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Brief Communication

Successful treatment with foscarnet for ganciclovir-resistant cytomegalovirus infection in a kidney transplant recipient: A case report

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Abstract

Cytomegalovirus (CMV) infection is the most common infectious complication following solid organ transplantation. Ganciclovir (GCV)-resistant CMV infection may be fatal, and is difficult to treat whilst avoiding allograft rejection. A 31-year-old woman received a second ABO-incompatible kidney transplant, from her father. Induction therapy consisted of basiliximab and rituximab followed by maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and methylprednisolone. Her CMV serostatus was D+/R- at second transplant and she received prophylactic low-dose valganciclovir (VGCV). BK polyoma virus nephropathy (BKVN) developed 7 months after transplant concurrent with CMV hepatitis and retinitis. VGCV was increased to a therapeutic dose combined with reduced immunosuppression with minimal methylprednisolone (2 mg/day) and everolimus (0.5 mg/day). However, pp65 antigenemia continued to increase for 6 weeks. Her CMV was defined as ganciclovir (GCV)-resistant. Foscarnet was therefore administered and her CMV disease resolved within 2 weeks. Kidney allograft dysfunction developed 9 months after transplant, and graft biopsy showed tubulointerstitial injury with crystal deposition suggesting foscarnet nephrotoxicity, with no findings of BKVN or rejection. Kidney function recovered after cessation of foscarnet and the patient had good
graft function 18 months after transplant. This case demonstrates the successful use of foscarnet to treat GCV-resistant CMV infection after ABO-incompatible kidney transplant complicated with BKVN, without acute allograft rejection. This case further highlights the need to establish appropriate management for CMV D+/R- patients to avoid the acquisition of GCV-resistant gene mutations.

**Key Words:** BK polyoma virus nephropathy, cytomegalovirus, foscarnet-induced nephropathy, ganciclovir-resistant, kidney transplantation
Background

Cytomegalovirus (CMV) infection is the most common infectious disease following solid organ transplantation \(^1\), with significantly higher mortality in cases with primary infection. Although the emergence of highly effective antiviral drugs such as ganciclovir (GCV) and its prodrug valganciclovir (VGCV) have dramatically reduced the incidence of severe CMV infection, GCV-resistant CMV infection can still be fatal, and is difficult to treat without reducing immunosuppression and thus risking allograft rejection. Here, we report a patient with primary GCV-resistant CMV infection following an ABO-incompatible second kidney transplant complicated by BK polyoma virus nephropathy (BKVN), who was successfully treated with foscarnet without acute allograft rejection. In addition, kidney allograft biopsy revealed crystal nephropathy suggesting foscarnet-induced tubulointerstitial toxicity, which resolved spontaneously after drug withdrawal.

Case Report

A 31-year-old woman (unknown original disease) underwent a second kidney transplant, with a kidney donated by her father. Her first transplant had been from her mother, but the allograft was lost after 10 years as a result of IgA nephropathy in the graft, complicated by
calcineurin inhibitor-induced arteriolopathy. For her second kidney transplant, immunosuppression was induced with basiliximab (20 mg) and rituximab (200 mg) followed by maintenance with tacrolimus, mycophenolate mofetil, and methylprednisolone.

Her CMV serostatus was D+/R−, and prophylactic VGCV (450 mg/day) was therefore initiated. She became pp65 antigen-positive (35 positive cells per 2×10^5 peripheral leukocytes) at 4 months post-transplant, with no symptoms, and her VGCV was increased to a therapeutic dosage (900 mg/day), with resolution of her antigenemia. Allograft dysfunction was revealed by an increase in serum creatinine (sCr) levels from 0.80 to 1.44 mg/dl 7 months post-transplant (Fig. 1), and she was diagnosed with BKVN, with positive staining for SV40T in the allograft biopsy (Fig. 2a, b; Banff classification: t0, i0, g0, v0, cg0, ci0, ct0, cv0, mm0, ptc0, c4d0, ti0, ah1, aah1, and ptcbm0), decoy cells detected by urine cytology, and BK virus DNA in her blood. Her pp65 antigenemia increased, accompanied by a fungal urinary tract infection, despite continuing VGCV prophylaxis.

VGCV was again increased to a therapeutic level and mycophenolate mofetil was replaced with everolimus, followed by a gradual reduction of other immunosuppression to methylprednisolone (2 mg/day) and everolimus (0.5 mg/day). However, her pp65 antigenemia continued to rise for 6 weeks up to 307 cells per 2×10^5 peripheral leukocytes,
with high fever, liver dysfunction, and retinitis. There were no other organ symptoms related to CMV infection. Based on a diagnosis of GCV-resistant CMV, the patient was administered foscarnet, after which her antigenemia became negative and her CMV symptoms resolved within 2 weeks. CMV genotyping revealed an A594V mutation in the UL97 gene, which has been associated with an 8.3-fold increase in resistance to GCV.

The patient’s kidney allograft function worsened (sCr increase from 1.2 to 1.7 mg/dl) followed by hypocalcaemia, and allograft biopsy revealed tubulointerstitial damage with increased crystal deposition in the tubules, presumably caused by foscarnet, with no signs of rejection or BKVN (Fig. 2c, d, e). Immunostaining for CMV was negative (not shown), and the Banff classification was as follows: t0, i1, g0, v0, cg0, ci2, ct2, cv0, mm0, ptc0, c4d2, ti3, ah0, aah0, and ptcbm0. Allograft function recovered spontaneously after withdrawal of foscarnet. Repeated allograft biopsy revealed disappearance of crystal deposition in the tubules 17 months post-transplant (Fig. 2f; Banff classification: t0, i0, g0, v0, cg0, ci1, ct1, cv0, mm0, ptc0, c4d0, ti1, ah0, aah0, and ptcbm0). The patient had stable graft function (sCr, 1.28 mg/dl) with no signs of opportunistic infection or drug toxicity 18 months after kidney transplant.
Discussion

The guanosine analogue GCV and its prodrug VGCV require phosphorylation, mediated by human CMV pUL97, for their antiviral activities. Phosphorylated GCV is then incorporated into the DNA, resulting in reduction and termination of DNA replication. Mutations in pUL97, a phosphotransferase encoded by the UL97 open reading frame and related to protein kinases, are the most common mutations leading to GCV resistance, responsible for increases in resistance up to 8-fold, compared with wild-type CMV. Many gene mutations have been identified as causes of GCV-resistance, of which UL97 A594V is the most frequent, resulting in an 8.3-fold increase in resistance to GCV. In contrast, foscarnet is a pyrophosphate analogue that does not require phosphorylation for its antiviral activity. Foscarnet terminates replication by blocking the release of pyrophosphate by DNA polymerase, independent of UL97.

Reported risk factors for GCV-resistance include an insufficient dose of GCV/VGCV and longer duration of treatment or prophylaxis. However, the appropriate duration and dosage of prophylactic VGCV in solid organ transplant recipients with D+/R- serostatus remain controversial. Stevens et al. reported that lower-dose VGCV prophylaxis was associated with breakthrough infection, though higher doses could increase
haematological events such as neutropenia. Prolonged prophylaxis can also cause late-onset CMV infection after cessation of prophylaxis. Accordingly, the Transplantation Society International CMV Consensus Group suggested a hybrid approach involving preemptive treatment followed by secondary prophylaxis, or prophylaxis followed by preemptive therapy. In the current case, prolonged and insufficient administration of prophylactic VGCV may have resulted in the observed GCV-resistant CMV infection.

Although no controlled studies have been performed, conversion to foscarnet is recommended in the updated guidelines for CMV management, especially in patients who demonstrate high resistance to GCV, such as the current case. Evidence for the efficacy of combination therapy of GCV and foscarnet is limited.

Nephrotoxicity caused by antiviral drugs is not rare, but is hard to confirm by renal needle biopsy, especially in patients with haemorrhagic events. Many kinds of antiviral drugs can cause nephrotoxicity via the deposition of calcium crystals. Calcium crystal deposition in the glomerular capillaries, rather than in the tubules, is more specific to foscarnet-induced nephrotoxicity. Kidney functional and pathological changes are reversible as long as the fibrotic changes are not severe and the patient receives adequate hydration. In our case, allograft rejection, recurrence of BKVN, CMV infection, and
calcineurin inhibitor nephrotoxicity were taken into consideration 9 months after transplant. Increased crystal deposition in the tubules, but not in the glomerular capillaries, revealed by allograft biopsy, together with the results of other laboratory tests and her subsequent clinical course, were suggestive of foscarnet-induced nephrotoxicity. In addition, repeated biopsy 17 months after transplant showed a marked decrease of calcium deposition with mild fibrotic changes.

In conclusion, we experienced a patient with primary GCV-resistant CMV infection following ABO-incompatible kidney transplant complicated by BKVN, who was successfully treated with foscarnet together with reduced immunosuppression, without the development of acute allograft rejection. Allograft biopsy also confirmed antiviral-drug-induced nephrotoxicity pathologically and recorded its improvement after foscarnet cessation. This case highlights the need to establish the optimal strategy for preventing and/or treating severe infection in CMV-seronegative recipients whilst avoiding the acquisition of GCV-resistance gene mutations.

**Competing interests**

The authors declare that they have no competing interests.
**Financial competing interests**

The authors declare that there are no financial competing interests in relation to this manuscript.

**Authors’ contributions**

DI, KM, HS, YO, HH, and NS were the treating physicians, and HF and KH evaluated the kidney allograft biopsies. All of the authors have contributed to the preparation of the manuscript. All the authors have read and agree to the manuscript as written.

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Written consent was obtained from the patient for the publication of this case report.
References


**Figure Legends**

**Fig. 1.** Clinical course of recipient after second ABO-incompatible kidney transplant complicated by GCV-resistant primary CMV infection. CMV: cytomegalovirus, CNI: calcineurin inhibitor, MMF: mycophenolate mofetil, MP: methylprednisolone, CsA: cyclosporin A, TACER: tacrolimus extended-release formulation, EVR: everolimus, UTI: urinary tract infection, VGCV: valganciclovir, GCV: ganciclovir, Bx: biopsy.

**Fig. 2.** Kidney allograft biopsies at 7 months post-transplant revealed BK polyoma virus nephropathy (a, b), at 9 months post-transplant suggested foscarnet-induced nephrotoxicity (c, d, e), and at 17 months post-transplant showing clearance of crystal precipitation (f). (a) Inclusion bodies were identified in a few nuclei of tubular epithelial cells (inset), only in the cortical-medullary junction area (haematoxylin and eosin staining, original magnification ×20). (b) Anti-SV40 staining was positive in some nuclei (inset) in the same area (original magnification ×20). (c) Crystal precipitation was detected in tubular lumina (haematoxylin and eosin staining, original magnification ×40). (d) Von Kossa staining showed black crystals (original magnification ×40). (e) Crystals were birefringent on polarization (original magnification ×40). (f) Hematoxylin and eosin
staining showed disappearance of crystal deposition with mild interstitial fibrotic changes (original magnification ×20).
Fig. 1

- **pp65 positive cells**: 0 0 5 0 61 171 55 161 270 385
- **anti-CMV drugs**: VGCV 450, GCV, foscarnet
- **CNI (mg/day)**: CsA 120, TACER 3, 2.5, 2, 1
- **MMF (mg/day)**: 1000, 500
- **EVR (mg/day)**: 1 0.5 2
- **MP (mg/day)**: 4 2
- **serum creatinine (mg/dl)**: 0.5 1 1.5 1.0 1.5 2.0
- **post-transplant (months)**: 7 8 9 10
- **events**: fever, liver dysfunction, retinitis, fungal UTI

**Legend**: pp65 positive cells (*/2x10^5 leukocytes*), post-transplant (months), serum creatinine (mg/dl), anti-CMV drugs (VGCV 450, GCV, foscarnet), CNI (mg/day) (CsA 120, TACER 3, 2.5, 2, 1), MMF (mg/day) (1000, 500), EVR (mg/day) (1 0.5 2), MP (mg/day) (4 2), serum creatinine (mg/dl) (0.5 1 1.5 1.0 1.5 2.0), post-transplant (months) (7 8 9 10), events (fever, liver dysfunction, retinitis, fungal UTI).