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Clinical Report

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Epstein–Barr virus-associated nephrotic syndrome

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Abstract
Acute infection with Epstein–Barr virus (EBV) causes fever, fatigue and pharyngitis. Renal involvement in systemic EBV infections typically manifests as acute tubular necrosis or tubulointerstitial nephritis. Rarely, EBV infection causes nephrotic syndrome due to minimal change disease. A 22-year-old male with infectious mononucleosis (IM) presented with nephrotic syndrome. Renal biopsy showed minimal change disease with diffuse foot process effacement of the podocytes. Treatment with methylprednisone led to rapid and complete clinical remission. Minimal change nephropathy is a very rare manifestation of EBV infection and should be considered in patients with IM and proteinuria.

Keywords: infectious mononucleosis; minimal change disease; nephrotic syndrome

Introduction

Epstein–Barr virus (EBV) commonly infects young adults and manifestations range from a benign course to infectious mononucleosis (IM). IM is a clinical syndrome of self-limited illness with a fever, pharyngitis and lymphadenopathy [1]. Subclinical renal involvement is common but renal parenchymal disease associations are very rarely reported.

The case

A 22-year-old male presented to his primary care physician with 1 week of fatigue, fever, sore throat, nausea and vomiting. Physical examination revealed tonsillitis. A rapid streptococcal throat test was negative and a diagnosis of IM was confirmed with a positive IgM antibody against the EBV capsid antigen. Rapid strep test was negative. Initial conservative management failed and tonsillitis worsened requiring two emergency room visits for dehydration. A urine analysis revealed normal microscopy but was significant for a random urine protein of 620 mg/dL, protein-to-creatinine ratio of 5.6 and predicted 24-h urine protein of 10.3 g. Subsequently, he was hospitalized with worsening tonsillitis, acute renal failure and proteinuria.

Physical exam revealed significant tonsillitis, periorbital swelling, bilateral lower extremity pitting edema and tachycardia. Laboratory investigations showed a normal complete blood count, creatinine and blood urea nitrogen. A total cholesterol and low-density lipoprotein cholesterol were elevated at 316 mg/dL (8.1 mmol/L) and 222 mg/dL (5.7 mmol/L), respectively. His serum total protein and albumin were low [4.6 g/dL (46 g/L) and 1.5 g/dL (15 g/L), respectively]. Subsequent blood evaluation for anti-deoxyribonuclease-B and anti-streptolysin titers were negative. Further evaluation included a negative anti-nuclear antibody and anti-neutrophil cytoplasmic antibodies screen, cryoglobulin and cryofibrinogen, normal C3 complement and mildly elevated C4 complement, 53 U/mL (normal: 15–45 U/mL). Cold agglutinins and anti-EBV-viral-capsid-antigen IgM were positive. IgG antibodies against the anti-EBV-viral-capsid-antigen were negative suggesting acute EBV infection. A CT scan of the head and neck did not show any peritonsillar abscesses.

A kidney biopsy was performed to further evaluate his proteinuria. Light microscopy showed well-preserved parenchyma and normal appearing glomeruli. Tubular epithelial cells contained protein re-absorption granules (Figure 1). Tissue immunofluorescence studies (IgA, IgG, IgM, C1q, C3, albumin, fibrinogen, kappa and lambda light chains) were negative. The mRNA (messenger RNA) *in situ* hybridization for EBV was negative. Electron microscopy revealed extensive effacement (>90%) of the foot processes of the visceral epithelial cells, consistent with minimal change disease (Figure 2).

The patient was commenced on dexamethasone 10mg on day one followed by a tapering dose of methylprednisolone beginning at 24mg per day, and tapered by 4mg daily to zero (starting at 16 mg/day) for persistent proteinuria and worsening tonsillitis. Three days after treatment was completed, he had marked improvement of sore throat and complete resolution of proteinuria.

Case discussion

Over 95% of adults worldwide become infected with EBV in their lifetime. IM is usually a clinical syndrome characterized by a self-limiting illness with fever, pharyngitis

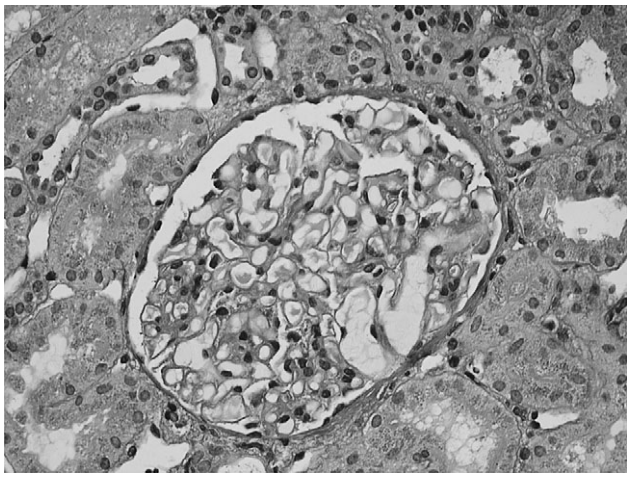

Fig. 1. Light microscopy showing normal glomeruli, renal tubules and interstitium. Tubular epithelial cells contained protein re-absorption granules.

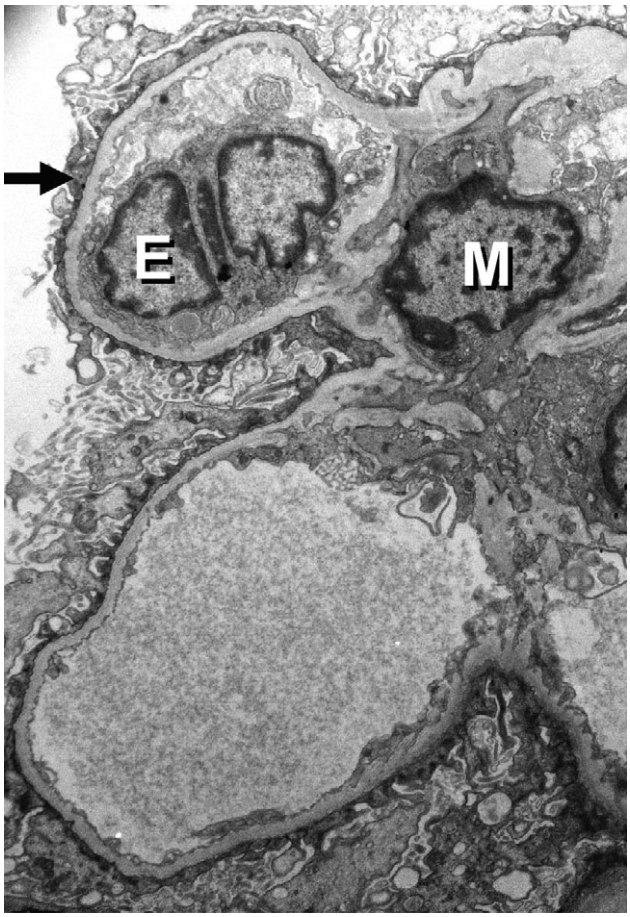

Fig. 2. Electron microscopy showing extensive effacement of podocyte foot processes (black arrow) (E, endothelial cells, M, mesangial cells, arrows point to foot process effacement).

and lymphadenopathy. The syndrome of IM usually occurs during the primary EBV infection [1]. Most recover without sequelae; however, several acute complications are associated with EBV.

Renal involvement can be seen in systemic EBV infections. Sub-clinical renal involvement is not uncommon; 16% of patients with IM have abnormalities in urinary sediment [2]. Acute kidney injury with significant parenchymal dysfunction is rare. This usually manifests as acute renal failure, rhabdomyolysis or immune complex glomerulonephritis and rarely minimal change disease, membranous nephropathy and cholemic nephrosis [2, 3].

A review of 27 cases of acute renal failure in heterophile positive IM by Meyer *et al.* [4], showed that 18% had rhabdomyolysis and myoglobinuria and one patient had minimal change disease. Only 13 of the 27 patients underwent kidney biopsies, 10 of whom had interstitial nephritis. Another two had immune-complex glomerulonephritis [4, 5]. In 1996, nephrotic syndrome was reported in a 19 month old infant with acute EBV infection. Proteinuria resolved after resolution of the viral infection. A renal biopsy was not done [6]. Two cases of EBV-associated renal failure were reported in 2000 and 2002 associated with interstitial nephritis and one of these also had minimal change disease [7, 8].

The pathogenesis of IM induced renal failure remains unclear. T lymphocytes may be activated having recognized EBV antigens in kidney tissue or there may be direct renal injury due to EBV [2]. Mayer's case review demonstrated a predominance of cases with cytotoxic T cells in the interstitium [4]. However, there was also evidence of EBV DNA detected by polymerase chain reaction (PCR) in renal tissue in patients with interstitial nephritis favoring direct virally mediated renal toxicity [9]. EBV receptors (CD21) were detected in proximal tubule cells and were up-regulated in the EBV-infected tissues [10].

In 2002, Okada *et al.* [8] reported a case of a patient with chronic active EBV infection who developed both acute tubulointerstitial nephritis and minimal change disease. Renal biopsy showed papillary infoldings of atypical tubular epithelium and lymphocytic interstitial infiltrates. EBV DNA was detected by PCR in some infiltrating lymphocytes but not in the tubular epithelial cells. It was proposed that EBV-infected T-cells activated other cells (educated T cells), which infiltrated into the interstitium and secreted cytokines and promoted tubular epithelial atypia and minimal change disease [8]. In our case, the kidney biopsy tissue was negative for EBV mRNA by *in situ* hybridization and there were no interstitial infiltrates.

Contrary to current literature where there is not strong evidence for steroid use in IM, our patient's nephrotic syndrome rapidly and completely responded to steroid therapy [1]. In conclusion, minimal change nephropathy is a rarely reported renal complication of IM with few cases reported and is exquisitely steroid responsive. IM should therefore be considered in all cases of minimal change disease preceded by viral prodromal illness.

Conflict of interest statement. None declared.

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