NDT Plus (2009) 2: 250–253
doi: 10.1093/ndtplus/sfp003
Advance Access publication 9 February 2009

NDT PLUS
Nephrology Dialysis Transplantation

*Teaching Point*
(Section Editor: A. Meyrier)

# Life-threatening adenovirus infection in a kidney transplant recipient

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**Keywords:** adenovirus; kidney transplantation; cidofovir

## Introduction

Adenovirus causes 5–10% of all childhood febrile illnesses [1]. In the immunocompetent host, infection is usually associated with mild, self-limiting upper respiratory tract syndromes. Most individuals have serologic evidence of prior adenoviral infection by age 10 [1]. Following initial infection, adenovirus establishes lifelong latent infection in lympho-epithelial tissues [2].

In immunocompromised hosts, the spectrum of adenovirus infection can range from asymptomatic shedding to fatal disseminated disease [2]. It may represent primary infection, usually the case in paediatric transplant recipients, or reactivation of latent disease. Latent viruses may be of donor or recipient origin [2].

Adenovirus infection has been documented in solid organ transplantation, but is relatively rare and therefore a paucity of epidemiologic data exists. This case of adenovirus infection in a kidney transplant recipient is unusual for the severity of allograft dysfunction and the life-threatening nature of disease. It highlights the need for consideration of adenovirus as a cause of fever of unknown origin in the post-transplant setting. Potential therapeutic options are discussed, including use of cidofovir in a dialysis-dependent patient.

## Case report

A 68-year-old man with end-stage kidney disease from hypertensive nephrosclerosis underwent deceased donor kidney transplantation. The kidney donor was an adult male. Induction immunosuppression consisted of methylprednisolone, basiliximab, cyclosporine and mycophenolate mofetil. Maintenance immunosuppression included cyclosporine (target trough level 250–350 μg/L), mycophenolate mofetil (1 g bd) and a tapering dose of prednisolone. The postoperative period was unremarkable apart from lower urinary tract symptoms of frequency and strangury from the time of catheter removal. The patient was discharged on Day 6 post-transplantation with improving renal function (Figure 1). Valganciclovir was administered for cytomegalovirus (CMV) prophylaxis.

On Day 14 post-transplantation, the patient was readmitted with fever to 40°C and rigors. He described ongoing frequency and strangury, but denied macroscopic haematuria, respiratory symptoms, diarrhoea or conjunctivitis. Physical examination was unremarkable. Inflammatory markers were elevated [C-reactive protein 65 mg/L, white blood cell count $14 \times 10^3/\mu L$ ($14 \times 10^9$/L)]. Allograft function was stable (serum creatinine 150 μmol/L) and liver function was normal. Urine microscopy showed 40 white blood cells and >500 red blood cells, but no bacteria or growth on culture.

Broad-spectrum antibiotics were commenced, but fevers continued. Immunosuppression was halved. Blood cultures were persistently negative. Acute infections with CMV, Epstein-Barr virus (EBV), herpes simplex virus (HSV), toxoplasmosis and BK virus were excluded on the basis of negative DNA testing. Review of donor cultures and serology prior to death showed no active infection, and the recipient of the matching kidney was well.

Macroscopic haematuria developed, and allograft function deteriorated. The patient became progressively agitated, tremulous and confused. Lumbar puncture-derived cerebrospinal fluid (CSF) was acellular, with normal biochemistry. CSF polymerase chain reaction (PCR) testing was negative for CMV, HSV and EBV. The patient required admission to intensive care for mechanical ventilation and continuous haemodiafiltration.

Five days later, a urine sample collected near the onset of macroscopic haematuria returned PCR positive for

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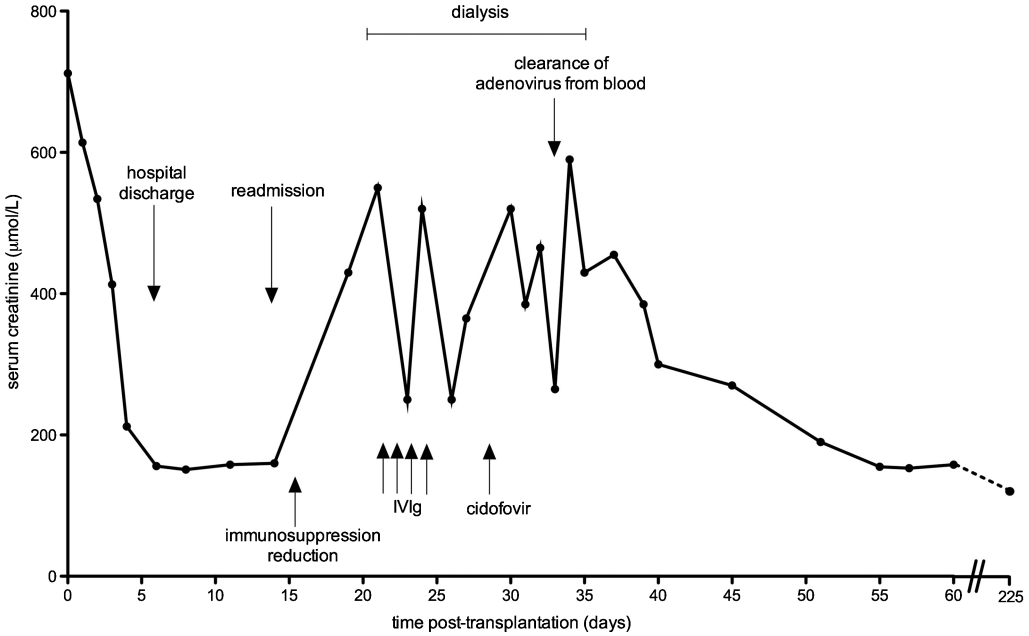


**Fig. 1.** Serum creatinine versus time post-transplantation.

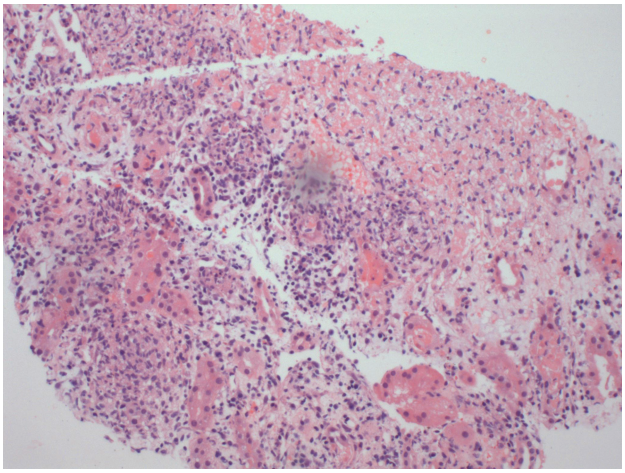

**Fig. 2.** Haematoxylin and eosin stain of a kidney allograft biopsy specimen showing severe, necrotizing tubulointerstitial nephritis with granulomas (original magnification ×100).

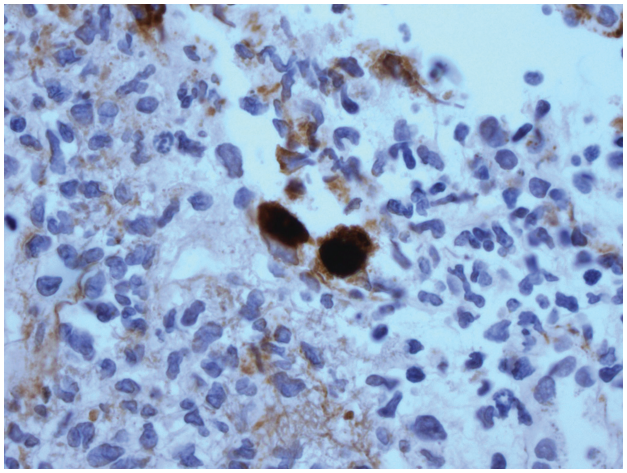

**Fig. 3.** Adenovirus immunoperoxidase stain showing strong nuclear and cytoplasmic staining of preserved tubular epithelial cells (original magnification × 400).

adenovirus. Subsequent blood PCR testing was also positive. The renal biopsy showed severe, necrotizing tubulointerstitial nephritis with granulomas (Figure 2). There was extensive tubular destruction with ∼60% of the cortical sample showing necrosis. Glassy intranuclear inclusions were seen in preserved tubular epithelial cells. Adenovirus immunoperoxidase stain showed positive nuclear and cytoplasmic staining in these cells (Figure 3). Adenovirus PCR on the renal tissue was positive. Stains for mycobacteria and fungi and immunoperoxidase stains for CMV and simian virus 40 were negative. An MRI of the brain was performed on suspicion of adenovirus encephalitis, but it showed only minor white matter changes. Adenovirus PCR on CSF was negative.

Four doses of intravenous immunoglobulin (IVIg) were administered (0.5 mg/kg/dose) without any change in the clinical condition of the patient. A Tc99m-labelled MAG 3 scan was performed to assess viability of the allograft, so that a non-viable kidney could be removed with the withdrawal of immunosuppression. It demonstrated delayed but adequate perfusion and uptake of tracer and because of the patient's strong desire not to return to dialysis, the graft was left *in situ*. A single dose of cidofovir (0.5 mg/kg) was administered.

Eight days later, PCR testing indicated clearance of adenovirus from blood. The patient spontaneously began to pass urine. There was no further macroscopic haematuria. Haemodiafiltration was ceased. There was gradual

improvement in allograft function and mental state, and the patient was discharged 1 month later. Blood adenovirus PCR remained negative although urine PCR was still positive. Creatinine was stable at 150–160 μmol/L (Figure 1). The patient remained well 8 months later.

## Discussion

This case illustrates the potential severity of adenovirus infection in kidney transplant recipients, and highlights the need for consideration of adenovirus infection as a cause of fever of unknown origin. It serves as a basis for discussion regarding potential therapeutic options, including the use of cidofovir in dialysis-dependent patients.

Adenoviral disease is well characterized in haematopoietic stem cell transplant (HSCT) recipients, with incidence ranging from 3 to 47% [2]. Reported clinical syndromes include pneumonia, colitis, hepatitis, haemorrhagic cystitis, tubulointerstitial nephritis and encephalitis. Disease is often disseminated, and the mortality rate for symptomatic patients approaches 26% [3].

Alternatively, adenovirus infection is a rare pathogen in solid organ transplant recipients. In kidney transplant recipients, the most common manifestation is haemorrhagic cystitis. A recent literature review [4] revealed 37 reported cases, 36 of which occurred within 1 year of transplantation. Thirty-four patients received high-dose steroids for treatment of symptoms of acute rejection. Four patients received antiviral medications. Disease was mild and self-limiting in all and no patient required dialysis. There was universal return of creatinine to near baseline [4,5].

Allograft biopsies have been performed in a minority of cases of adenovirus infection: the usual finding is non-specific lymphocyte infiltration or virus-like particles on electron microscopy [6]. There have been rare reports of necrotizing tubulointerstitial nephritis [7–9]. Treatment in these cases varied from IVIg [7] to reduction of immunosuppression [8] to cidofovir [9]. Despite severe changes on biopsy, near complete recovery of allograft function was seen in all.

Only three cases of life-threatening adenovirus infection in kidney transplant recipients have been previously reported. In 1975, Myerowitz *et al*. [10] reported a fatal case; while an autopsy study showed viral infection and cytopathic changes of allograft tubular epithelial cells, the predominant disease manifestation was diffuse interstitial pneumonia. Death occurred despite immunosuppression reduction. Rosario *et al*. [11] described colitis in a kidney transplant recipient, with adenovirus isolated from both blood and faeces. Intravenous ganciclovir was administered, but again disease was fatal. The third patient died of adenovirus pneumonitis despite supportive therapy, with post-mortem isolation of virus from the lung, kidney, gastrointestinal tract, heart and liver [12].

Adenovirus was detected in our patient in the urine, blood and renal allograft. Although the detection of viral DNA in the urine could represent asymptomatic urinary shedding, the clinical presentation and the detection of adenovirus DNA in the blood were consistent with disseminated adenoviral infection. It also portended severity of disease—consistent with experience in HSCT recipients—with viraemia predicting the development of disseminated or fatal infection [13].

Given the rarity of severe disease within this patient group, there was little literature to guide therapy. Thus, decisions regarding treatment were based largely on experience with severe viral infections in other immunosuppressed groups. The three treatment strategies utilized were reduction of immunosuppression, administration of IVIg and anti-viral therapy.

For kidney transplant recipients with adenovirus infection, immunosuppression reduction has been associated with viral clearance. Asim *et al*. [8] reported rapid normalization of allograft function and ultimately viral clearance in a patient with severe necrotizing allograft disease. However, reports in HSCT recipients with more severe disease have shown progression of viral load despite immunosuppression reduction [14]. We saw progressive allograft dysfunction and clinical deterioration despite a $>50\%$ reduction in immunosuppression, suggesting that this strategy alone was insufficient to control disease.

IVIg has been shown to be effective in prevention and treatment of CMV disease [15] and may have a role in treatment of BK nephropathy [16]. It is unknown whether its efficacy is the consequence of permitting a reduction of immunosuppression under a veil of immunotherapy or due to antiviral activity [16]. There is little documentation of use of IVIg as sole treatment for adenovirus. Bordigoni *et al*. [17] reported lack of efficacy of high-dose IVIg in HSCT recipients at high risk for disseminated disease. Given theoretical rationale and a good safety profile, we administered IVIg using a dosing regimen similar to that prescribed for BK nephropathy.

The best-tried antiviral agents for treatment of adenovirus infection include ribavirin and cidofovir although neither has been subjected to randomized, prospective trials. Ribavirin is a guanosine analogue, and while initial reports suggested *in vitro* anti-adenoviral activity, more recent data have shown variable results ranging from no activity to only limited activity against serotype C [5,18,19]. Case reports and small clinical series have also shown inconsistent results, confounded by use of concomitant additional therapies and different disease severities.

Cidofovir is a cytosine nucleoside analogue that inhibits viral DNA polymerase. It demonstrates broad *in vitro* anti-viral activity, including against a range of adenovirus serotypes. Clinical trials in HSCT recipients suggest favourable outcomes compared with retrospective controls [20,21]. The major limiting factor associated with cidofovir administration is nephrotoxicty and its use is generally contraindicated with renal impairment. However, cidofovir is highly concentrated in urine and renal tissue [22], suggesting that lower doses might be adequate for treating an infectious process localized to or originating in the kidney or lower urinary tract.

Reports exist of successful treatment with low-dose cidofovir in patients with renal impairment as a result of BK nephropathy [16]. There is one case report of use for adenovirus infection in a dialysis-dependent patient. Alsaad *et al*. [19] administered 100 mg IV cidofovir to a kidney transplant recipient who developed renal

failure as a consequence of adenovirus infection 12 years post-transplantation, with consequent improvement allowing cessation of dialysis.

We administered a single dose of 52.5 mg (0.5 mg/kg) IV cidofovir. Within 8 days, PCR testing indicated clearance of adenovirus from the blood. There are many possible explanations for this success: (1) the low-dose cidofovir exhibited anti-viral activity that eradicated the adenovirus; (2) delayed immune reconstitution from reduction of immunosuppression facilitated viral clearance; (3) the immunomodulatory effects of IVIg contributed and (4) the combination of treatments were successful. Likely, the latter was true. However, we believe that cidofovir may have played a significant role in clearing adenovirus infection, largely on the basis of documented success above other therapies in HSCT recipients with severe disease and because the time course between drug administration and viral clearance was consistent with previous reports. This report describes the first successful outcome of disseminated adenovirus infection in a kidney transplant recipient.

## Teaching points

Adenovirus infection is rare in kidney transplantation. While the most common manifestation is haemorrhagic cystitis, disseminated life-threatening disease can occur. It should be considered as a cause of fever of unknown origin.

(1) Therapeutic options include reduction of immunosuppression, administration of IVIg and anti-viral therapy. No therapy has been tried in a randomized, prospective manner.

(2) Dose-adjusted cidofovir can be safely used in patients with marked renal impairment and in combination with other less toxic therapies can lead to adenoviral clearance.

(3) Despite severe changes on biopsy, complete recovery of allograft function can occur.

*Conflict of interest statement*. None declared.

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*Received for publication: 3.1.09; Accepted in revised form: 6.1.09*