Case Report

Polyoma virus-associated interstitial nephritis in a patient with acute myeloic leukaemia and peripheral blood stem cell transplantation

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Introduction

In 1971, two human polyoma viruses, BK and JC, were isolated and named after the patients in whom they were first identified \cite{1}. BK virus (BKV) was isolated from the urine of a kidney transplant patient and JC virus (JCV) from the brain of a patient with Hodgkin’s lymphoma and progressive multifocal leukoencephalopathy. Primary infection with these DNA viruses occurs early in childhood and 70–80\% of adults are seropositive. After primary infection, BKV and JCV become latent in kidney and peripheral blood. Reactivation can occur spontaneously, but happens more commonly during cellular immune deficiency syndromes.

Renal failure due to BKV has been described in a child with cartilage-hair hypoplasia and Hodgkin’s lymphoma \cite{2} and in a patient with leukaemic infiltration of the kidney and polyoma virus infection \cite{3}. Reactivation of BKV has been associated with haemorrhagic cystitis in bone marrow transplanted patients \cite{4}. In renal transplant recipients, reactivation of BKV is increasingly recognized as a cause of severe renal-allograft dysfunction \cite{5}. However, tubulointerstitial nephritis due to BKV in the patient’s own kidneys remains a rare condition.

Case

A 28-year-old Caucasian woman (height 168 cm, weight 72 kg) was admitted in June 1999 due an increasing serum creatinine. The patient suffered from acute myeloic leukaemia, first diagnosed in 1995. She was severely and prolonged immunocompromised due to a haploidalidentical, T-cell depleted peripheral blood stem cell transplantation (PBSTC) in July 1998. Prior conditioning consisted of 12 Gy whole body irradiation and 120 mg/kg cyclophosphamide plus 10 mg/kg thiotepa. After transplantation, the patient suffered from recurrent episodes of cytomegalovirus (CMV) reactivation, which were successfully treated by ganciclovir and foscarnet. Her immunosuppressive medication at the time of discharge in September 1998 consisted of mycophenolate mofetil 2 g/day and prednisolone. Prednisolone was given in varying doses (maximally 30 mg/day) due to recurrent exanthema that was interpreted as mild chronic graft vs host disease of the skin. Total numbers of white blood cells were normal (4700–7500 cells/µl). However, lymphocytes were markedly reduced (200–300 cells/µl). A bone marrow biopsy in November 1998 had shown a complete remission of the acute myeloic leukaemia.

Creatinine and urea values constantly rose between January and June 1999 (from 102 to 296 mmol/l), which was attributed to drug toxicity. Therefore, ganciclovir and co-trimoxazole prophylaxis were stopped in May 1999 at a serum creatinine level of 236 mmol/l. Routine urinary diagnostic measures were carried out by urine dipstick, which showed inconsistently erythrocytes positive. CMV-early antigen was negative in this period.

On admission, physical examination showed no abnormalities. Laboratory evaluations revealed a serum creatinine concentration of 386 µmol/l and a serum urea concentration of 31.8 mmol/l. Tests for antinuclear antibodies were negative. Routine urinary diagnostic measures showed normal urinary sediment, normal amounts of electrolytes in the urine, a normal Addis count and no proteinuria. Cytology or Papanicolau staining was not performed, so decoy cells might have been missed. First, CMV-nephritis was suspected due to CMV-early antigen detection in blood cells (10 positive cells/500 000 blood cells). However, CMV-early antigen and cell culture in urine were
negative and also tests for urinary CMV DNA were negative. Ultrasound examination of the kidneys showed normal size of both kidneys (10 × 4 cm) with intensified echogenic renal parenchyma.

A kidney biopsy was performed and light microscopy showed, especially pronounced in the outer medulla, focally damaged tubular cells, some of which contained enlarged nuclei with basophilic inclusions. The tubules were surrounded by an oedematous interstitium sparsely infiltrated by some plasma cells and mononuclear cells (Figure 1A). Light microscopically and immunohistologically, first, a CMV infection was suspected. Immunohistological re-examination, however, gave negative results. Finally, the diagnosis of polyoma virus-associated tubular damage was suspected by electron microscopy (Figure 1C) and then was also confirmed by immunohistochemistry (Figure 1B). We then tested urine for BKV and found positivity for polyoma virus (BKV) DNA in urine. We did not test BKV DNA in plasma.

Treatment of polyoma virus-associated tubulointerstitial nephritis was started with cidofovir, which was given once at 5 mg/kg. However, the following day, the patient developed fever and pre-emptively was given antimicrobial therapy and the fever resolved. One day later, the patient became oligo-anuric and needed haemodialysis. After 2 weeks, renal biopsy was repeated to investigate whether polyoma-viral inclusions were still present, because the patient stayed completely anuric. Again, the kidney biopsy showed by light and electron microscopy as well as by immunohistochemistry, the presence of polyoma virions and, concomitantly, now, severe tubulointerstitial and glomerular scarring. The patient stayed on haemodialysis.

Discussion

We present a rare case of tubulointerstitial nephritis in the patient’s own kidneys due to BK polyoma virus infection in a severely immunocompromised patient who had received a T-cell depleted PBSCT with prior radioimmune conditioning. Renal biopsy revealed the unexpected diagnosis. In allogeneic bone marrow transplant recipients, BKV is a known but rare cause of haemorrhagic cystitis [4]. In renal transplant recipients, recurrent rejection episodes and high-dose immunosuppressive therapy, including tacrolimus and mycophenolate mofetil, are risk factors for manifest polyoma virus kidney graft infection, which has a poor prognosis for graft survival [5]. However, renal involvement of BKV in non-renal transplant recipients is a rare condition.

Most of the knowledge about BKV nephropathy is derived from renal transplant patients. Even though, asymptomatic polyoma virus infection in renal transplant recipients documented by urine cytology or serology is well known, but the clinical course of biopsy-proven tubulointerstitial nephritis is not well defined. The definite diagnosis can only be made histologically [5].
Currently, no established antiviral therapy is available. Lowering of the dose of immunosuppression to better control viral replication has been proposed [5,6]. This, however, was not possible in our PBSCT patient. Even after reducing the dose of immunosuppression in renal transplant recipients, it has been reported that BKV nephropathy was associated with graft loss in 45% of affected patients [6]. To save the patient’s kidney function, we therefore decided in favour of a treatment trial with cidofovir.

Cidofovir is an antiviral nucleotide analogue of cytosine with a broad spectrum against herpesviruses, papillomaviruses and poxviruses in vitro [7] and is approved for treatment of CMV infections in immunocompromised patients. Nephrotoxicity is the major treatment-limiting adverse event, but toxicity can be diminished by hydration and probenecid pre-treatment. Normal cidofovir elimination half-life is 3–4 h, but it increases to 45 h in renal failure [8]. Recently, cidofovir has been used against polyomavirus infection in a renal transplant recipient [9], but controlled studies are missing.

However, after cidofovir was given once at 5 mg/kg, our patient developed fever, persistent leukopenia and the treatment regimen was discontinued due to bone marrow toxicity. Control kidney biopsy disclosed that polyoma virus still persisted. A prolonged cidofovir treatment would have been required, at least. This perspective was no longer promising. The patient became anuric and needed maintenance haemodialysis.

In summary, we could show an unexpected cause of tubulointerstitial nephritis in a PBSCT patient that was not accompanied by haemorrhagic cystitis. With the use of new immunosuppressive regimens, like T-cell depletion, in bone marrow transplanted patients, polyoma virus-associated tubulointerstitial nephritis is an increasing entity that should be considered in the differential diagnosis of renal impairment in these patients. Cidofovir, though not approved, appears to be the only treatment option at present, as immunosuppression cannot be lowered in this condition.

Conflict of interest statement. None declared.

References