CASE REPORT

Cytomegalovirus Glomerulopathy in a Kidney Allograft With Response to Oral Valganciclovir

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Cytomegalovirus is an important viral pathogen in the kidney transplant population. Reports of direct cytopathic effects of cytomegalovirus in the kidney allograft are infrequent, with the majority of earlier reports highlighting tubulointerstitial involvement. We report a 58-year-old man who presented with an acute decrease in kidney allograft function 3 months posttransplantation. At presentation, both cytomegalovirus and polyomavirus blood polymerase chain reaction results were positive. Biopsy showed predominant glomerular endothelial involvement by cytomegalovirus with positive immunohistochemistry results. Polyomavirus was not detected in the biopsy specimen. He was treated with oral valganciclovir and a decrease in immunosuppression. He had a complete response, with clearance of viremia and return of allograft function to baseline. Recent reports of glomerular involvement may reflect changing practices in antiviral chemoprophylaxis and immunosuppressive regimen. Oral valganciclovir may have a role in the treatment of patients with mild viremia with tissue-invasive kidney disease.
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INDEX WORDS: Kidney; transplant; cytomegalovirus (CMV); glomerulopathy; valganciclovir; polyoma.

Cytomegalovirus (CMV) is an important cause of allograft dysfunction and systemic morbidity in the renal transplant population. Approximately 8% to 32% of kidney transplant recipients who are not on antiviral prophylaxis therapy develop symptomatic infection.[1] The routine use of antiviral prophylaxis has significantly reduced the incidence of CMV infection and disease in solid-organ transplant recipients.[2] Invasive CMV disease in the kidney allograft is uncommon, with the typical pattern of involvement being tubulointerstitial.[3] We present a case of a 58-year-old white man with an acute decrease in allograft function with blood polymerase chain reaction (PCR) positive for polyomavirus and CMV, whose biopsy showed only glomerular CMV involvement.

CASE REPORT

A 58-year-old CMV-negative white man with end-stage renal disease secondary to diabetes mellitus received a cadaveric kidney from a CMV-positive donor in April 2007. Induction therapy consisted of daclizumab, and he was started on prednisone, tacrolimus, and mycophenolate mofetil (MMF) as maintenance immunosuppression. Posttransplantation kidney function improved by day 6 to a serum creatinine level of 2.9 mg/dL (256 μmol/L). On day 7, serum creatinine level worsened to 3.4 mg/dL (301 μmol/L). An allograft biopsy performed at the time showed features of antibody-mediated rejection with diffuse C4d staining in peritubular capillaries. Acute tubular injury was present. There was minimal interstitial inflammation without tubulitis. Moderate glomerulitis was present without viral atypia. CMV stain was negative. Donor-specific antibodies were positive. He was treated with 4 sessions of plasmapheresis with intravenous immunoglobulin and 2 doses of thymoglobulin. Oral ganciclovir for CMV prophylaxis was started. During the next 5 days, kidney function improved, and he was discharged on day 15 with a baseline serum creatinine level of 1.4 mg/dL (124 μmol/L) and estimated glomerular filtration rate of 52 mL/min/1.73 m^2 (0.87 mL/s/1.73 m^2) using the Modification of Diet in Renal Disease Study equation. Discharge medications included prednisone, 10 mg/d; MMF, 1 g twice daily; tacrolimus, 3 mg twice daily; and ganciclovir, 1 g twice daily. At his 3-month visit, he had a stable serum creatinine level of 1.4 mg/dL (124 μmol/L), with an estimated glomerular filtration rate of 52 mL/min/1.73 m^2 (0.87 mL/s/1.73 m^2). During this visit, his only symptom was diarrhea, which was considered to be related to MMF therapy, and the dose was decreased to 750 mg twice daily. He was noted to have a platelet count of 92 $\times$ $10^3/\mu$L (92 $\times$ 10^9/L), white blood cell count of 4.2 $\times$ $10^3/\mu$L (4.2 $\times$ 10^9/L), and hemoglobin level of 12.3 g/dL (123 g/L). Ganciclovir therapy was discontinued.

The patient presented 2 weeks later with persistent diarrhea (3 to 4 loose stools daily) and worsening kidney function, with a serum creatinine level of 2.4 mg/dL (212

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μmol/L). Systemic and urinary symptoms were absent. Blood pressure was 140/78 mm Hg, and he was not orthostatic. Peripheral pulse was 68 beats/min, and he was afebrile. He appeared well and had normal physical examination findings. There was no allograft tenderness. Urinalysis showed 1+ protein, and urine microscopy showed 1 to 2 red blood cells/high-power field. Urine protein-creatinine ratio was 0.4, and urine cytological examination results were normal. Blood BK polyomavirus PCR at this time was 5,681 copies/mL, and CMV PCR showed 4,000 copies/mL (normal, <200 copies/mL). His blood was positive for CMV immunoglobulin G and immunoglobulin M antibodies. Other abnormal laboratory values included serum creatinine level of 2.2 mg/dL (194 μmol/L), platelet count of $98 \times 10^3/\mu L$ (98×10^9/L), and hemoglobin level of 11.6 g/dL (116 g/L). Ultrasound of the allograft was unremarkable. Differential diagnoses included acute rejection, polyomavirus nephropathy, and CMV infection.

A kidney biopsy was performed to further evaluate the acute decrease in allograft function. Sections consisted of renal cortex containing 15 glomeruli. All glomeruli showed endocapillary hypercellularity (Fig 1). Periodic acid–Schiff and Jones silver stains showed early segmental capillary loop double-contour formation in affected areas of glomeruli. Endocapillary cells showed marked nuclear atypical features with enlargement and smudgy basophilic transformation of the nuclei. Focal "owl eye" appearance of the nuclei typical of CMV infection was present. Immunohistochemical stain for CMV showed diffuse strong nuclear positivity in endothelial cells of all glomeruli (Fig 2). There was mild and focal interstitial inflammation. Tubulitis was absent. One arteriolar endothelial cell also contained a nuclear inclusion typical of CMV. There was no evidence of tubular or interstitial involvement. C4d stain was negative in peritubular capillaries. Immunohistochemical stain (SV40) for polyomavirus was negative. Arteries were unremarkable.

The patient was started on oral valganciclovir therapy, 450 mg/d, which was later increased to 450 mg twice daily in light of improvement in kidney function. The dose of MMF was decreased to 500 mg twice daily. Tacrolimus was continued with a target level of 6 to 8 ng/mL. Serum creatinine level on last follow up was at his baseline of 1.4 mg/dL (124 μmol/L), with estimated glomerular filtration rate of 52 mL/min/1.73 m^2 (0.87 mL/s/1.73 m^2). Diarrhea resolved. Repeated urine protein-creatinine ratio was 0.2, and serum CMV PCR was negative.

DISCUSSION

Tissue-invasive CMV infection in the kidney can be in the form of tubulointerstitial or glomerular involvement.[4-7] Reports of glomerular involvement include a distinct CMV glomerulopathy and immunotactoid, membranoproliferative, and crescentic glomerulonephritis.[8-10] The existence of CMV-associated glomerulopathy has been debated.[6,11] A distinct glomerulopathy associated with CMV viremia was first reported by Richardson et al[12] in 1981. A similar lesion was also reported by Tuazon et al.[13] However Herrera et al[11] disputed this association. The investigators concluded that these glomerular changes represented transplant glomerulopathy or some form of endothelial injury secondary to rejection.[11] Andersen et al[14] also found no evidence of CMV antigen or DNA in 15 biopsy specimens from kidney allograft recipients with viremia and glomerulopathy. More sensitive methods of de-

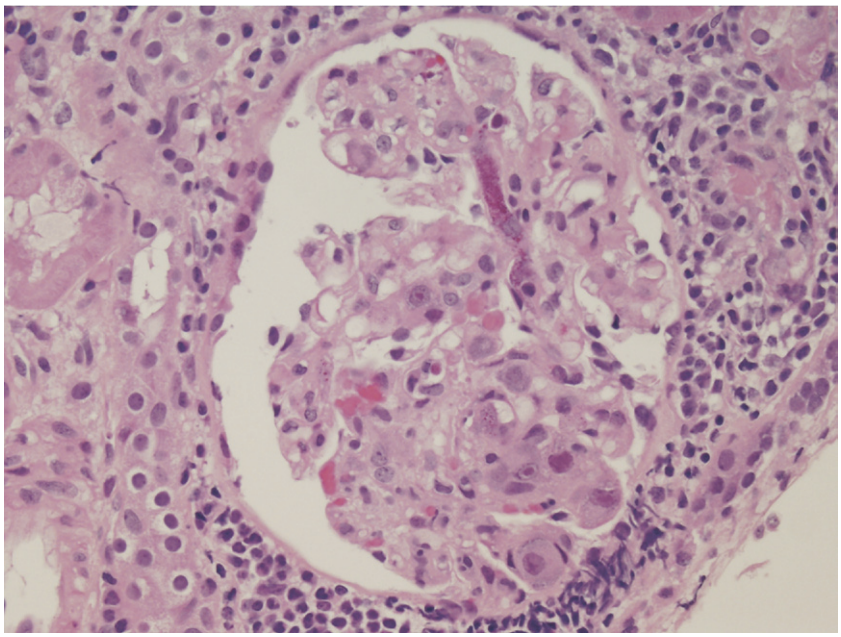

Figure 1. Glomerulus with enlarged atypical nuclei in the endothelial region causing endocapillary occlusion. One cell contains an "owl-eye" intranuclear inclusion typical of cytomegalovirus. (Hematoxylin and eosin stain; original magnification ×400.)