Short Communication

NEPHRON

Nephron 2002;92:490–494

Accepted: January 18, 2002

Late-Onset Cytomegalovirus-Associated Interstitial Nephritis in a Kidney Transplant

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Key Words
Cytomegalovirus · Ganciclovir · Interstitial nephritis · Kidney transplantation · Chronic rejection

Abstract
Cytomegalovirus is the most important viral infection in kidney transplants, but rarely affects the allograft after the sixth month posttransplantation. We present a patient who developed renal failure eighteen months post-transplant; a kidney biopsy showed cytomegalovirus inclusions, acute tubular necrosis and mild interstitial nephritis. After intravenous ganciclovir, renal function transiently improved. Cytomegalovirus pp65 antigen was weekly reported as negative. One month later another biopsy was performed due to renal failure. The findings were consistent with tubular atrophy and severe interstitial nephritis. No cytomegalovirus cellular inclusions were found on histology, including immunohistochemical and polymerase chain reaction studies; pp65 antigen studies were persistently negative. Despite an attempt to recover renal function with steroid therapy, the patient restarted hemodialysis 20 months posttransplantation. This report suggests that cytomegalovirus should be considered as a late cause of kidney failure even in the absence of infection-related symptoms. The irreversible allograft damage can be caused despite the successful eradication of the virus with intravenous ganciclovir.

Introduction

Cytomegalovirus (CMV) infections occur in 65% of kidney transplant patients, and 14–46% of infections are symptomatic, the vast majority of them being diagnosed between the second and sixth month posttansplantation [1–4]. The most likely clinical presentation is a flu-like picture. Other documented clinical manifestations include pneumonia, liver dysfunction, pancreatitis, colonic or esophageal ulcers, meningoencephalitis, and rarely myocarditis, chorioretinitis and skin involvement [5–7].

The renal allograft is frequently the site of latent CMV infection [8]. In situ hybridization techniques have documented CMV genomes in about 40% of routine graft biopsies [1]. However, the documentation of CMV inclusions in renal transplant biopsies is infrequently seen (<1%) [1]. CMV infection is rarely documented after the sixth month posttransplantation. We present a case in which a kidney allograft biopsy was performed 18 months

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0028–2766/02/0922–0490$18.50/0

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Table 1. Summarized laboratory results

	18th month 1st biopsy done	1 day postbiopsy ganciclovir started	7 days postbiopsy	9 days postbiopsy lowest creatinine	14 days postbiopsy ganciclovir stopped	30 days postbiopsy	45 days postbiopsy 2nd biopsy done	50 days postbiopsy steroids started	2 months postbiopsy HD reinstituted
Hematocrit, %	32	30	29	31	33	31	29	23	24
Leukocytes/mm^3	6,500	6,900	5,800	6,000	2,800	7,400	7,200	4,400	7,300
Platelets/mm^3	162,000	110,000	100,000	208,000	167,000	186,000	175,000	189,000	195,000
Urea, mg/dl	174	141	67	54	102	138	169	183	248
Creatinine, mg/dl	3.7	3.2	2.4	2.2	2.9	3.1	4.5	4.8	6.1
Glucose, mg/dl	106	88	100	97	83	92	93	99	108
Sodium, mEq/l	145	138	123	124	127	131	144	128	144
Potassium, mEq/l	4.6	4.9	3.4	4	5.3	4.3	3.7	3	3.7
Calcium, mg/dl	9.1	9.1	8.2	8.5	8.4	7.1	6.2	7.1	6.9
Phosphorus, mg/dl	4.9	4.1	3.8	4.1	3.2	4.6	6.6	4.9	5.8

posttransplant due to renal failure and showed CMV inclusions plus mild interstitial nephritis. Despite ganciclovir therapy, renal failure recurred one month later and another biopsy showed chronic and severe interstitial nephritis. No CMV particles were found in the blood or urine and immunohistochemical plus polymerase chain reaction (PCR) techniques performed in the biopsy were negative. This case suggests that despite correct CMV eradication, the virus can lead to interstitial nephritis and graft loss in a short period of time.

Case Report

A 57-year-old Japanese man with a cadaveric kidney transplant (D+/R+) developed renal failure 18 months posttransplant [7]. The patient received intravenous ganciclovir for the first 14 days posttransplant and then oral ganciclovir for 3 months. He had a previous history of CMV disease with skin involvement and renal failure that resolved with 14 days of intravenous ganciclovir administration 4 months postransplant. At 18 months posttransplant the patient was on methylprednisone 6 mg/day, mycophenolate mophetil 2 g/day and FK-506 4 mg/day (trough levels 8–12 ng/dl) as immunosuppressants, when renal function started to worsen (table 1). The patient was asymptomatic and CMV pp65 antigens were negative. A Doppler ultrasound was normal. A kidney biopsy was consistent with mild interstitial nephritis, moderate acute tubular necrosis and several nuclear inclusions in the tubular epithelium related to CMV (fig. 1); glomeruli were reported as normal. Deferred immunoperoxidase and PCR techniques confirmed CMV presence. The patient was scheduled for a 21-day course of intravenous ganciclovir adjusted to renal function, but it had to be discontinued after 14 days of therapy due to leukopenia. Weekly CMV pp65 tests were negative. Renal function had a partial and transient recovery, but it soon restarted to deteriorate (table 1). FK-506 was discontinued but renal function did not improve. One month later another kidney biopsy (fig. 2) was consistent with interstitial nephritis (40%), tubular atrophy (30%) and interstitial sclerosis (20%); CMV immunoperoxidase staining and PCR for CMV were negative; glomeruli appeared normal. No tubulitis or vascular abnormalities due to rejection were found. Immunohistochemical studies of the interstitial lymphocytic infiltrate showed that the vast majority of the lymphocytes were CD45 positive, meaning a preponderance of T cells. In an attempt to recover renal function oral methylprednisone 1 mg/kg/day was started but without positive results (table 1). Another Doppler ultrasound was unremarkable. Twenty months posttranplant chronic hemodialysis was reinstituted.

Discussion

CMV is a frequent infectious complication in renal transplantation, particularly between the second and sixth month posttransplantation. As a herpesvirus, CMV has two properties that determine its actions: latency and cell association. Once infected, the patient harbors the virus for life. Activation from latency is induced by immunosuppressants, allogeneic reactions and systemic inflammation. Immunosuppression promotes the persistence and spread of CMV by suppresing the T-cell population [9].

As mentioned previously, CMV effects in transplant recipients can be classified as direct and indirect [9]. Direct variants include an acute viral syndrome, leukopenia, thrombocytopenia, infection of native tissues and infection of allografts (hepatitis, pneumonitis, myocarditis, nephritis). Indirect effects can be either acute and chronic and comprise allograft rejection and injury, bacterial superinfection, atherosclerosis, bronchiolitis obliterans and glomerulopathy.

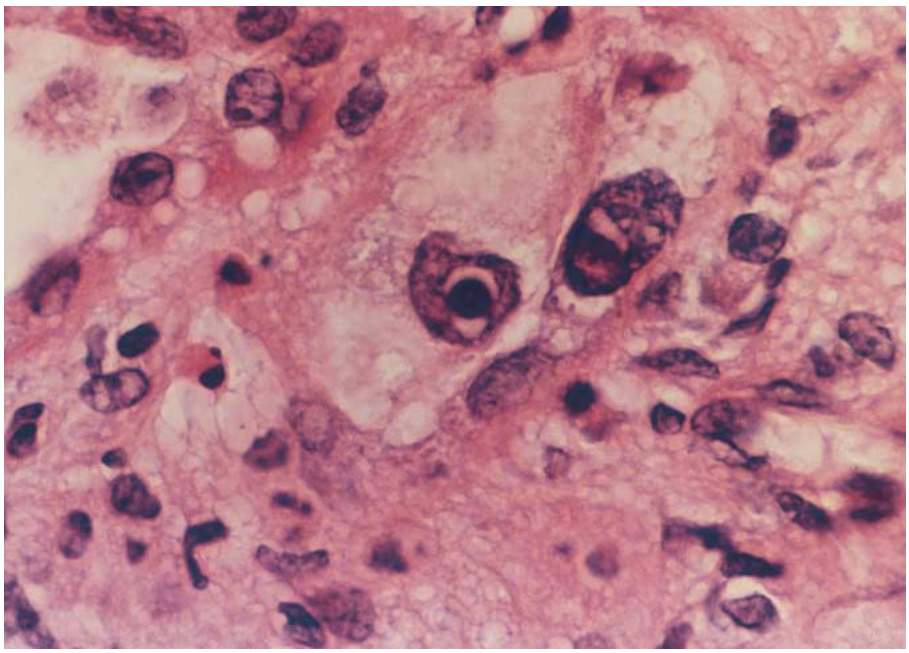

Fig. 1. Hyperchromatic large oval basophilic intranuclear inclusions. HE. × 1,000.

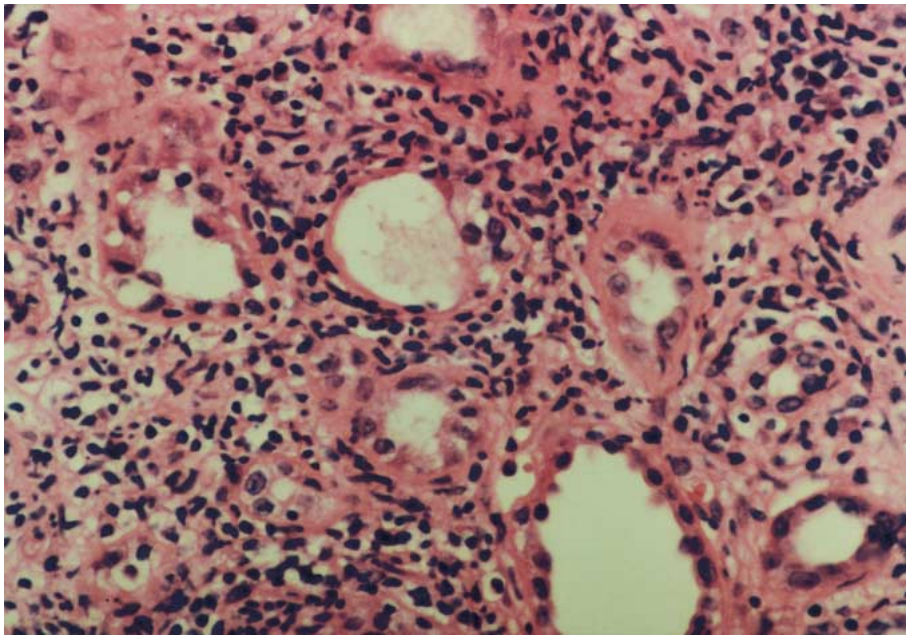

Fig. 2. Heavy interstitial infiltrate composed primarily of mononuclear cells. HE. × 400.

In the setting of kidney transplantation, CMV direct effects occur frequently, but the typical viral inclusions have rarely been found in kidney biopsies. Indeed, CMV inclusions have been reported in less than 1% of renal biopsies when examined by light microscopy [1], albeit the presence of viral inclusions per se does not mean the renal failure is solely due to CMV. The inability to demonstrate CMV inclusions may be due to the very small sample size. In addition, it is interesting to note that although CMV inclusions can be absent by light microscopy, viral components can be identified by immunoperoxidase and PCR [10]; as these techniques are not always performed they can contribute to false negative results. Moreover, Chen et al. [11] consider PCR tests are more sensitive and specific for the diagnosis of CMV disease than serologic or histologic studies and faster than viral cultures.

Both direct and indirect effects of the virus on the kidney can act synergistically and hasten the appearance of chronic allograft nephropathy [9, 12].

In the present report, several features deserve to be mentioned. Our patient had chronic CMV disease, which occur in 10% of CMV previous acute episodes [9]: He had a history of a flu-like syndrome, probable CMV colitis and biopsy-proven CMV skin disease four months posttransplant [7]. After appropriate treatment, CMV recurred 18 months posttransplantation, showing that CMV must be considered as a possible cause of graft dysfunction beyond the classical time-frame of 1 to 6 months posttransplant. Emerging data suggest that universal prolonged prophylaxis may lead to a shift in the time course of CMV infection and may delay the onset of CMV disease in transplant recipients [13]. Despite efficient treatment with biopsy-proven CMV graft eradication, renal function was lost due to an important interstitial nephritis and tubular atrophy two months later. As renal insufficiency progressed over time, mycophenolate levels could have increased and the patient could have been exposed to higher immunosuppression than expected. CMV could have certainly triggered the release of inflammatory cytokines that caused the interstitial lymphocyte infiltration finally observed. Another possible cause of interstitial nephritis could be ganciclovir, but previous administrations of the drug did not cause renal dysfunction.

Repeated Doppler ultrasounds were informed as normal and pp65 antigen assays were negative. Although Doppler ultrasonography is useful for the diagnosis of acute rejection, there is agreement that changes in renal function are not accompanied by consistent changes in blood wave from shape in other situations as chronic allograft nephropathy and interstitial nephritis [14, 15]. With respect to pp65 antigenemia assay, it is a rapid semiquantifiable method that is labor intensive and requires a specially trained technician. Sensitivity decreases drastically with a delay of processing exceeding 6 h [12].

Both patient and donor were CMV positive. This situation bears the worst long-term outcome, perhaps due to the prevalence of multiple CMV virotypes and also because these recipients have a double CMV exposure with reactivation of differing latent donor and recipient CMV.

Interstitial nephritis needs to be differentiated histologically mainly from chronic rejection and from calcineurin inhibitor nephrotoxicity, all included as components of chronic allograft dysfunction. The normal appearance of the wall of the arteries, the absence of tubulitis, the most prominent findings being localized in the medulla and the lack of immune deposits in the immunoflourescence suggest that this lymphocyte infiltration was related to viral interstitial nephritis. In addition, the first kidney biopsy did not show features of chronic rejection, but the second one showed the lymphocyte infiltration of the interstitium. The short time that separates both biopsies makes the diagnosis of chronic rejection more improbable. Despite FK-505 dose was diminished, renal function did not improve, against a drug-induced nephrotoxicity hypothesis. Finally, CMV interstitial nephritis has been described, albeit infrequently, as a cause of renal failure both in native kidneys [16, 17] and in renal allografts [1, 18]. Gnann et al. have shown that principal CMV-infected cells in kidney transplants with CMV infections were interstitium-infiltrating inflammatory cells [10]. Although in a recent series of 10 cases with CMV inclusions in the allograft and florid interstitial nephritis in seven no graft loss was attributable to CMV [1], in our report we suggest that the possible immune alterations caused by the virus can sometimes lead to graft loss.

Finally, in many centers when antirejection therapy is indicated to treat acute rejection episodes, ganciclovir prophylaxis is started regardless of CMV antigenemia or viremia. In this setting, as immunoperoxidase or PCR techniques are infrequently performed, sometimes the viral tissular presence could be the cause of the structural damage, and ganciclovir alone could succesfully lead in certain cases to renal function recovery, as shown by others [19].

In conclusion, CMV should be considered as a possible cause of late kidney allograft dysfunction and eventually renal failure, particularly in those cases in which ganciclovir was used in the early posttransplant period, and despite successful viral graft eradication. Kidney failure could be due to CMV-deferred cytokine-induced chronic release. Immunoperoxidase and PCR techniques should be performed in the biopsy whenever possible to increase the diagnosis of CMV infection, particularly when blood or urinary assays are negative and CMV infection is under suspicion.

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