CASE REPORT

WILEY

Native kidney cytomegalovirus nephritis and cytomegalovirus prostatitis in a kidney transplant recipient

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Abstract

We present a case of cytomegalovirus (CMV) native kidney nephritis and prostatitis in a CMV D+/R- kidney transplant recipient who had completed six months of CMV prophylaxis four weeks prior to the diagnosis of genitourinary CMV disease. The patient had a history of benign prostatic hypertrophy and urinary retention that required self-catheterization to relieve high post-voiding residual volumes. At 7 months post-transplant, he was found to have a urinary tract infection, moderate hydronephrosis of the transplanted kidney, and severe hydroureteronephrosis of the native left kidney and ureter, and underwent native left nephrectomy and transurethral resection of the prostate. Histopathologic examination of kidney and prostate tissue revealed CMV inclusions consistent with invasive CMV disease. This case highlights that CMV may extend beyond the kidney allograft to involve other parts of the genitourinary tract, including the native kidneys and prostate. Furthermore, we highlight the tissue-specific risk factors that preceded CMV tissue invasion. In addition to concurrent diagnoses, health care providers should have a low threshold for considering late-onset CMV disease in high-risk solid organ transplant recipients presenting with signs and symptoms of genitourinary tract pathology.

1 | CASE

A 56-year-old man was hospitalized on day 209 after undergoing kidney transplantation for worsening kidney function (serum creatinine 4.2 mg/dL, baseline 2.3 mg/dL) and hydronephrosis of the transplant kidney.

The patient's history was notable for primary obstructive megaureter requiring bilateral ureteral re-implantation 15 years before transplant. Subsequently he had bilateral hydronephrosis and benign prostatic hypertrophy. Eight years before transplant, the patient developed end-stage kidney disease from sustained acute tubular necrosis in the setting of myocardial infarction and resultant cardiogenic shock. Since the myocardial infarction, he remained on hemodialysis until he received a 1/6 HLA-antigen matched, deceased donor kidney transplant. The patient was unsensitized prior to transplantation, but deemed to be at higher immunologic

risk due to delayed graft function. Induction therapy consisted of rabbit anti-thymocyte globulin (4.7 mg/kg) and he remained on tacrolimus (target trough 8-10 ng/mL), mycophenolate mofetil (MMF), and prednisone for maintenance immunosuppression. The recipient was cytomegalovirus (CMV) seronegative prior to transplant and the donor was CMV seropositive. Both donor and recipient were Epstein-Barr virus (EBV) seropositive. He received valganciclovir for CMV prophylaxis through the first six months of transplantation[1] and remained on trimethoprim/sulfamethoxazole for *Pneumocystis jirovicii* prophylaxis, per institutional protocol.
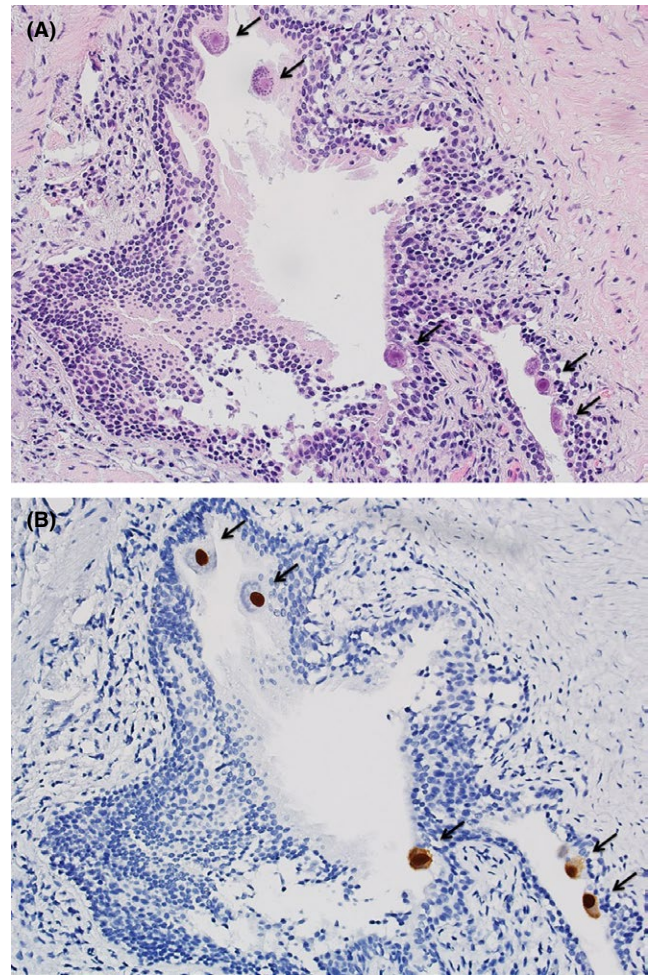
The early post-transplant course was complicated by urinary retention, two episodes of enterococcus urinary tract infections, and BK virus nephropathy. In the weeks following transplantation, the patient developed significant post-voiding residual volumes that required self-catheterization at least three times a day. Urodynamic studies revealed the presence of both bladder outlet obstruction
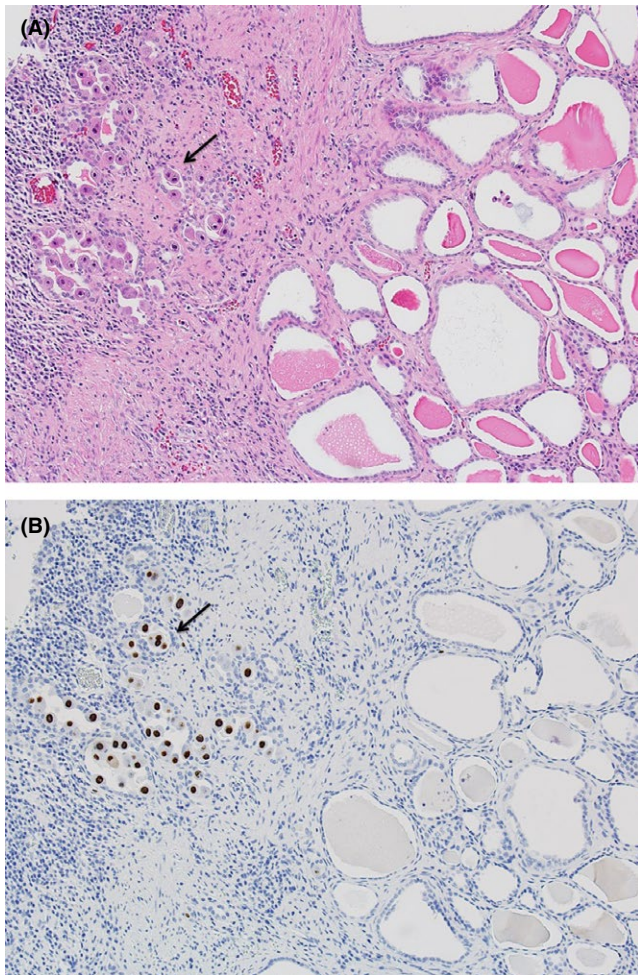
FIGURE 1 Left kidney nephrectomy. A, Hematoxylin and Eosin (H&E) stained sections reveal a dense inflammatory infiltrate surrounding calyces with numerous tubular epithelial cells with viral cytopathic changes (large intranuclear inclusions surrounded by a clear halo) that are morphologically consistent with cytomegalovirus (CMV, arrow). The background kidney shows cystically dilated renal tubules consistent with end-stage kidney disease. B, Immunohistochemical staining for CMV using a mouse monoclonal antibody highlights the infected cells (arrow)

FIGURE 2 Transurethral resection of the prostate. A, H&E sections show presence of characteristic CMV inclusions, both large intranuclear and smaller granular cytoplasmic ones, within the prostatic epithelium (arrows). B, Immunohistochemical staining for CMV is positive (arrows)

and a poorly contractile bladder. Three months after transplant, the patient developed BK virus viremia and biopsy-confirmed polyomavirus associated nephropathy. The BK virus load was >1 million copies/mL; this resolved after discontinuation of MMF, dose reduction of tacrolimus (trough 5-6 ng/mL), and two intravenous infusions of biweekly cidofovir 0.25 mg/kg. MMF was restarted at 250 mg once daily and tacrolimus dose increased to trough 7-9 ng/mL 6 months after transplant and approximately a month prior to presentation.

On presentation at day 209 post-transplant, the patient reported fatigue, a cough productive of clear phlegm, loose stools, and painful spasms while voiding. He reported trauma during self-catheterization two weeks prior, followed by gross hematuria and clots. He was afebrile and had a normal white blood cell count. Serum creatinine was 4.2 mg/dL (baseline 2.3 mg/dL). Urinalysis was positive for 3+ leukocyte esterase with a full field of leukocytes and 100-200 red

blood cells per high power field. Urine culture grew >100 000 CFU/mL of coagulase-negative *Staphylococcus* and *Enterococcus* species. A renal ultrasound showed moderate hydronephrosis of the transplanted kidney. A voiding cystogram revealed severe hydroureteronephrosis of the native left kidney and ureter. There was high-grade vesicourethral reflux into a dilated left ureter and native left kidney, reflux up the mid-right ureter, and no reflux into the transplanted kidney.

A foley catheter was placed to relieve hydronephrosis, presumably from bladder outlet obstruction. He was treated with intravenous piperacillin/tazobactam and vancomycin. To prevent recurrent urinary tract infections and improve his urodynamics, the patient underwent native left nephrectomy and transurethral resection of the prostate (TURP). Pathology of the left kidney revealed end-stage kidney disease with chronic pyelonephritis, reflux nephropathy, and superimposed CMV infection. Tubular epithelial cells with CMV intranuclear and cytoplasmic inclusions were visualized and confirmed by immunohistochemical staining (Figure 1A,B). Immunohistochemical

staining for polyomavirus was negative. The prostatic tissue also revealed CMV inclusions within the prostatic epithelium (Figure 2A,B). A biopsy of the kidney allograft was not performed. Plasma CMV DNA levels by quantitative PCR were 5322 IU/mL. Treatment for the patient's CMV genitourinary disease consisted of IV ganciclovir at induction doses adjusted for renal clearance until CMV viremia resolved, followed by maintenance dose valganciclovir for a total of 3 months. His renal function returned to baseline.

2 | DISCUSSION

Cytomegalovirus is among the most common opportunistic infections after solid organ transplantation and a significant cause of morbidity in kidney transplantation. CMV is known to cause severe tissue-invasive disease in immunocompromised hosts, particularly pneumonitis, gastrointestinal disease, hepatitis, and, less commonly, retinitis, myocarditis, pericarditis, pancreatitis, cholecystitis, encephalitis, transverse myelitis, Guillain-Barre syndrome, and adrenalitis.[2] CMV also has a predilection for involvement in the transplant allograft, likely due to local aberrant immune responses.[3] However, invasive CMV disease of the kidney is rare, even among kidney transplant recipients. This case highlights that CMV infection may extend beyond the kidney allograft and that other parts of the genitourinary tract may also be sites for CMV disease.

Here, we report a first case of CMV involvement in the native kidney and highlight the presence of concurrent CMV prostatitis in a kidney transplant recipient. Our case illustrates the tissue risk factors of CMV disease. In addition to being at high-risk based on donor and recipient CMV serologic status (D+/R-)

and induction with a lymphocyte depleting agent, our patient had numerous uroepithelial insults: pre-existing genitoureteral abnormality, delayed graft function which correlates with ischemic injury to the transplant ureter,[4] repeated mechanical microinjury from self-catheterization, and preceding or concomitant uroepithelial infections by bacteria and BK virus. Such tissue injuries result in a proinflammatory environment that is linked to CMV reactivation.[5,6] CMV reactivates from latently infected cells under inflammatory stimuli, particularly tumor necrosis factor (TNF)-α. TNF-α binds to TNF receptors on latently infected cells and leads to downstream nuclear factor-kB (NF-kB) activation, which translocates into the nucleus, binds to the immediate-early enhancer region of CMV, and initiates viral replication. [7-9] Reactivation of CMV is associated with elevated serum TNF-α levels in patients with sepsis, atopic dermatitis, transplant organ rejection in solid organ transplant recipients, and graft-versus-host-disease in hematopoietic cell transplant recipients.[5] Other proinflammatory mediators such as prostaglandins and stress catecholamines that act via TNF-α independent pathways have also been found to trigger viral reactivation.[10-12] Thus, local inflammation in tissues produced by traumatic, mechanical, toxic, or infectious injury, as in our patient, can promote a susceptible environment for CMV reactivation and infection.

Though several reports of CMV infection in the transplanted kidney or ureter exist,[13-19] this is a first report of CMV nephritis of the native kidney in a kidney transplant recipient. CMV infection of the native ureter was reported in one liver-kidney transplant recipient 7 years after transplantation. Notably, the patient also had preceding uroepithelial injury from bacterial pyelonephritis requiring decompression with a ureteral stent. Shortly after completing antibiotic

TABLE 1 Reports of cytomegalovirus prostatitis in transplant recipients

Age (y)	Transplant	Time post-transplant	Signs/Symptoms	Risk factors	CMV by IHC	Treatment	Outcome	Reference
39	Kidney	5 mo	Fevers, chills, dysuria	Concurrent bacterial prostatitis	Yes	Valganciclovir	Dead	[23]
48	Kidney	1 y	Elevated PSA, tenderness on prostate exam	Undergoing treatment for rejection	Yes	Not reported	Alive	[21]
41	Kidney	5 y	Elevated PSA, symptoms not reported	Undergoing treatment for rejection	Yes	Not reported	Alive	[21]
72	Liver	2 y	Elevated PSA, mild urinary retention	Undergoing treatment for rejection	Yes	Not reported	Alive	[21]
59	Heart	1 y	Elevated PSA, nocturia	CMV D+/R-	Yes	Valganciclovir	Alive	[22]

CMV, cytomegalovirus; D+/R-, donor seropositive and recipient seronegative; IHC, immunohistochemistry; PSA, prostate-specific antigen.

therapy and removal of the stent, she developed fever and right flank pain with an edematous right ureter that was demonstrated on retrograde pyelogram for which she underwent native right nephroureterectomy. Numerous inflammatory cells and CMV inclusions were observed in the glomerular and peritubular capillaries, interstitial inflammatory cells, and endothelial cells of the submucosal ureteric vessels. This case highlights the predisposition for CMV invasion in damaged uroepithelial tissue. The authors similarly concluded that CMV ureteritis of the allograft or native ureters should be included in the differential diagnosis for any post-transplant recipient with upper urinary tract symptoms and/or an increasing serum creatinine with hydronephrosis.[20] While concurrent and repeated urinary tract infections and reflux likely contributed to the development of native kidney CMV disease in our patient, the role of other risk factors such as time on dialysis or cause of kidney failure is unknown.

CMV prostatitis has also been reported rarely in immunocompromised hosts, particularly among HIV-positive patients, solid organ transplant recipients, and a patient with multiple myeloma receiving chemotherapy.[21-26] Among transplant recipients, CMV prostatitis has been reported in 3 kidney, 1 liver, and 1 heart transplant recipient (Table 1).[21-23] Most presented with mild obstructive symptoms and elevated prostate-specific antigen several years after transplantation while undergoing concurrent treatment for allograft rejection. However, in the one report of a kidney transplant recipient who developed early CMV prostatitis within the first year of transplantation, the patient also had bacterial prostatitis, suggesting that CMV can co-occur with bacterial infections in abnormal tissue, and that despite an initial diagnosis of bacterial infection, CMV disease should remain on the differential diagnosis in at-risk patients.

While prophylactic treatment strategies for CMV have significantly attenuated the incidence of CMV disease, approximately 20%-30% of kidney transplant recipients develop late-onset CMV disease, defined as CMV infection or disease after cessation of prophylaxis.[27] Risk factors for developing late-onset CMV disease include CMV seronegative recipients who receive organs from CMV seropositive donors (D+/R-), treatment with lymphocyte-depleting agents, and lower estimated glomerular filtration rate at prophylaxis cessation,[3,28,29] all features of our case. Immune monitoring for the presence of CMV-specific or global immunity may have also identified this patient as at-risk for late-onset CMV disease, such that extending the duration of antiviral prophylaxis or preemptive CMV DNA PCR monitoring could be considered. Immune monitoring is of increasing interest in transplantation, as it may improve risk-stratification and lead to tailoring of immunosuppression and antiviral prophylaxis practices according to the individual's risk profile. In particular, emerging data suggest that CMV-specific interferon-γ release assays may identify kidney transplant recipients most likely to develop CMV viremia and disease.[30-32] Identification of optimal biomarkers for immune monitoring, in combination with previously established clinical risk factors, may help optimize transplant outcomes and personalize management in the future.

In conclusion, we report a rare case of late-onset CMV disease in the native kidney and prostate in a kidney transplant recipient who recently completed six months of CMV prophylaxis. This case highlights that the prostate and native kidneys can also be sites of CMV disease and illustrates the tissue-specific risk factors. Clinicians should have a high suspicion for late-onset CMV disease as a diagnosis in at-risk solid organ transplant recipients with global and local risk factors presenting with signs and symptoms of genitourinary tract pathology.

AUTHOR CONTRIBUTIONS

ST: Concept/design, drafting manuscript, critical revision of article; XC: Concept/design, critical review of article; CK: Concept/design, critical review of article; JW: Concept/design, critical review of article; BP: Concept/design, critical review of article; HG: Concept/design, critical review of article; SB: Concept/design, critical review of article; AS: Concept/design, critical review of article; JT: Concept/design, critical review of article.

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