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Review Article

Disseminated adenovirus infection in kidney transplant recipient

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ABSTRACT:

Adenoviruses are common pathogens that have the potential to cause opportunistic infections with significant morbidity and mortality in immunocompromised hosts. The significance of adenoviral infection and disease is incompletely known in the setting of kidney transplantation. Reported adenovirus infections in renal transplant recipients have typically manifested as haemorrhagic cystitis and tubulointerstitial nephritis. Pneumonia, hepatitis and enteritis are often seen in other solid organ recipients. However, disseminated or severe adenovirus infections, including fatal cases, have been described in renal transplant recipients. There is uncertainty regarding monitoring and treatment of this virus. Although not supported by randomized clinical trials, cidofovir is used for the treatment of adenovirus disease not responding to reduction of immunosuppression. We present a case series of 2 patients with disseminated adenovirus infection in our centre who presented at different times from the time of transplantation.

CASE 1

The patient is a 70-year-old female with background of adult polycystic kidney disease (APKD), who received her first kidney transplant from a deceased donor in 2009. She was maintained on prednisolone (10 mg), tacrolimus (1 mg twice daily) and mycophenolate mofetil (500 mg twice daily). She presented to the hospital 27 months after kidney transplant with chills, rigors and fever up to 39.6°C for the previous 6 days. Subsequently she had loose, watery stool and haematuria. All basic septic screens at initial presentation were unremarkable. She was started on broad spectrum antibiotic with no significant improvement. Subsequently her urine, stool, blood culture and respiratory secretion were positive for adenovirus assessed by polymerase chain reaction (PCR). All her immunosuppression was withheld except for prednisolone.

She deteriorated clinically requiring ICU admission for haemodynamic instability with new onset atrial fibrillation (AF). Gradually her renal function declined from her baseline creatinine of 115 μmol/L and peaked at 232 μmol/L. She was treated with Cidofovir 3 mg/kg weekly for 3 weeks. Her kidney was subsequently biopsied which showed moderate interstitial infiltrates with moderate to severe tubulitis. No inclusion viral bodies were seen on light or electron microscopy. Immunofluorescence was negative for C4d.Immunohistochemistry was negative for BKV and CMV. She was treated with IVIG 0.1 mg/kg (total 10 doses).She made gradual recovery over few weeks and she cleared the adenovirus by PCR after 5 weeks of therapy with well-functioning graft with creatinine of 126 μmol/L.

CASE 2

The patient is a 60-year-old woman with ESRF secondary to polycystic kidney disease. She had been on PD for 4 months prior to undergo deceased-donor renal transplantation with a single HLA mismatch in 2013. The donor was CMV and EBV positive. Standard induction therapy was administered with basiliximab, prednisolone, mycophenolate mofetil and tacrolimus (0.05 mg/kg). Immediate postoperative care was unremarkable and a creatinine nadir of 49 μmol/L was seen within the first week. Protocol biopsy on day 12 revealed borderline cellular rejection with variable lymphocytic infiltrate and mild-moderate tubulitis with no change in serum creatinine. Immunofluorescence failed to show staining for c4d. She was treated with three doses of 500 mg IV methylprednisolone and repeat biopsy at day 29 showed no further evidence of rejection with a creatinine of approximately 50 μmol/L. Immunosuppressant dosage remained unchanged.

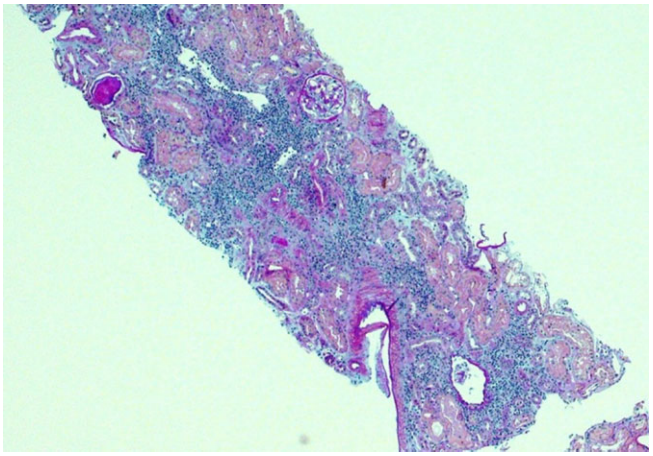

Fig. 1 Banff IIB vascular rejection.

Around 4 weeks post-transplant she began complaining of dysuria and frequency and fever of 40°C. She was treated empirically with amoxicillin/clavulanic acid but failed to grow a bacterial pathogen. After one week of oral antibiotics her symptoms did not improve and thus immunosuppression was reduced and a single dose of gentamicin (4 mg/kg) was administered, and a 7 day course of ciprofloxacin was commenced to cover protocol removal of the ureteric stent. After 3 further days of antibiotics and second negative urine culture, the patient developed diarrhoea and was admitted for inpatient management. Stool, plasma and urine specimens were positive for adenovirus confirming suspicion of systemic adenovirus. Given the well-matched donor, and concern for progressive and high risk adenovirus infection, immunosuppression was reduced further. With severe, almost half-hourly urinary frequency and dysuria, in spite of being systemically well with a normal white cell count, cidofovir was commenced at 1 mg/kg thrice-weekly intravenous infusions. The dysuria and diarrhoea slowly improved after one week of therapy. Serum and plasma adenovirus was undetectable by PCR after the fourth infusion although the virus continued to shed through the urine and stool albeit reduced by 2–3 logs in semi-quantitative analysis.

Subsequently her clinical condition deteriorated with the development of high grade temperatures and severe malaise and worsening renal transplant function. This had not been a feature of her initial presentation and raised concern about cidofovir toxicity necessitating immediate cessation. Over the subsequent 3 days, she developed a renal tubular acidosis and her creatinine rose sharply to 170 μmol/L. Abdomino-pelvic CT showed evidence only of mild perinephric stranding and no obstruction. Her creatinine rose to 238 μmol/L the following day and renal biopsy performed showed Banff grade IIB vascular rejection (Fig. 1) with moderate interstitial inflammatory cell infiltrate and moderate tubulitis. There was also evidence of moderate peritubular capillaritis. Electron microscopy and fluorescence failed to show evidence of viral inclusions and stains for BKV, CMV or HSV were negative. Immunofluorescence was negative for C4d. Because of concerns about rejection in the face of possible ongoing viral nephropathy and possible nephrotoxicity from cidofovir, intravenous immunoglobulin (IVIG) was administered at 1 mg/kg weekly and the cidofovir stopped. Over the following 3 days, her fever settled immediately and her creatinine, after peaking at 339 μmol/L, begun to fall sharply. By day 5 her creatinine had fallen to 175 μmol/L, she remained afebrile and her systemic malaise had improved. Her creatinine timeline and therapy as shown in Fig. 2. Discharged home for convalescence, the patient continued to receive a further 3 weekly doses of IVIG (1 mg/kg) and her creatinine continued to fall such that 3 weeks post biopsy the creatinine was 127 μmol/L. Adenovirus PCR remains positive in the urine and respiratory secretions however have been undetectable in the serum and plasma since the last day of cidofovir. Repeat transplant biopsy at day 98 did not show ongoing vascular rejection or viral inclusions but there was a mild ongoing cellular infiltrate.

DISCUSSION

These cases illustrate the potential severity of adenovirus infection in kidney transplant recipients, and highlight the need for consideration of adenovirus infection as a cause of fever of unknown origin in such patients. They also illustrate that disseminated adenovirus infection can present early as well as late from the time of transplantation. Both cases also illustrate the potential renal toxicity of cidofovir.

Adenoviral disease is well characterized in haematopoietic stem cell transplant (HSCT) recipients, with incidence ranging from 3% to 47%.[1] 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%.[2]

However adenovirus is a rare pathogen in solid organ transplant recipients. In kidney transplant recipients, the most common manifestation is hemorrhagic cystitis which both of our patients presented with. A recent literature review[3] 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.[3,4]

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.[5] There have been rare reports of necrotizing tubulointerstitial nephritis.[6–8] Treatment in these cases varied from IVIG[6] to reduction of immunosuppression[7]

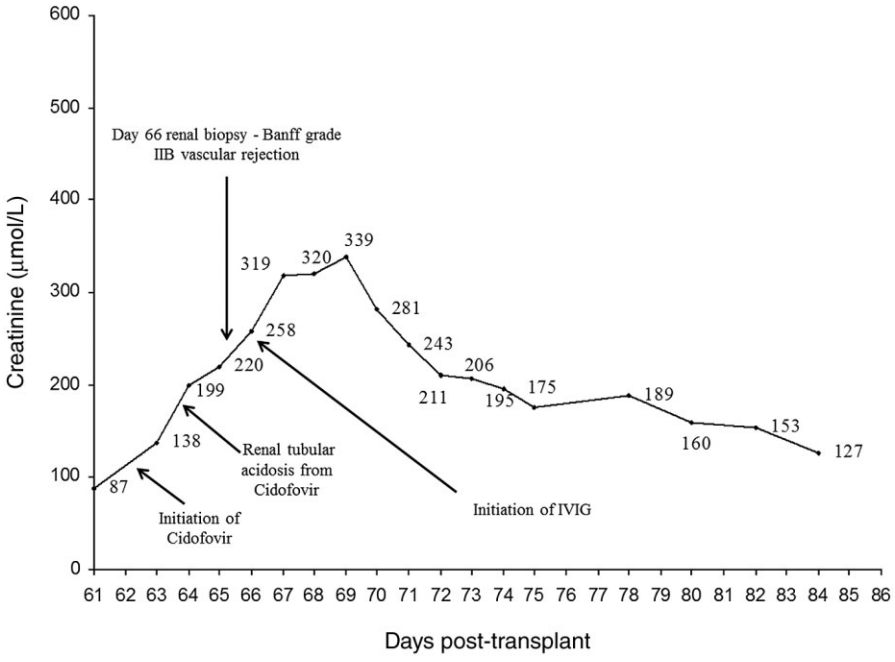

Fig. 2 Creatinine timeline.

to cidofovir.[8] Despite severe changes on biopsy, near complete recovery of allograft function was seen in all. Both of our patients had lymphocytic infiltration which could have represented cellular rejection or viral nephropathy. However patient 2 had definite evidence of vascular rejection.

Only three cases of life-threatening adenovirus infection in kidney transplant recipients have been previously reported. In 1975, Myerowitz *et al*.[9] 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*.[10] 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.[11]

Adenovirus was detected in our patients 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.[12]

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 used 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*.[7] 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.[13] 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[14] and may have a role in treatment of BK nephropathy[15] and also rejection. 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.[15] There is little documentation of use of IVIG as sole treatment for adenovirus. Bordigoni *et al*.[16] 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 to both patients using a dosing regimen similar to that prescribed for BK nephropathy. In patient 2, the IVIG was also considered as treatment for her histologically documented vascular rejection.

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.[4,17,18] 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* antiviral activity, including against a range of adenovirus serotypes. Clinical trials in HSCT recipients suggest favourable outcomes compared with retrospective controls.[19,20] 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,[21] suggesting that lower doses might be adequate for treating an infectious process localized to or originating in the kidney or lower urinary tract. This was the approach used in both of our patients.

Reports exist of successful treatment with low-dose cidofovir in patients with renal impairment as a result of BK nephropathy.[15] There is one case report of use for adenovirus infection in a dialysis-dependent patient. Alsaad *et al*.[18] 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.

In conclusion, both of our patients presented with disseminated adenovirus infection at different times from their kidney transplantation and had significant clinical deterioration and successfully treated with cidofovir and IVIG. They both had well-functioning grafts at the end of the disease course. The second case, although she had concomitant rejection and viral nephropathy demonstrated the potential toxicity of cidofovir with drug induced fever and renal tubular acidosis as well as increased creatinine. These settled dramatically after cessation of the cidofovir.

REFERENCES

1. Ison MG. Adenovirus infections in transplant recipients. *Clin. Infect. Dis.* 2006; **43**: 331–9.
2. La Rosa AM, Champlin RE, Mirza N *et al*. Adenovirus infections in adult recipients of blood and marrow transplants. *Clin. Infect. Dis.* 2001; **32**: 871–6.
3. Hofland CA, Eron LJ, Washecka RM. Hemorrhagic adenovirus cystitis after renal transplantation. *Transplant. Proc.* 2004; **36**: 3025–7.
4. Hoffman JA. Adenoviral disease in pediatric solid organ transplant recipients. *Pediatr. Transplant.* 2006; **10**: 17–25.
5. Kim SS, Hicks J, Goldstein SL. Adenovirus pyelonephritis in a pediatric renal transplant patient. *Pediatr. Nephrol.* 2003; **18**: 457–61.
6. Tomoe H, Onitsuka S, Nishino S *et al*. Adenovirus-induced kidney graft pyelonephritis following renal transplantation. *Hinyokika Kiyo* 1994; **40**: 1005–8.
7. Asim M, Chong-Lopez A, Nickeleit V. Adenovirus infection of a renal allograft. *Am. J. Kidney Dis.* 2003; **41**: 696–701.
8. Alsaad KO, Tobar A, Eet B. al. Late-onset acute haemorrhagic necrotizing granulomatous adenovirus tubulointerstitial nephritis in a renal allograft. *Nephrol. Dial. Transplant.* 2007; **22**: 1257–60.
9. Myerowitz RL, Stalder H, Oxman MN *et al*. Fatal disseminated adenovirus infection in a renal transplant recipient. *Am. J. Med.* 1975; **59**: 591–8.
10. Rosario RF, Kimbrough RC, Van Buren DH *et al*. Fatal adenovirus serotype-5 in a deceased-donor renal transplant recipient. *Transpl. Infect. Dis.* 2006; **8**: 54–7.
11. Ardehali H, Volmar K, Roberts C *et al*. Fatal disseminated adenoviral infection in a renal transplant patient. *Transplantation* 2001; **71**: 998–9.
12. Echavarria M, Forman M, van Tol MJ *et al*. Prediction of severe disseminated adenovirus infection by serum PCR. *Lancet* 2001; **358**: 384–5.
13. Kadambi PV, Josephson MA, Williams J *et al*. Treatment of refractory BK virus-associated nephropathy with cidofovir. *Am. J. Transplant.* 2003; **3**: 186–91.
14. Farrugia E, Schwab TR. Management and prevention of cytomegalovirus infection after renal transplantation. *Mayo Clin. Proc.* 1992; **67**: 879–90.
15. Sener A, House AA, Jevnikar AM *et al*. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: One-year follow-up of renal allograft recipients. *Transplantation* 2006; **81**: 117–20.
16. Bordigoni P, Carret AS, Venard V *et al*. Treatment of adenovirus infections in patients undergoing allogeneic hematopoietic stem cell transplantation. *Clin. Infect. Dis.* 2001; **32**: 1290–97.
17. Naesens L, Lenaerts L, Andrei G *et al*. Antiadenovirus activities of several classes of nucleoside and nucleotide analogues. *Antimicrob. Agents Chemother.* 2005; **49**: 1010–16.
18. Morfin F, Dupuis-Girod S, Mundweiler S *et al*. In vitro susceptibility of adenovirus to antiviral drugs is species-dependent. *Antivir. Ther.* 2005; **10**: 225–9.
19. Muller WJ, Levin MJ, Shin YK *et al*. Clinical and in vitro evaluation of cidofovir for treatment of adenovirus infection in pediatric hematopoietic stem cell transplant recipients. *Clin. Infect. Dis.* 2005; **41**: 1812–16.
20. Ljungman P, Ribaud P, Eyrich M *et al*. Cidofovir for adenovirus infections after allogeneic hematopoietic stem cell transplantation: A survey by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2003; **31**: 481–6.
21. Cundy KC. Clinical pharmacokinetics of the antiviral nucleotide analogues cidofovir and adefovir. *Clin. Pharmacokinet.* 1999; **36**: 127–143.