The Bench to Bedside Transition - Exceptional Case

Native kidney BK virus nephropathy associated with chronic lymphocytic leukaemia

Richard McCrory¹, Moyra Gray², Niall Leonard¹, John Smyth¹ and Alastair Woodman¹

¹Renal Unit, Ulster Hospital, Belfast, UK and ²Department of Pathology, Royal Group Hospitals, Belfast, UK

Correspondence and offprint requests to: Alastair Woodman; E-mail: alastair.woodman@setrust.hscni.net

Abstract
BK virus nephropathy (BKVN) is a well-recognized complication of renal transplantation. Several cases of native kidney BKVN following other solid organ or bone marrow transplants have been reported. We describe a patient with chronic lymphocytic leukaemia who presented with deteriorating renal function with no history of solid organ or bone marrow transplantation. Renal biopsy demonstrated tubular injury characteristic of viral infection, confirmed as BK virus by immunohistochemistry and elevated serum BK viral titres. Treatment with leflunomide reduced serum viral titres and stabilized renal function. This is the first biopsy-proven case of native kidney BKVN in a patient with no previous transplantation history.

Keywords: BK virus nephropathy; chronic lymphocytic leukaemia; leflunomide

Background

The BK virus is endemic in the human population, with a high seropositive prevalence in healthy individuals [1]. Primary infection in immune competent individuals occurs asymptomatically, and the virus remains dormant in the renal tract. BK virus nephropathy (BKVN) is a well-recognized complication following renal allograft transplantation and an increased incidence has been observed following the introduction of more potent immunosuppressive regimens [2]. There are case reports of BKVN affecting native kidneys in other solid organ and bone marrow transplant (BMT) recipients [3, 4], and various chemotherapeutic agents have been used to aid viral clearance in these patients, including the pyrimidine synthesis inhibitor leflunomide [5].

Case report

A 73-year-old Caucasian man was diagnosed with chronic lymphocytic leukaemia (CLL) in 1995 and received two courses of fludarabine, resulting in remission. He had a clinical relapse in January 2009 and was successfully treated with a further cycle of fludarabine. From that time, he required ongoing full-dose prophylactic intravenous immunoglobulin repletion for immunoglobulin deficiency.

He presented to the Nephrology Clinic in January 2010 with worsening renal function and his serum creatinine having climbed from 115 to 260 μmol/L over 9 months. Significant medical history included an 8-year history of Type 2 diabetes controlled with oral agents and mild pulmonary fibrosis treated with prednisolone since February 2009. There had been evidence of microalbuminuria in 2005 prompting commencement of an angiotensin-converting enzyme (ACE) inhibitor. The ACE inhibitor and metformin were discontinued prior to clinic assessment. Blood pressure at clinic was elevated at 174/90 mmHg. Imaging revealed normal-sized kidneys with a 4.5 cm simple cyst at the lower pole of the right kidney. Urinalysis revealed no blood or protein in the urine and autoimmune and vasculitic serological tests were negative. Immunoglobulin therapy was temporarily stopped, and a renal biopsy was performed.

Light microscopy demonstrated renal tubular cells with clumped intranuclear inclusions and extensive cytoplasmic vacuolation. There was focal interstitial fibrosis associated with these tubular changes and thickening of the tubular basement membranes. The glomeruli were normal and there was mild vascular arteriosclerosis. An immunohistochemical panel for viral infection stained strongly positive for polyomavirus large T antigen and localized to the renal tubules (Figure 1). Electron microscopic examination showed virus particles in the nuclei of renal tubular cells (Figure 2). There was no leukaemic infiltration identified.

Urine microscopy detected ‘decoy’ cells and quantitative polymerase chain reaction assay revealed a serum BK virus copy number of 4.8 × 10⁶ copies/mL (C/mL), establishing the diagnosis of BKVN (Figure 3). The patient was commenced on leflunomide 20 mg daily and viral load fell to <5000 C/mL after 6 months of therapy and eventually <150 C/mL 1 year post-diagnosis. Immunoglobulin therapy was reinstated for prophylaxis and leflunomide was eventually stopped in January 2011 following the development of thrombocytopenia and diarrhoea. Low viral titres were sustained. Estimated glomerular filtration rate stabilized between 15 and 19 mL/min/1.73m² for just over a year, but in March 2011, his clinical course was complicated by
recurrence of his leukaemia and he died from infective complications of his immunodeficiency 3 months later.

Discussion

This patient with a history of CLL and Type 2 diabetes presented with renal failure associated with a bland urinalysis and normal renal imaging. The differential diagnosis included tubular injury secondary to immunoglobulin treatment or previous chemotherapy, hypertensive nephrosclerosis or leukaemic infiltration of the kidney.

Acute renal failure secondary to intravenous immunoglobulin therapy has been reported in over 100 patients and can produce similar patterns of tubular epithelial cell injury with vacuolization seen under light microscopy as in this biopsy [6]. However, the intranuclear inclusion bodies visualized could not be explained by immunoglobulin therapy alone, prompting an investigation for a viral aetiology.

BKVN was an unexpected diagnosis and relied on biopsy-proven detection. There are a small number of case reports documenting an association between CLL and BK virus infection. Van de Bij et al. [4] reported a case of BKVN in a patient with CLL who had undergone BMT and had leukaemic involvement of the kidneys pre-transplant. Although treatment with leflunomide was established, the patient developed end-stage renal disease requiring dialysis soon after. Similarly, Boudville et al. [7] reported a patient with renal failure deemed attributable to leukaemic infiltration with no transplantation history; re-activation of BK virus in the biopsied tissue was also detected. Fogazzi et al. [8] also documented a patient with CLL and acute renal failure where BK virus copy numbers were elevated and ‘decoy cell’ shedding was noted on urine cytology, though a renal biopsy was unable to be performed to confirm the diagnosis.

This is the first reported case of native kidney BKVN in a CLL patient without any form of transplant. We also describe successful treatment with leflunomide and stabilization of renal function. The patient had multiple factors (CLL, fludarabine chemotherapy, immunoglobulin deficiency and prednisolone) contributing to his immunosuppressed state in 2009, potentially triggering activation of the BK virus.

Leflunomide and its active metabolites demonstrate potent in vitro activity against BK virus replication and have been successful in treating renal allograft BKVN [9]. Hepatic dysfunction and leucopenia commonly dictate intensity of therapy. Monthly immunoglobulin repletion was continued and there is evidence to suggest that human immunoglobulin contains neutralizing antibodies towards BK virus, which may aid viral clearance [10].

In conclusion, this case highlights BKVN as a differential diagnosis to be considered in selected groups of patients with CLL and Type 2 diabetes presenting with renal failure.
immunosuppressed patients presenting with deteriorating renal function and indicates a role for leflunomide in aiding viral clearance beyond its use in renal allograft recipients.

Acknowledgements. Transparency declaration. This case report was presented as a poster presentation at The British Renal Society/Renal Association Conference on the 8 June 2011 in Birmingham.

Conflict of interest statement. None declared.

References


Received for publication: 15.6.11; Accepted in revised form: 31.12.11