NDT Plus (2008) 5: 319–321
doi: 10.1093/ndtplus/sfn098
Advance Access publication 4 July 2008

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

Membranoproliferative glomerulonephritis associated with an Epstein–Barr virus infection

Lazarus Karamadoukis[1], Tibor Toth[2] and Charlie Tomson[1]

[1]The Richard Bright Renal Unit and [2]Department of Histopathology, Southmead Hospital, Westbury on Trym, Bristol BS10 5BW, UK

Abstract

Type 1 membranoproliferative glomerulonephritis (MPGN) is an immune complex-mediated disorder that has been associated with certain viral infections including hepatitis C, hepatitis B, hepatitis G, HIV and Hantavirus. We describe a patient with type 1 MPGN in native kidneys and nephrotic syndrome in whom there was strong evidence that a primary Epstein–Barr virus (EBV) infection played a causative role. This patient was treated with an angiotensin 2-receptor blocker and the nephrotic syndrome resolved within 6 months from presentation. Our case report suggests that MPGN presenting with nephrotic syndrome may have a relatively benign course when it is associated with an acute EBV infection.

Keywords: Epstein–Barr virus; membranoproliferative glomerulonephritis; nephrotic syndrome

Introduction

Membranoproliferative glomerulonephritis (MPGN) is a group of immune complex-mediated disorders characterized by common histopathological features. Type 1 MPGN has been associated with certain viral infections that stimulate chronic immune complex production, such as hepatitis C, hepatitis B, hepatitis G, HIV and Hantavirus [1]. We describe a patient with nephrotic type 1 MPGN in native kidneys in whom there was strong evidence that a primary Epstein–Barr virus (EBV) infection played a causative role.

Case report

A 54-year-old female presented with angina, progressive fluid retention and recent onset hypertension. Her past medical history included bacterial meningitis and recurrent urinary tract infections with a normal renal ultrasound and cystoscopy. Seven years previously, a persistent IgG lambda band had been detected in her serum that was too small to quantify with no urinary Bence Jones proteins (BJP). Her regular medications included ramipril 10 mg od, furosemide 40 mg od, lansoprazole 15 mg od, cefradine 250 mg od and beclometasone dipropionate metered inhaler prn.

On admission to hospital she was hypertensive (blood pressure 166/98 mmHg), had a pan systolic murmur consistent with mitral regurgitation and marked peripheral oedema but no elevation of jugular venous pressure. There was no rash and no peripheral lymphadenopathy, and examination was otherwise unremarkable.

Initial laboratory investigations revealed normal electrolytes, liver enzymes and excretory kidney function with serum creatinine 60 μmol/L. The serum albumin was 18 g/L, C-reactive protein 12 mg/L, haemoglobin 10.8 g/dl, white cell count 7.2×10^9/L, platelet count 572×10^9/L, mean corpuscular volume 89 fL and neutrophil count 4.4×10^9/L. Serological testing showed an atypical antineutrophil cytoplasmic antibody with a titre of 1:40, but specific ELISAs for antibodies to proteinase 3 and myeloperoxidase were negative. Tests for autoantibodies including antids DNA were also negative. Serum C3 complement was 0.62 g/dL and C4 0.14 g/dL. Serum electrophoresis showed an IgG lambda band that was too small to quantify, and an assay for BJP was negative. A random urinary protein to creatinine ratio (PCR) was 526 mg/mmol. An ultrasound showed kidneys that were normal in appearances with the right kidney measuring 12 cm and the left 13 cm.

A renal biopsy demonstrated enlarged and hypercellular glomeruli with lobulated tufts (Figure 1). There was mesangial expansion due to massive matrix accumulation and mesangial cell proliferation. The glomerular capillary wall showed a double contour and mesangial cell interposition. Immunostaining revealed intensive IgG, IgM, C1q and weaker C3 reaction along the mesangium and the peripheral segments of the glomeruli. These findings were consistent with MPGN type 1.

Computed tomography of chest and abdomen revealed no abnormalities apart from simple liver cysts. Hepatitis B surface antigen, hepatitis A IgM, hepatitis C antibodies and cryoglobulins were all repeatedly negative.

Correspondence and offprint requests to: Lazarus Karamadoukis, The Richard Bright Renal Unit, Southmead Hospital, Westbury on Trym, Bristol BS10 5BW, UK. Tel: +0117-959-5433; Fax: +0117-959-5432; E-mail: lazarus.karamadoukis@nbt.nhs.uk

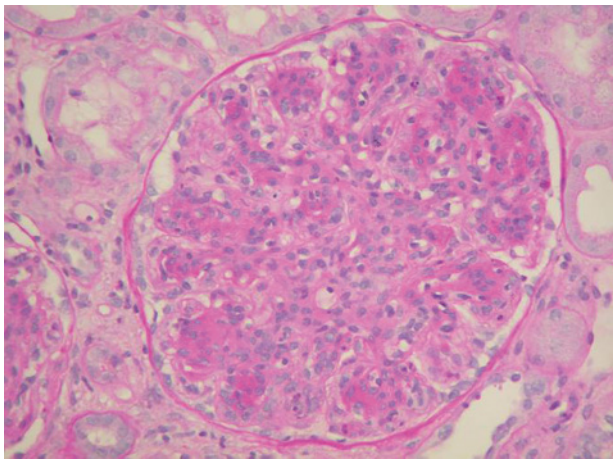

Fig. 1. Large hypercellular glomerulus with lobular appearance (periodic acid-Schiff stain, 200× magnification).

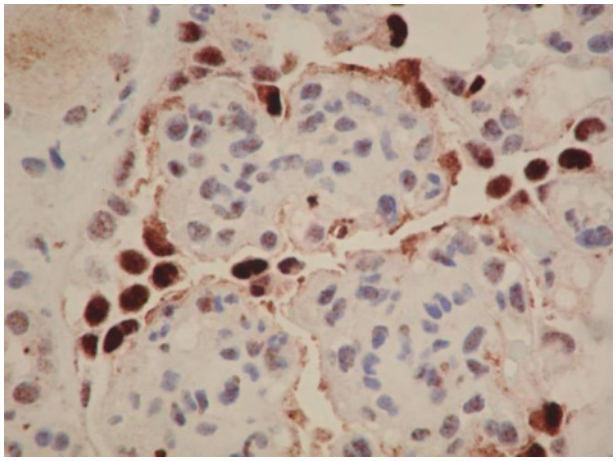

Fig. 2. Intranuclear EBV latent membrane protein immune reaction is seen in the glomerular epithelial cells (400× magnification).

The patient was treated with furosemide 250 mg twice daily and ramipril 10 mg daily that was changed to candesartan 16 mg daily because of a persistent cough. Urine protein excretion progressively fell, and 6 months later PCR was 27 mg/mmol. The furosemide was therefore discontinued. A viral hepatitis screening 1 year after presentation with nephrotic syndrome revealed a positive EBV nuclear antigen antibody and a positive EBV capsid IgG antibody, but a negative EBV capsid IgM antibody, consistent with the past EBV infection. When immunostaining was performed on paraffin sections of the renal biopsy using monoclonal mouse antibodies against the EBV-encoded latent membrane protein 1 (LMP1) obtained from Dako (Denmark), abundant EBV-infected glomerular epithelial cells were present (Figure 2).

Discussion

EBV is a member of the herpesvirus family that causes infectious mononucleosis and is implicated in the pathogenesis of certain lymphomas including post-transplant lymphoproliferative disorder. Although EBV infects primarily human B cells via the CD21 receptor, it could also infect renal tissue since the CD21 molecule has also been detected in proximal tubule cells of normal kidney [2]. An acute EBV infection has therefore been associated with the development of certain renal diseases such as acute interstitial nephritis [3], chronic interstitial nephritis [2] and nephrotic syndrome [4,5].

This case report describes a patient with nephrotic type 1 MPGN who also had serological evidence of past EBV infection. Immunostaining of the renal biopsy for EBV LMP1 confirmed the presence of abundant EBV-infected glomerular epithelial cells suggesting a possible association between the EBV infection and the development of type 1 MPGN. An acute EBV infection is known to cause a strong immune response that includes production of antibodies that form immune complexes and activation of complements, leading to hypocomplementaemia [6]. The deposition of these immune complexes in the glomerulus could induce glomerular damage and changes the characteristics of MPGN.

Andres *et al*. reported a patient with infectious mononucleosis who died of Gram-negative septicaemia complicated by oliguric renal failure [7]. The renal tissue demonstrated IgM and C3 mesangial granular deposits, mesangial electron dense deposits and infiltration of the interstitium by mononuclear cells including atypical lymphocytes. The presence of Paul–Bunnell antibodies and antigens was confirmed in the renal tissue.

Andresdottir *et al*. have reported a patient with type 1 MPGN who developed a recurrence of his disease after transplantation coinciding with a primary EBV infection [8]. Immunohistochemical examination of the biopsy of the transplant kidney for EBV viral capsid antigen demonstrated the presence of EBV in the cytoplasm of the glomerular podocytes. It was pointed out that the presence of viral antigens in the glomerulus does not necessarily establish a causal relationship between MPGN and acute EBV infection, since it may simply represent non-specific trapping of the antigen in the glomerular capillaries.

Finally, Lande *et al*. described a patient with immune complex-mediated glomerulonephritis and leukocytoclastic vasculitis associated with an acute EBV infection [6]. Immunochemical staining of the renal and skin biopsy failed to demonstrate the presence of EBV LMP1 in these tissues. However, this could be explained by the formation of immune complexes by other EBV antigens or endogenous antigens released by EBV-infected cells.

Previous case reports have suggested that nephrotic syndrome in patients with an acute EBV infection is usually self-limiting and resolves when the infection with EBV subsides [4,5]. Our case report also suggests that MPGN presenting with nephrotic syndrome may have a relatively benign course when it is associated with an acute EBV infection. A prospective study of EBV serology amongst patients presenting with MPGN would provide further information.

Conflict of interest statement. None declared.

References

1. Schena FP, Johnson RJ, Alpers CE. Membranoproliferative glomerulonephritis and cryoglobulinemic glomerulonephritis. In: Johnson RJ and Feehally J (eds). *Comprehensive Clinical Nephrology*. London: Mosby, 2003, 309–318
2. Becker JL, Miller F, Nuovo GJ *et al*. Epstein-Barr virus infection of renal proximal tubule cells: possible role in chronic interstitial nephritis. *J Clin Invest* 1999; 104: 1673–1681
3. Nadasdy T, Park CS, Peiper SC *et al*. Epstein-Barr virus infection-associated renal disease: diagnostic use of molecular hybridization technology in patients with negative serology. *J Am Soc Nephrol* 1992; 2: 1734–1742
4. Gilboa N, Wong W, Langent JA *et al*. Association of infectious mononucleosis with nephrotic syndrome. *Arch Pathol Lab Med* 1981; 105: 259–262
5. Blowey DL. Nephrotic syndrome associated with an Epstein-Barr virus infection. *Pediatr Nephrol* 1996; 10: 507–508
6. Lande MB, Mowry JA, Houghton DC *et al*. Immune complex disease associated with Epstein-Barr virus infectious mononucleosis. *Pediatr Nephrol* 1988; 12: 651–653
7. Andres GA, Kano K, Elwood C *et al*. Immune deposit nephritis in infectious mononucleosis. *Int Arch Allergy Appl Immunol* 1976; 52: 136–144
8. Andresdottir MB, Assman KJM, Hilbrands LB *et al*. Primary Epstein-Barr virus infection and recurrent type I membranoproliferative glomerulonephritis after renal transplantation. *Nephrol Dial Transplant* 2000; 15: 235–1237

Received for publication: 13.6.08
Accepted in revised form: 17.6.08