CMV NEPHRITIS WITH MULTI-DERMATOMAL HERPES ZOSTER CO-INFECTION IN A KIDNEY TRANSPLANT RECIPIENT: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract. Cytomegalovirus (CMV) is a viral pathogen that can cause infection in kidney transplant recipients. We report a case of a 50-year-old Thai male kidney transplant recipient with a history of multiple episodes of urinary tract infection, presented with fever and vesicular rash. He was diagnosed with having CMV nephritis proven by immunohistochemistry stains on kidney biopsy and multi-dermatomal herpes zoster (HZ) co-infection proven by pathological findings on skin biopsy. The infections improved with immunosuppressive therapy reduction and intravenous ganciclovir for 2 weeks, followed by oral valganciclovir for 3 months. CMV nephritis and HZ are fairly common in kidney transplant recipients but have never been reported together as a co-infection. CMV nephritis/HZ co-infection should be considered in transplant recipients who present with impaired renal function and multi-dermatomal vesicular lesions.

Keywords: cytomegalovirus; nephritis; herpes zoster; co-infection; post-kidney transplant infection

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INTRODUCTION

Kidney transplantation is a therapeutic option for selected end-stage renal disease patients. However, transplantation is associated with increased risk for morbidity and mortality due to complications, such as allograft rejection and infection. Cytomegalovirus (CMV) and varicella zoster virus (VZV) are the members of the Herpesviridae family (Davison *et al*, 2009). After primary infection, these

viruses can establish lifelong latency and reactivate during immunosuppression (Forte *et al*, 2020; Sorel and Messaoudi, 2018). CMV is an important pathogen among kidney transplant recipients and can cause multi-organ dysfunction, graft rejection, and graft failure (Cukuranovic *et al*, 2012). VZV can cause localized mono-dermatomal zoster, multi-dermatomal zoster, and visceral involvement (Kotton and Fishman, 2005). Kidney transplant recipients are at high risk for developing infections caused by a variety of pathogens, including bacteria, fungi, protozoa, parasites and viruses because of their immunocompromised status (Karuthu and Blumberg, 2012). We report here a case of CMV nephritis with multi-dermatomal herpes zoster (HZ) co-infection in a kidney transplant recipient.

Case report

A-50-year-old Thai man with a history of hypertension, type 2 diabetes mellitus and end-stage renal disease due to diabetes on hemodialysis for 2 years underwent kidney transplantation 3 months prior to presentation. He was treated with basiliximab induction followed by immunosuppression with tacrolimus at a dose of 18 mg per day, mycophenolate mofetil at 1,250 mg per day, and prednisolone at 15 mg per day. Both the donor and the recipient had CMV immunoglobulin G (IgG) antibodies at the time of transplant. Our institution has not employed universal CMV prophylaxis or CMV viral load monitoring.

Three months post-transplantation the patient presented to our hospital with fever and cloudy urine. On admission his blood pressure was 130/80 mmHg, heart rate was 90/min, body temperature was 37.8°C and respiratory rate was 18 per minute.

Physical examination revealed no tenderness and no sign of inflammation in the transplanted kidney area.

A complete blood count revealed a leukocyte count of 16,800 cells/mm^3, 91.3% neutrophils, 2.2% lymphocytes, a hemoglobin of 7.4 g/dl, a platelet count of 200,000 cell/mm^3 and acute kidney failure with a creatinine of 3.64 mg/dl; an increase from his prior creatinine of 1.6 mg/dl. Urinalysis revealed a leukocyte count of >100 cells/high powered field (HPF) and an erythrocyte count of 10-20 cells/HPF. Empiric antibiotic therapy with piperacillin-tazobactam was started after obtaining blood and urine cultures on admission. Twenty hours after admission the blood and urine cultures grew out ceftriaxone-resistant *Escherichia coli*.

He was diagnosed with recurrent graft pyelonephritis and bacteremia due to ceftriaxone-resistant *E. coli*. Antibiotic therapy was switched from piperacillin-tazobactam to meropenem. The fever subsided in a few days with a renally-adjusted dose of intravenous meropenem 1 g intravenously twice daily.

Four days after admission, the patient developed a fever of 37.8°C and multiple, discrete, vesicular, crusting lesions on the right forehead, left temple, and left flank.

Laboratory testing revealed a serum creatinine level of 7.12 mg/dl. A complete blood count revealed a leukocyte count

of 5,100 cells/mm^3, 80% neutrophils, 5% lymphocytes, a hemoglobin of 6.7 g/dl and a platelet count of 206,000 cell/mm^3.

Ultrasonography of the transplanted kidney and non-contrast computerized tomography of the whole abdomen revealed diffuse swelling of the transplanted kidney with perinephric fat stranding, compatible with acute pyelonephritis. A plasma CMV viral load was 14,400 copies/ml.

A renal graft biopsy was performed and histopathology showed diffuse, mixed interstitial inflammation, and tubulitis with tubular basement membrane destruction without evidence of acute antibody-mediated rejection (Fig 1). Further immunohistochemical studies were positive for CMV inclusion bodies in the biopsied graft tissue (Fig 2). Biopsy of the vesicular skin lesions revealed multinucleated giant cells and rimming cells in the epidermis (Fig 3). A diagnosis of HZ was made based on the clinical and histopathological findings, although no confirmation polymerase chain reaction testing was performed. Based on the above evidence the patient was diagnosed with having CMV nephritis and multi-dermatomal HZ co-infection.

The mycophenolate mofetil was stopped and the tacrolimus dosage was reduced to 16 mg per day. The prednisolone was continued at the same dose. The patient was treated for the CMV nephritis with intravenous ganciclovir at a dose of 1.25 mg per kg once daily for 2 weeks followed by oral valganciclovir 450 mg every other day based on creatinine clearance.

All signs and symptoms of infection resolved within 2 weeks. The plasma CMV viral load was monitored weekly and found to be undetectable by 4 weeks of therapy. The oral valganciclovir was continued for a total of 3 months. The patient's serum creatinine reduced to 4.2-4.7 mg/dl and he did not need dialysis. His tacrolimus and prednisolone were maintained at the same dosages. He has not had a relapse of the CMV disease or the HZ.

DISCUSSION

CMV can cause a latent infection following the primary infection but can reactivate in an immunocompromised patient. Our study subject shows without prevention, CMV infection can recur within 3 months of solid organ transplant (SOT) in the setting of high-level immunosuppression. The recurrence may be delayed longer in SOT patients receiving CMV prophylaxis (Brennan, 2001; Razonable *et al*, 2013; Hryniewiecka *et al*, 2014). The CMV serostatus of both the donor and the recipient is the primary risk factor for CMV infection in the recipient. When the donor is CMV positive and the recipient is CMV negative, the recipients are at higher risk for developing CMV disease than if both the donor and the recipient are positive for CMV (Hartman *et al*, 2006; Abbott *et al*, 2002; Uslu *et al*, 2019; Humar *et al*, 2009). The most common tissue invasive CMV disease among SOT recipients is gastrointestinal disease (Paya *et al*, 2004). CMV disease in kidney transplant recipients can result in allograft dysfunction, but histopathologic evidence of direct kidney allograft

involvement by CMV, such as cytopathic changes or CMV inclusion bodies from biopsied graft tissue is rare (Wong *et al*, 2000).

Fourteen cases of CMV disease involving the kidney allograft were reviewed and are summarized in Table 1. The most common presenting symptoms of kidney allograft CMV infection in these 14 patients were diarrhea and abdominal pain. One patient presented with pulmonary nodules, which was presumed to be CMV pneumonitis (Posadas Salas *et al*, 2019). All 14 of these patients had allograft dysfunction and CMV allograft infection was proven by histopathological findings. The findings in these 14 cases suggest CMV nephritis is usually a part of multiorgan involvement. Fever was reported in only 4 of these 14 patients (Detwiler *et al*, 1998; Andresdottir *et al*, 2000; Wong *et al*, 2000; Onuigbo *et al*, 2002; Tiple *et al*, 2009; Vichot *et al*, 2013; Prema *et al*, 2019; Posadas Salas *et al*, 2019). The patient reported in our study here presented with fever, acute kidney injury, and multi-dermatomal HZ without gastrointestinal tract symptoms.

The diagnosis of CMV disease is based on the presence of typical signs and symptoms of infection combined with detecting CMV viral replication through finding pp65 antigenemia or having a positive PCR test for CMV DNA in an organ (Humar and Snydman, 2009; De Keyzer *et al*, 2011). Cytopathic changes in the kidney caused by CMV infection are seen in tubular epithelial cell cytoplasm and nuclei (Prema *et al*, 2019). CMV infected cells are enlarged (cytomegaly) and their nuclei contain

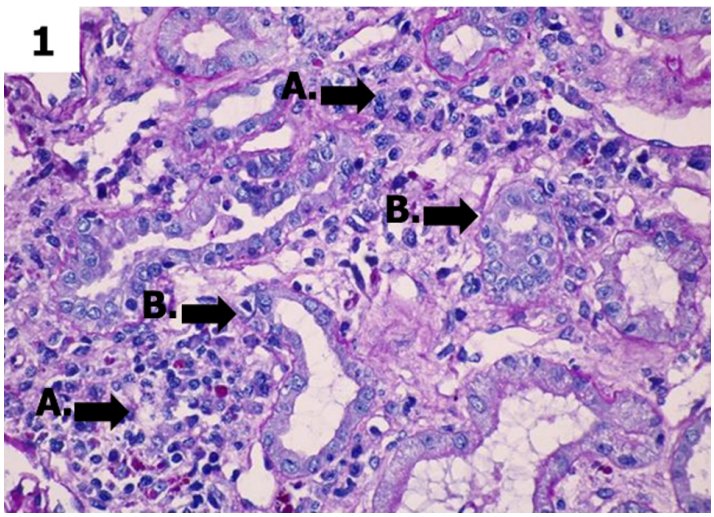

Fig 1 - Renal graft histopathology (hematoxylin and eosin staining) showing diffuse mild to moderate inflammation with interstitial edema (A), diffuse tubular injury and tubular basement membrane destruction (B)

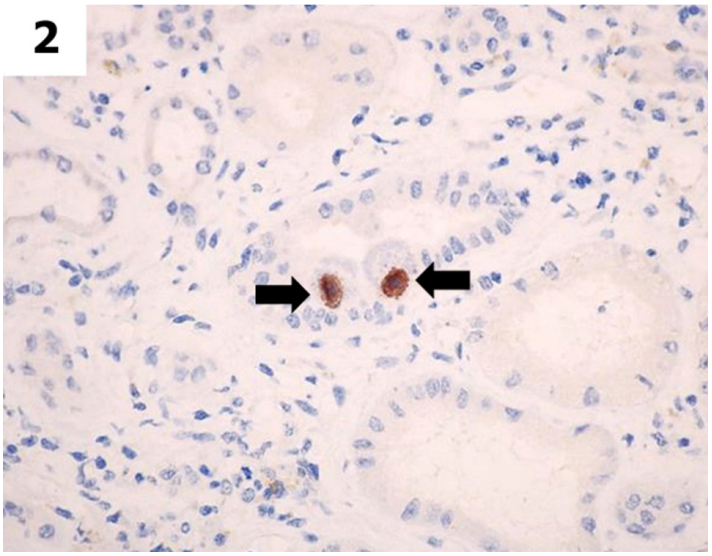

Fig 2 - Immunohistochemistry staining showing cytomegalovirus-positive tubular epithelial cells (arrows)

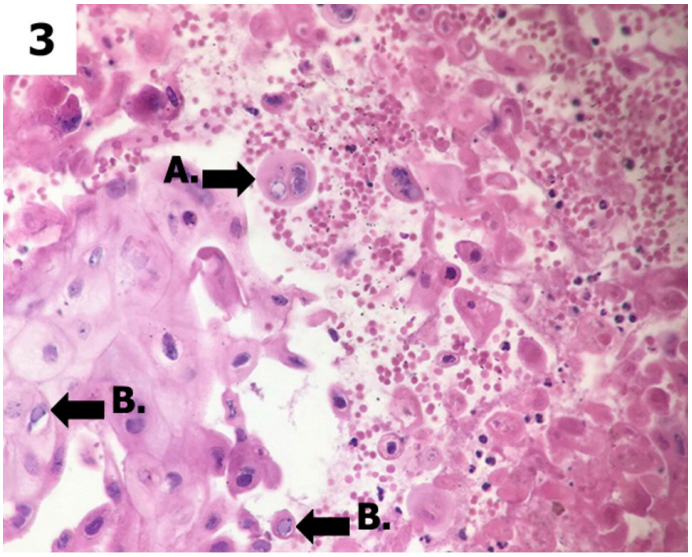

Fig 3 - Hematoxylin and eosin staining of skin biopsy showing multinucleated giant cells (A) and rimming cells (B) in epidermis

Table 1

Summary of reported cases of CMV disease of kidney allograft in kidney transplant recipients

Study	Age	Gender	CMV serostatus	Type of transplant	Induction immuno-suppression	Maintenance therapy	CMV prophylaxis	Signs and symptoms	Histopathology	CMV inclusion	Treatment	Outcome
Detwiler *et al*,1998	35	Male	D+/R-	Living related donor	OKT3 induction therapy	Azathioprine, cyclosporine, prednisolone	IV ganciclovir for 7 days, switched to acyclovir	Sinusitis, diarrhea, proteinuria, AKI	Diffuse glomerulone-phritis with crescents	Glomerular endothelial cells	Ganciclovir	Cr improvement, above baseline
Andres-dottir *et al*, 2000	40	Female	D+/R-	Deceased donor	N/A	Cyclosporine, MMF, prednisolone	N/A	Fever, abdominal pain, transaminitis, AKI	Type I MPGN	Negative	Ganciclovir	Transplantec-tomy due to intra-abdominal infection with *Aspergillus fumigatus*
Wong *et al*, 2000	30	Female	N/A	Deceased donor	N/A	Cyclosporine, prednisolone	N/A	Fever, AKI, pancytopenia	Interstitial nephritis	Tubular epithelial cells	Foscarnet	Cr returned to baseline
Onuigbo *et al*, 2002	46	Male	D+/R-	Deceased donor (kidney and pancreas)	ATG	Tacrolimus, MMF, prednisolone	Ganciclovir	Bloody diarrhea, AKI	Enlarged glomerular endothelial cells	N/A	Ganciclovir	Cr returned to baseline
Onuigbo *et al*, 2002	18	Male	D+/R-	Deceased donor	Basiliximab	Tacrolimus, MMF, prednisolone	Ganciclovir	Asymptomatic, AKI, leukopenia	Focal glomer-ulonephritis, enlarged cytopathic endothelial cells	Glomerular endothelial cells	Ganciclovir	Cr improvement, above baseline

Table1 (cont)

Study	Age	Gender	CMV serostatus	Type of transplant	Induction immuno-suppression	Maintenance therapy	CMV prophylaxis	Signs and symptoms	Histopathology	CMV inclusion	Treatment	Outcome
Tiple *et al*, 2009	57	Male	D+/R-	Deceased donor	N/A	Tacrolimus, MMF, prednisolone	Valganci-clovir for 5 months	Edema, proteinuria, AKI	Interstitial nephritis with acute tubular necrosis and tubulitis	Medullar tubular epi-thelial cells	Ganciclovir	Cr improvement, above baseline
Vichot *et al*, 2013	48	Male	D+/R-	Deceased donor	N/A	Tacrolimus, MMF, prednisolone	Valganci-clovir	Soft stool, proteinuria, AKI	Enlarged glomerular endothelial cells, interstitial nephritis	Glomerular endothelial cells and intraca-pillary monocytes, interstitium	Foscarnet, switched to cidofovir plus CMV immu-noglobulin	Hemodialysis (No expectation of kidney recovery)
Prema *et al*, 2019	58	Male	D+/R+	N/A	N/A	N/A	N/A	Asymp-tomatic, proteinuria, AKI	Collapsing glomeru-lopathy and necrotizing glomerulone-phritis	Tubular epithelial cells	valganciclovir	Cr returned to baseline
Posadas Salas *et al*, 2019	32	Male	D+/R+	Deceased donor	ATG	Tacrolimus, MMF, prednisolone	Valganci-clovir for 3 months	Diarrhea, AKI, leukopenia	CMV-associated collapsing glomerulopathy	N/A	Valganciclovir, CMV immuno-globulin	Cr returned to baseline
Posadas Salas *et al*, 2019	18	Male	D+/R-	Deceased donor	Basiliximab	Tacrolimus, MMF, prednisolone	Valganci-clovir	Abdominal pain, diarrhea, AKI	N/A	Glomerular endothelial cells	Ganciclovir followed by valganciclovir prophylactic dose	Cr returned to baseline

Table1 (cont)

Study	Age	Gender	CMV serostatus	Type of transplant	Induction immuno-suppression	Maintenance therapy	CMV prophylaxis	Signs and symptoms	Histopathology	CMV inclusion	Treatment	Outcome
Posadas Salas *et al*, 2019	29	Male	D+/R-	Deceased donor	ATG	Tacrolimus, MMF, prednisolone	Valganciclovir for 6 months	Fever, leukopenia, AKI	N/A	Glomerulus	Ganciclovir followed by valganciclovir prophylactic dose	Cr improvement, above baseline
Posadas Salas *et al*, 2019	58	Male	D+/R-	Deceased donor	ATG	Tacrolimus, MMF, prednisolone	Valganciclovir for 3 months	Diarrhea, leukopenia, AKI	Thrombotic microangiopathy, smudgy endothelial cell nuclei within the glomeruli	Glomerular endothelial cells	Ganciclovir	Hemodialysis
Posadas Salas *et al*, 2019	44	Male	D-/R+	Deceased donor	Basiliximab	Tacrolimus, MMF, prednisolone	N/A	AKI, proteinuria	Enlarged tubular cells, severe chronic tubulointerstitial changes	Tubular epithelial cells	Valganciclovir	Slightly improvement in proteinuria; Cr did not improve
Posadas Salas *et al*, 2019	37	Male	D+/R-	Deceased donor	ATG	Tacrolimus, MMF, prednisolone	N/A	Low-grade ever, night sweats, fatigue, exertional dyspnea, pulmonary nodules, leukopenia, AKI	PVAN	Tubular epithelial cells	Ganciclovir followed by valganciclovir prophylactic dose, intravenous immuno-globulin	Cr returned to baseline

N/A: data not available; Cr: creatinine; D+: donor cytomegalovirus seropositive; R+: recipient cytomegalovirus seropositive; D-: donor cytomegalovirus seronegative; R-: recipient cytomegalovirus seronegative; ATG: anti-thymocyte globulin; MMF: mycophenolate mofetil; MPGN: Membranoproliferative glomerulonephritis; CMV: cytomegalovirus; AKI: acute kidney injury; PVAN: polyomavirus-associated nephropathy

a central inclusion (Prema *et al*, 2019). In our case, CMV disease was suspected because the donor was CMV positive, the recipient had signs and symptoms of infection and detectable CMV in the plasma on the CMV viral load test. The diagnosis of CMV nephritis in our patient was confirmed by histopathology and immunohistochemical studies on the biopsied graft tissue.

In our study subject there was a delay in the diagnosis and treatment of his CMV nephritis because he also had pyelonephritis and bacteremia, which was presumed to be the sole cause of his decline in renal function. Our patient had renal function improvement with CMV treatment. The initial bacterial pyelonephritis might have occurred partly due to the immunomodulatory effect of CMV (Freeman, 2009; Kotton, 2013).

VZV reactivation leads to HZ (Oxman, 1995). The incidence of HZ in SOT patients has been reported to be 8-11% during the first 4 years post-transplant (Pergam *et al*, 2009). The most common clinical manifestation of HZ is mono-dermatomal HZ; multi-dermatomal HZ is less common and visceral VZV is rare (Fernández-Ruiz *et al*, 2018; Ko *et al*, 2013; Pavlopoulou *et al*, 2015).

CMV is known to have immuno-modulatory effects on many virus-specific T-cells, including VZV-specific T-cells, resulting in hyporesponsiveness of these T-cells against latent VZV (Fletcher *et al*, 2005). Further supportive evidence is that CMV infection has been found to be associated with reactivation of VZV (Ogunjimi *et al*, 2015; Ogunjimi *et al*, 2014). This might be the additional explanation of CMV and HZ co-infection in our patient apart from the effects of immunosuppressive agents.

The treatment of CMV disease and HZ in SOT recipients consists of the combination of antiviral therapy and a reduction in immunosuppressive therapy. Our patient is the first reported case of CMV nephritis with multi-dermatomal HZ co-infection in Thailand. The patient was treated with intravenous ganciclovir followed by oral valganciclovir; which are active against both CMV and VZV.

In conclusion, CMV nephritis with multi-dermatomal HZ co-infection should be suspected in kidney transplant recipients who presented with worsening renal function and multi-dermatomal vesicular lesions. Early diagnosis and appropriate treatment with antiviral therapy are important to control the infection, prevent graft failure, and reduce co-morbidity and mortality in the transplant recipients.

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CONFLICTS OF INTEREST DISCLOSORE

The authors declare no conflicts of interest.

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