy proteinuria (12 g/day) with preserved/low albumin and intermittent peripheral oedema. Between 7 and 12 g proteinuria persisted despite well-controlled blood pressure on four antihypertensive agents.

By 2002, his renal function had slowly declined with the creatinine rising to 283 µmol/l. Despite the low HBV viral load and normal serum transaminases, he remained hepatitis B surface antigen positive. He was seen by the authors and a repeat biopsy was performed, and renal histology revealed more advanced membranous changes, with the addition of some mesangial deposits and proliferation, making a diagnosis of immune complex GN with features of membranous and mesangiocapillary GN.

Figure 1 Graph of 1/creatinine ($\mu\text{mol/l}$) versus time. Diamonds pretreatment, crosses with tenofovir and lamivudine, triangles after stopping these drugs and open circles on entecavir. Dotted lines indicate the trendlines in each section.

TREATMENT

We felt that low level viral replication was the likeliest cause of the glomerular lesion identified at biopsy. Since his renal function was rapidly declining, he was commenced on a therapeutic trial of tenofovir 300 mg alternate day and lamivudine 50 mg alternate days, doses having been adjusted for impaired renal function.

OUTCOME AND FOLLOW-UP

Following this intervention, we observed a rapid slowing of the rate of decline of his renal function (figure 1). We also noted an improvement in urinary protein (figure 2) and a reduction in the number of antihypertensive agents required to control his blood pressure. He tolerated the combination of tenofovir and lamivudine between September 2002 and January 2008. However, in March 2008 he developed abdominal pain, vomiting and abnormal liver function tests and the antiviral agents were stopped. A diagnosis of cholecystitis was made and he underwent open cholecystectomy later that year and remained off antivirals. Having discontinuing antiviral medication his renal function declined and his protein worsened. His HBVsAg titres increased (311 pg/ml) and he was restarted on entecavir. Unfortunately, this was unsuccessful in preventing further decline in renal deterioration and he was commenced haemodialysis in August 2009.

DISCUSSION

HBV infection is a major public health problem with over 350 million chronic carriers worldwide.¹ The chronic carrier state occurs in up to 10% of infected subjects with the risk being higher if the infection is contracted in childhood. Hepatitis B related renal disease remains a major problem. It is present in ~5% of HBV carriers. Membranous GN was first described in the context of hepatitis B infection by Combes *et al* in 1971² and is the most frequently identified glomerular lesion associated with HBV infection. Mesangiocapillary GN has also been described.

The clinical course of HBV associated GN has been described in children and adults.^{3 4} While spontaneous remission of GN is well described in children, the majority of adults have either persistent proteinuria or slowly progressive renal failure. It has been suggested that in this context proteinuria might improve with treatment of hepatitis B but use of antiviral drugs in patients without deranged liver enzymes has only been described in one previous case.⁴

We were unable to find evidence of hepatitis B in this patient's kidney biopsy samples although identification of HBV antigens in patients with membranous GN is described in the literature.⁵ This disparity may reflect variation in immunohistochemical methodology, viral load or host factors.

Interferon- α and the viral DNA polymerase inhibitors (lamivudine, adefovir and entecavir) have been widely used in the treatment of hepatitis B. Interferon- α and lamivudine have been reported to be beneficial in the treatment of hepatitis B related membranous nephropathy. The results of trials with interferon- α for this indication, although promising in children,⁶ have been disappointing in adult subjects.^{7 8} Lamivudine has been used in nephrotic subjects with good outcomes⁹ and a recent meta-analysis suggests that lamivudine is appropriate first-line treatment.¹⁰

However, lamivudine monotherapy can lead to the early selection of a mutant HBV known as the 'YMDD' (based on the amino acid motif of part of the mutant viral DNA polymerase).¹¹ This is managed either by the addition or a switch to adefovir or entecavir. We were keen to avoid lamivudine resistance in a patient in whom prolonged therapy might be needed. Adefovir has been associated with renal tubular toxicity and worsening renal function in some studies,¹¹ and primary adefovir resistance has been recently described.¹²

Tenofovir has been used in subjects with cirrhosis following HBV infection¹³ and in HBV/HIV co-infection. Subjects who developed adefovir resistance, responded

Figure 2 Urinary protein leak declined on tenofovir and lamivudine but increased again on stopping antivirals.

to treatment to tenofovir.¹² It is reported as having better anti-HBV activity than adefovir.¹⁴ Tenofovir is not without renal problems and in the HIV population has been associated with proximal tubular defects and renal dysfunction.¹⁵ However, in this case we employed a reduced dose and with careful monitoring did encounter problems despite deranged renal function at initiation of therapy. We reasoned that long-term tenofovir monotherapy would be likely to encourage mutation and that moving to a combination of antiviral agents would give the greatest chance of successful treatment.

Therapy with a combination of lamivudine and tenofovir was associated with improvements in proteinuria and prolonged renal survival. This approach had led to an improvement in the patient's quality of life, continued employment and an unanticipated period without renal replacement. The annual cost of tenofovir and lamivudine for this patient was estimated as €3500 compared to ~€30 000 for haemodialysis.

We acknowledge that we cannot be completely confident that our intervention in this case was causally related to the marked change in his rate of renal decline, although the temporal relationship is suggestive. We have been unable to identify HBV antigens in his renal biopsy material to prove conclusively that his GN was related to his HBV infection. An alternative hypothesis is that the HBV and membranous GN are not linked and that spontaneous partial remission occurred. However, despite these limitations we feel that there is strong circumstantial evidence that this novel approach was effective and might be applicable in other cases. This lamivudine and tenofovir combination was well tolerated over a prolonged period, without escape mutation. The hypothesis that stopping low level viral replication might attenuate the progressive renal injury, even in those without a liver indication for antiviral treatment, merits further investigation.

Learning points

- ▶ Screening for HBV infection should be performed in all patients with renal biopsy proven membranous glomerulonephritis.
- ▶ HBV-associated membranous glomerulonephritis has been treated with interferon- and viral DNA polymerase inhibitors with varying success.
- ▶ Antiviral therapy should be considered for nephrotic patients to reduce proteinuria and its impact on renal function.
- ▶ Combination antiviral therapy such as lamivudine and tenofovir may prevent the development of escape mutations.
- ▶ Treatment doses of antiviral medication should be tailored to the individual patient's renal function to avoid further kidney injury.

Competing interests None.

Patient consent Obtained.

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