An Unusual Cause of Kidney Allograft Dysfunction

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Case Description
A 68-year-old woman with ESKD of unknown etiology received a second deceased-donor kidney transplant in 2019. She previously underwent a deceased-donor kidney transplant in 2005, and returned to dialysis in 2018. The patient was negative for cytomegalovirus (CMV) and the second allograft donor was CMV positive. Induction immunosuppression consisted of alemtuzumab and methylprednisolone, and maintenance immunosuppression was initially mycophenolate mofetil (500 mg twice a day) and tacrolimus (1 mg twice a day; target of 5–7 ng/ml). Initial infection prophylaxis included 450 mg valganciclovir daily for 6 months.

Nine months post-transplant, the patient exhibited CMV viremia (133,000 IU/ml) and was treated with valganciclovir (900 mg twice a day, and then 450 mg twice a day), and switched to 1.5 mg extended-release tacrolimus daily. At 11 months, CMV viremia decreased to 856 IU/ml but rebounded to 326,000 IU/ml 3 weeks later, and CMV genetic analysis revealed ganciclovir resistance (UL97 gene). The patient also reported missed valganciclovir doses. Serum creatinine (sCr) remained at baseline, 0.8–1.0 mg/dl. Foscarnet therapy (4.8 g intravenously, three times per day, for 200 mg/kg, and then 3.6 g intravenously, three times per day, for 150 mg/kg) commenced and immunosuppression was decreased (0.5 mg tacrolimus twice a day, mycophenolate mofetil held, and 10 mg prednisone added). One month later, CMV viremia declined to near undetectable levels (<137 IU/ml) with a concurrent rise in sCr to 2.00 mg/dl. A kidney allograft biopsy sample showed mild interstitial inflammation and marked tubular injury, without crystal formation, CMV viral inclusions, or evidence of rejection (Figure 1A). The findings were attributed to foscarnet nephrotoxicity and coincided with foscarnet-associated electrolyte imbalances. Foscarnet was reduced (6 g every other day) with improvement in sCr to 1.48 mg/dl 1 month later, but increased CMV viremia (7700 IU/ml). Several weeks later, sCr increased to 3.2 mg/dl and CMV viremia persisted (3000 IU/ml). The patient was readministered 4 g foscarnet daily and immunosuppression was again reduced. Unfortunately, both CMV viremia and sCr worsened (15,400 IU/ml and 5.00 mg/dl, respectively), and a second biopsy was performed.

The second biopsy showed abundant crystals, involving 50%–75% of glomeruli (Figure 1B). The crystals were large, expansile, and polarized on unstained slides (Figure 1C). The tubulointerstitium showed epithelial injury, moderate interstitial fibrosis, and few crystals with associated inflammation and foreign-body giant cells. Foscarnet was reduced to every other day, daily 480 mg letermovir was added, and immunosuppression was further reduced (daily 5 mg prednisone monotherapy). Repeat CMV resistance testing revealed additional mutations (UL54 gene), further limiting antiviral strategies. Seven weeks later, the patient requires dialysis but CMV viremia is near undetectable (<137 IU/ml).

Foscarnet is an antiviral pyrophosphate analogue that inhibits the CMV DNA polymerase (1). It is a common second-line agent to treat CMV infection, particularly in the setting of ganciclovir resistance. Foscarnet nephrotoxicity is well described and, in its most severe form, manifests as glomerular foscarnet salt (phosphonoformate) crystalline deposits with less reversibility than the more commonly observed toxicity limited to the tubulointerstitium (2–5). To our knowledge, this is the first report of foscarnet nephrotoxicity initially manifesting as biopsy sample–proven, tubulointerstitial–limited disease and then, subsequently, as extensive glomerular crystalline deposition. The case raises the possibility that the multiple described nephrotoxic manifestations of foscarnet may represent a spectrum with shared pathogenesis.

Teaching Points
- Foscarnet nephrotoxicity can manifest as tubulointerstitial injury alone or frank glomerular crystal deposition, and these forms can be distinguished on the kidney biopsy sample.
- Crystalline deposits in foscarnet nephrotoxicity may be observed in both glomeruli and the interstitium and are associated with inflammation and foreign-body giant cells in the latter.
- Foscarnet nephrotoxicity associated with glomerular crystalline deposits may show a precipitous and potentially irreversible decline in kidney function.

Disclosures
All authors have nothing to disclose.

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Author Contributions
B. Amante, G. S. Markowitz, and P.E. Rosenstiel reviewed and edited the manuscript; B. Amante and P.E. Rosenstiel were responsible for data curation; G. S. Markowitz and P.E. Rosenstiel conceptualized the study; and P.E. Rosenstiel wrote the original draft and was responsible for formal analysis.

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