Review Article

Cytomegalovirus infection in kidney allografts: a review of literature

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Abstract: Cytomegalovirus (CMV) is an important cause of renal transplantation complications. It can cause different syndromes or end-organ diseases that can lead to unfavourable clinical outcomes and kidney allograft dysfunction. Although well documented as a systemic disease on renal transplant patients, affecting non-renal tissue, as gastrointestinal and respiratory tract, few cases have been reported in English-language indexed journals involving renal allograft lesions secondary to CMV. As an important differential diagnosis and etiological agent to acute and chronic rejection, the possibility of CMV kidney direct infection needs prompt recognition for effective treatment. In this paper, we will review the current literature about CMV nephritis and discuss the findings from each case report.

Keywords: Cytomegalovirus (CMV); cytomegalovirus nephritis; cytomegalovirus kidney transplant; transplantation pathology; kidney pathology

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Introduction

Cytomegalovirus (CMV) infection is an important cause of morbidity and mortality and the most important viral pathogen in kidney transplant recipients. Kidney allograft CMV infection is a rare event, but it needs consideration as a differential diagnosis of any seropositive patient with graft dysfunction.

Methods

We performed a systematic literature review on English-language indexed journals from PubMed, Cochrane Library and Mendeley databases. The following terms were employed: cytomegalovirus nephritis, cytomegalovirus transplant and cytomegalovirus kidney. Exclusion criteria were: non-English language studies, not accessible to the University of São Paulo nor "Periódicos CAPES, institutional e-resources and irrelevant manuscripts (e.g., non-human, experimental reports) Eleven CMV nephritis case reports were reviewed. Data was compiled for the following variables: demographics, risk factors, clinical presentation, histopathological aspects, treatment and outcome.

Results

Twelve cases were reviewed and are summarized on *Tables 1-4*. The most affected kidney transplant group was the recipients (83%, 10/12). The age range varied between 16 and 80 years (*Table 1*). Nine patients received cadaveric kidneys (75%, 9/12) and three of the allografts originated from living donors (25%, 3/12). All kidney

Table 1 Demographic and pre-transplant clinical data

Study	Age (years)	Gender	Race	Pre-existing condition	Rec Stat	Don Stat	Type of transplant
Birk *et al.* 1997 (1)	16	Female	–	Type 1 MPGN	CMV–	CMV+	Living donor, related
Detwiler *et al.* 1998 (2)	35	Male	Black	ESRD secondary to FSGS	CMV–	CMV+	Living donor, related
Shaver *et al.* 1999 (3)	26	Male	White	ESRD of unknown cause	CMV–	CMV+	Cadaveric kidney
Wong *et al.* 2000 (4)	30	Female	–	Chronic glomerulonephritis	CMV–	–	Cadaveric kidney
Onuigbo *et al.* 2002 (5)	46	Male	Hispanic	Diabetic ESRD	CMV–	CMV+	Cadaveric kidney and pancreas
	18	Male	White	ESRD of unknown cause	CMV–	CMV+	Cadaveric kidney
Suneja *et al.* 2008 (6)	58	Male	White	ESRD due to diabetes	–	CMV+	Cadaveric kidney
Cathro *et al.* 2008 (7)	51	Male	Black	Hypertensive ESRD	CMV–	CMV+	Cadaveric kidney
Bae *et al.* 2012 (8)	48	Male	Asian	Hypertensive ESRD	–	–	Living donor, not specified
Vichot *et al.* 2014 (9)	48	Male	–	Diabetic and Hypertensive ESRD	CMV–	CMV+	Cadaveric kidney
Batal *et al.* 2016 (10)	80	Male	–	Hypertensive ESRD	CMV–	CMV+	Cadaveric kidney
Tan *et al.* 2018 (11)	56	Male	–	Primary obstructive megaureter	CMV–	CMV+	Cadaveric kidney

–, negative; +, positive. ESRD, end-stage renal disease; Rec Stat, kidney transplant recipient CMV status; Don Stat, kidney transplant donor CMV status.

transplant recipients were negative for CMV (100%, 10/10) while all donors had positive viral serology (100%, 10/10). CMV infection was detected between 3 to 58 weeks post transplantation (*Table 2*). Four patients were asymptomatic (33%, 4/12). The main symptom reported was diarrhoea (33%, 4/12). Conventional bright-field microscopy histological evaluation (*Table 3*) was suffice to detect viral inclusions by hematoxylin and eosin (H&E) in eleven cases (92%, 11/12), through viral inclusion detection. In one case with normal histological description CMV was not detected on H&E stain, but immunohistochemical positivity confirmed the diagnosis. Five cases showed minimal histological changes besides viral cytopathic inclusions (42%,5/12). One case revealed crescents with glomerular necrosis (8%, 1/12). In terms of treatment and clinical outcomes (*Table 4*), nine patients used Ganciclovir (75%, 9/12), two received valganciclovir (16%, 2/12) and one used Foscarnet (8%, 1/12). Kidney function was posteriorly improved to normal in five patients (42%, 5/12), four had improvement of renal function, maintaining serum creatinine levels above baseline (33%, 4/12). Four patients had dismal outcomes (33%, 4/12) one developed transplant glomerulopathy one year after transplantation (8%, 1/12), one developed collapsing focal segmental glomerulosclerosis and acute cellular rejection (8%, 1/12), one patient developed transplant glomerulopathy one year after transplantation (8%, 1/12), and one patient developed end-stage renal disease with need for hemodialysis (1/12). No lethal outcomes were reported.

Discussion

Human CMV is part of the order Herpesvirales, family *Herpesviridae*, sub-family *betaherpesvirinae*, genus

Table 2 Infection clinical data

Study	Induction immunosuppression	CMV prophylaxis scheme	Symptoms	Ons (wks)	Bs Cr (mg/dL)	Pk Cr (mg/dL)
Birk *et al.* 1997 (1)	–	–	Asymptomatic	–	0.8	1.5
Detwiler *et al.* 1998 (2)	OKT3 induction therapy	Ganciclovir. Switched to acyclovir	Sinusitis, diarrhea, postural hypotension	6	1.9	2.5
Shaver *et al.* 1999 (3)	Thymoglobulin	CMV IV Ig	Asymptomatic	58	1.2	2.1
Wong *et al.* 2000 (4)	–	–	Fever	8	1.3	5.3
Onuigbo *et al.* 2002 (5)	Thymoglobulin	Ganciclovir	Bloody diarrhea	18	0.9	3.5
	Basiliximab	Ganciclovir	Fever	22	1.8	3.2
Suneja *et al.* 2008 (6)	Daclizumab	Ganciclovir	Diarrhea	16	1.4	2.4
Cathro *et al.* 2008 (7)	Thymoglobulin	Valganciclovir	Malaise and sinusitis	10	2	3.7
Bae *et al.* 2012 (8)	–	–	Asymptomatic	3	3.1	2.2
Vichot *et al.* 2014 (9)	Thymoglobulin	Valganciclovir	Diarrhea	12	1.6	7.6
Batal *et al.* 2016 (10)	–	CMV IV Ig and valganciclovir	Fever and fatigue	24	2.2	3.2
Tan *et al.* 2018 (11)	Thymoglobulin	Valganciclovir	Cough, diarrhea, abdominal pain	30	2.3	4.2

CMV, cytomegalovirus; IV Ig, intravenous immunoglobulin; Ons, onset; wks, weeks; Bs Cr, creatinine baseline levels after transplant; Pk Cr, maximum creatinine levels after infection.

Cytomegalovirus and species *Human Herpesvirus 5* (12). It is one of the most frequent viral pathogens associated with renal transplantation (13). CMV infection is defined as CMV virus isolation in any body fluid or specimen (14). An average of 60% of renal transplant recipients develop active infection and 20% develop symptomatic disease (15). It represents an important cause of opportunistic infections after solid organ transplantation, causing local or disseminated invasive disease. Usually affecting immunocompromised hosts, CMV can cause a myriad of end-organ diseases like pneumonitis, colitis, esophagitis, gastritis, hepatitis, nephritis, among others (16). As other herpes viruses, CMV establishes lifelong latency within the host, with the possibility of reactivation, more common in immunocompromised individuals (16). Risk factors that influence CMV disease after solid organ transplantation include the CMV serostatus of the donor and recipient and the level of immunosuppression (17). There are three paths to CMV infection, each with a different chance of causing clinical disease: primary CMV infection, CMV infection reactivation, and superinfection. In kidney transplantation the source of infection in the majority of allograft recipients (80–90%) is a kidney from a seropositive donor. The remaining infections (10–20%) are due to leukocyte-containing blood products CMV-positive blood donors. Approximately 90% of seronegative kidney transplant recipients that receive kidneys from seropositive cadaveric donors, as opposed to 70% of seronegative recipients of kidneys from seropositive living-related donors, develop laboratory evidence of primary CMV infection after transplantation (18). CMV viremia is defined as the isolation of CMV viral culture. CMV antigenemia is as the detection of CMV pp65 in leukocytes. CMV DNAemia or RNAemia are the detection of the specific

Table 3 Histological features. Histological pattern and location of viral inclusions

Study	Histology pattern	Viral (cytopathic) inclusion
Birk *et al.* 1997 (1)	Type I MPGN	Glomerular epithelium
Detwiler *et al.* 1998 (2)	Diffuse glomerulonephritis with crescents	Endothelial cells
Shaver *et al.* 1999 (3)	Near normal (mild changes, inclusions only)	Tubular epithelium
Wong *et al.* 2000 (4)	Tubulointerstitial nephritis	Tubular epithelium
Onuigbo *et al.* 2002 (5)	Near normal (mild changes, inclusions only)	Vascular viral inclusions
	Near normal (mild changes, inclusions only)	Vascular viral inclusions
Suneja *et al.* 2008 (6)	Diffuse Glomerulonephritis	Endocapillary cells
Cathro *et al.* 2008 (7)	Near normal (mild changes, inclusions only)	Glomerular epithelium
Bae *et al.* 2012 (8)	Near normal	None
Vichot *et al.* 2014 (9)	Near normal (mild changes, inclusions only)	Endothelial cells and monocytes
Batal *et al.* 2016 (10)	Near normal (mild changes, inclusions only)	Endothelial cells and monocytes
Tan *et al.* 2018 (11)	End-stage kidney disease with chronic pyelonephritis	Tubular epithelium

MPGN, membranoproliferative glomerulonephritis.

Table 4 CMV treatment, immunosuppression changes and clinical outcome

Study	Maintenance therapy	CMV treatment	Immunosuppression change	Outcome
Birk *et al.* 1997 (1)	–	Gan, then acyc	Aza suspension	Cr improvement, above baseline
Detwiler *et al.* 1998 (2)	Pred, Aza, Cyc	Gan	Immunosuppression maintenance	Cr improvement, above baseline
Shaver *et al.* 1999 (3)	Tac, MMF and Pred	Gan, then acyc	MMF suspension	Cr improvement, above baseline
Wong *et al.* 2000 (4)	Tac, MMF and Predni	Foscarnet	Cyc suspension, Predni reduction	Renal function returned to baseline value
Onuigbo *et al.* 2002 (5)	Tac, MMF and Pred	Gan	MMF and Tac suspension	Renal function returned to baseline value
	Tac, MMF and Pred	Gan	MMF and Tac suspension. Sirolimus initiation	Transplant glomerulopathy 1 year after transplant
Suneja *et al.* 2008 (6)	Tac, MMF and Pred	Valgan	MMF reduction	Renal function returned to baseline value
Cathro *et al.* 2008 (7)	Tac, MMF and Pred	Gan	MMF suspension	Collapsing FSGS and acute cellular rejection
Bae *et al.* 2012 (8)	Tac, MMF and Predni	Gan	MMF suspension, Tac reduction	Creatinine improvement, above baseline
Vichot *et al.* 2014 (9)	–	Valgan	MMF suspension	ESRD (hemodialysis)
Batal *et al.* 2016 (10)	Cyc, MMF and Pred	Gan	–	Renal function returned to baseline value
Tan *et al.* 2018 (11)	Tac, MMF and Pred	Gan	–	Renal function returned to baseline value

CMV, cytomegalovirus; Pred, prednisone; Aza, azathioprine; Cyc, cyclosporine; Tac, tacrolimus; MMF, mycophenolate mofetil; Gan, ganciclovir; Valgan, valganciclovir; FSGS, focal segmental glomerulosclerosis; ESRD, end-stage renal disease.

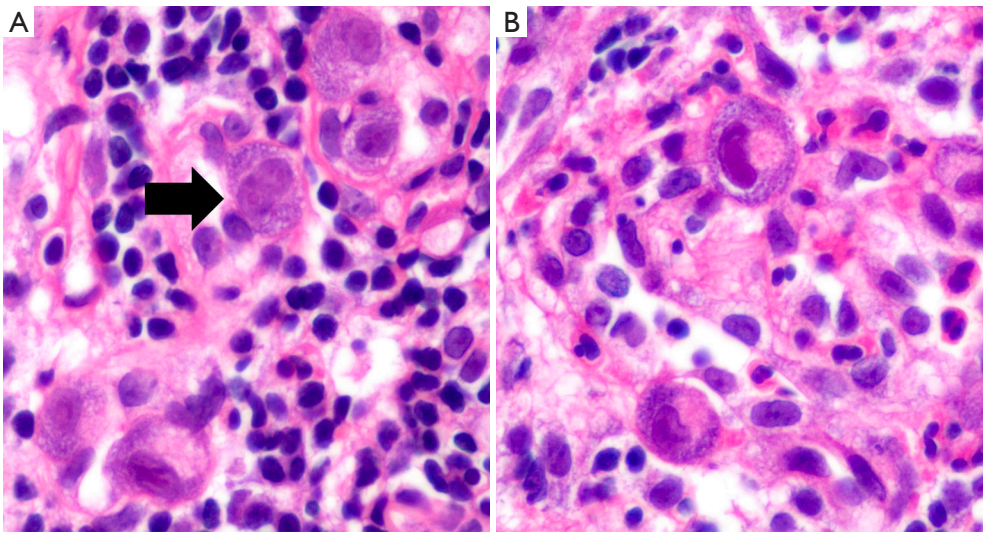

Figure 1 Cowdry type A nuclear inclusion in CMV affected epithelial and endothelial cells, illustrated by eosinophilic intranuclear inclusion of hyaline material; binucleations may lead to the "owls eyes" characteristics (A, arrow). (A, endothelium predominant; B, epithelial compartment predominant; H&E, ×400) (from author's archives). CMV, cytomegalovirus.

nucleic acid through specific diagnostic procedures like PCR, for example (14). The diagnosis of CMV infection is made by detection of the virus in body fluid or tissue specimen in association with a typical clinical manifestation of the disease (19). Tests of antigenemia or DNAemia are preferred over serologic testing or cell cultures (16). Histological examination is useful for differentiating kidney alterations secondary to CMV and allograft rejection. The histological hallmark of CMV infection is the presence of Cowdry Type A viral inclusions, also known as "Owl Eye Inclusions" (20), illustrated in *Figure 1*. Incidence of primary CMV infections in high-risk patients (patients IgG seropositive for CMV transplant to recipient IgG seronegative) kidney transplants is significantly reduced with valganciclovir prophylaxis (21). Active CMV disease is treated with a combination of antiviral therapy, reduction of immunosuppression and immunomodulation (22). Antivirals (acyclovir, ganciclovir and valganciclovir), have substantially reduced the incidence of CMV-associated disease during early post-transplantation period. Adverse effects, such as neutropenia and impaired cell-mediated immunity are possible (23).

Conclusions

In this systematic literature review, we have summarized the main clinical findings and natural history from 12 CMV kidney allograft infection reported cases in English-language literature. Positive donor serological status was the most influential factor for post-transplant infection, which developed over a wide variety of both clinical and histological presentations. Clinical presentation was mostly symptomatic and clinical outcomes were self-limited in the majority of cases. Prompt pathological diagnosis was a consequence of visualization of viral inclusions in H&E in more than 90% of reports. Awareness as a differential diagnosis in clinical and pathological grounds should be elicited, as in a minority of cases graft failure might be reported.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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