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Nephrology Dialysis Transplantation

Case Report

BK transplant nephropathy successfully treated with cidofovir

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Introduction

BK-virus-induced interstitial nephritis (BK nephropathy) is a recently recognized condition affecting renal allografts that may lead to graft failure [1]. BK-virus infection is endemic worldwide with seroprevalence rates in normal adults of 60–80% [1]. Risk factors for BK nephropathy include high levels of immunosuppression, particularly involving tacrolimus [2]. There is no established treatment other than reduction of immunosuppression to aid viral clearance, which risks acute irreversible rejection [3]. There are *in vitro* data showing that cidofovir inhibits BK virus replication, but there are no studies in renal transplant recipients [4]. We report a case of BK nephropathy successfully treated with intravenous cidofovir and a modest reduction in immunosuppression.

Case

A 47-year-old male with chronic renal failure due to an undefined chronic glomerulonephritis received a non-HLA matched kidney transplant from his wife in July 2001. BK virus was undetectable by polymerase chain reaction (PCR) in the donor's blood and urine following the transplant. The recipient's comorbidities included hypertension, hypercholesterolaemia, gastro-oesophageal reflux and gout. The initial immunosuppression used was prednisolone, sirolimus and tacrolimus as part of a clinical trial. There were no episodes of clinical rejection in the first 6 months post-transplantation. A biopsy performed at insertion and day 10 showed no evidence of rejection or BK viral infection. The only significant early complication was the development of type 2 diabetes mellitus. At 6 months his baseline serum creatinine level was 0.13 mmol/l (0.05–0.12 mmol/l).

Eight months following the transplant his serum creatinine rose to 0.18 mmol/l, confirmed on repeat testing. At that time he was receiving 2 mg of tacrolimus twice daily with a trough level of 9.5 μg/l (5.0–20.0 μg/l), sirolimus 8 mg daily with a trough level of 14 μg/l (10.0–20.0 μg/l) and prednisolone 5 mg daily. He underwent a renal biopsy which contained 10 glomeruli but no medulla. Histological examination showed multiple viral inclusions in tubular cell nuclei associated with an acute interstitial nephritis, consistent with BK viral infection (Figure 1A). Many tubular cells showed a viral cytopathic effect and cytoplasmic alterations with vacuolation. The biopsy corresponded to Drachenberg *et al.*'s [5] 'pattern B', with histological evidence of cytopathic changes and diffuse tubulo-interstitial inflammation and atrophy. Acute cellular rejection was considered less likely given the presence of inclusion bodies and the later biochemical improvement with a reduction of immunosuppression. Immunohistochemistry using an antibody against SV40 antigen (which cross-reacts with BK virus) was strongly positive for the viral inclusions (Figure 1B). Urine cytology showed decoy cells and using Drachenberg *et al.*'s grading there were 1–4 infected cells per cytospin. The urine PCR testing was positive for BK virus. The initial BK PCR assay on blood did not detect the virus. On retrospective testing of this sample with a more sensitive PCR assay, BK virus was present in the blood at 10 000 copies/ml. Hirsch *et al.* [6] found that the viral load in plasma increased to >7700 copies/ml in all patients who had histological evidence of BK nephropathy.

The patient's immunosuppression was reduced to a total of 2.5 mg tacrolimus daily, 5 mg prednisolone and sirolimus was ceased and replaced with mycophenolate mofetil 500 mg twice daily. He was treated with eight doses of 0.25 mg/kg intravenous cidofovir every 2 weeks. The standard dose of cidofovir used is 5 mg/kg and the dose chosen in this case was reduced to minimize the risk of nephrotoxicity [7]. The patient's serum creatinine level fell to 0.16 mmol/l following

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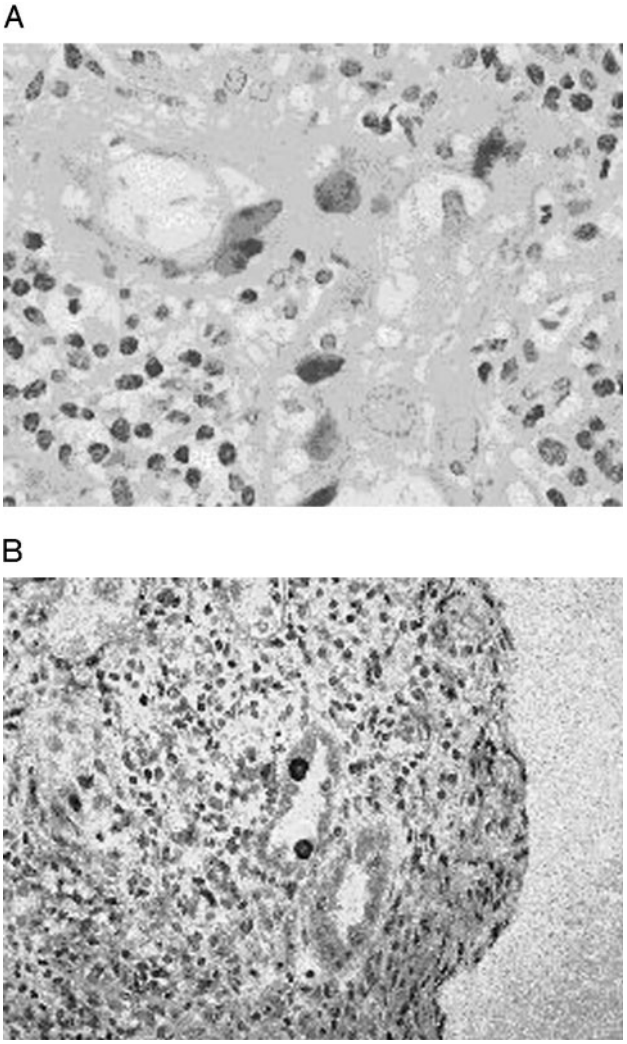

Fig. 1. (**A**) Haematoxylin and eosin stain 400× magnification showing viral inclusion bodies in tubular cell nuclei. (**B**) Immunohistochemical stain using SV40 antibody 200× magnification.

reduction of the tacrolimus and cessation of sirolimus. During the cidofovir treatment the serum creatinine fell further to 0.14 mmol/l and remained at that level 6 months after the course was completed. Following the cidofovir therapy, BK virus was undetectable on blood PCR. After the cidofovir therapy there were no decoy cells present in the urine, but the urine PCR remained positive. A repeat renal biopsy was performed 3 months after the initial biopsy. This specimen contained 15 glomeruli and showed resolution of the BK viral infection with a marked reduction in interstitial inflammation, absence of viral inclusions and cytopathic changes and negative SV40 immunohistochemistry.

Discussion

There have been limited descriptions of the use of cidofovir in the treatment of BK nephropathy [1]. This is the first report using intravenous cidofovir to show histological clearance of the BK virus and the associated interstitial nephritis in a renal transplant recipient. The persistent urine PCR positivity after treatment confirms the difficulty of relying on urine PCR alone to monitor disease activity. The absence of decoy cells following cidofovir therapy was a useful negative marker, as found by other larger studies [8]. While the modest reduction of immunosuppression may have contributed to the resolution of this process, this manoeuvre alone is usually unsuccessful [3]. We consider it most likely that cidofovir was crucial to the histological improvement seen in the second renal biopsy. The low level BK viral load may have aided the response to cidofovir. Further issues that arise from this case include the optimal dose and duration of intravenous cidofovir therapy.

Conflict of interest statement. None declared.

References

1. Lin PL, Vats AN, Green M. BK virus infection in renal transplant recipients. *Paed Transplant* 2001; 5: 398–405
2. Nickeleit V, Hirsch HH, Zeiler M *et al*. BK-virus nephropathy in renal transplants: tubular necrosis, MHC-class II expression and rejection in a puzzling game. *Nephrol Dial Transplant* 2000; 15: 324–332
3. Mylonakis E, Goes N, Rubin RH *et al*. BK virus in solid organ transplant recipients: an emerging syndrome. *Transplantation* 2001; 72: 1587–1592
4. Andrei G, Snoeck R, Vandeputte M *et al*. Activities of various compounds against murine and primate polyomaviruses. *Antimicrob Agents Chemother* 1997; 41: 587–593
5. Drachenberg RC, Drachenberg CB, Papadimitriou JC *et al*. Morphological spectrum of polyoma virus disease in renal allografts: diagnostic accuracy of urine cytology. *Am J Transplantation* 2001; 1: 373–381
6. Hirsch HH, Knowles W, Dickenmann MD *et al*. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. *N Engl J Med* 2002; 347: 488–496
7. Gonzalez-Fraile MI, Canizo C, Caballero D. Cidofovir treatment of human polyomavirus-associated acute haemorrhagic cystitis. *Transpl Infect Dis* 2001; 3: 44–46
8. Ramos E, Drachenberg CB, Papadimitriou JC *et al*. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. *J Am Soc Nephrol* 2002; 13: 2145–2151

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