Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Persistent cytomegalovirus infection in kidney allografts is associated with inferior graft function and survival

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Keywords
chronic allograft nephropathy, chronic graft dysfunction, cytomegalovirus, kidney transplantation.

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Received: 9 February 2006
Revision requested: 18 March 2006
Accepted: 6 June 2006

doi:10.1111/j.1432-2277.2006.00364.x

Summary

The long-term effects of cytomegalovirus (CMV) infections on kidney allografts are unknown. We examined the impact of persistent intragraft CMV infection on long-term kidney allograft function and survival. CMV was diagnosed in 82/172 renal transplant recipients by antigenemia test and viral cultures. Biopsies from 48 of 82 patients taken after CMV infection and from 15 patients with no previous CMV infection detected were available for the immunohistochemical demonstration of CMV antigens and DNA hybridization *in situ*. Five-year follow-up data from these 63 patients were analysed. In 17 patients, CMV antigens and/or DNA persisted in the biopsy >2 months after the last positive finding in blood or urine. Patients with persistent intragraft CMV had reduced graft survival ($P = 0.041$) and Cox regression analysis showed persistent CMV as a risk factor for reduced graft survival (RR: 3.5). Recipients with persistent intragraft CMV had reduced creatinine clearance 1 and 2 years after transplantation ($P = 0.007$) and in multivariate logistic regression analyses including several potential pre- and posttransplant risk factors, persistent CMV was an independent risk factor for lower clearance at 1 and 2 years (OR: 4.4 and 4.9). Our novel findings show that persistent intragraft CMV infection was associated with reduced kidney allograft function and survival.

Introduction

Cytomegalovirus (CMV) is a major cause of morbidity in organ transplant recipients. The impact of CMV on long-term kidney allograft function and survival is, however, still a matter of debate. Evidence supports a role for CMV in the development of acute rejection [1,2], which is thought to be the most important risk factor for chronic allograft nephropathy [3,4]. Some studies suggest an association between CMV and chronic allograft nephropathy, especially together with acute rejection episodes [5,6]. Conversely, other studies have failed to show any correlation between CMV and acute rejection or CMV and chronic renal transplant dysfunction [7].

Persistence of CMV-DNA in the transplant has been associated with chronic rejection in liver transplantation [8,9]. In human kidney allografts, CMV is able to persist for a long period after viremia and active infection, and this persistence has been associated with chronic changes in the graft [10]. We have demonstrated that persistent CMV in the kidney allograft is associated with increased expression of molecules thought to be important in the development of chronic allograft nephropathy [11]. Little is yet known, however, about the nature and the clinical

relevance of this persistence observed in kidney transplants.

Our aim was to investigate the impact of persistent intragraft CMV, together with several pre- and post-transplant factors, on kidney allograft function and survival during a 5-year time-period after transplantation.

Patients and methods

Patients

The adult patients included in this study received a kidney transplant between 1992 and 2000 and remained at follow-up at the Helsinki University Hospital district. All had a clinical suspicion of CMV, and had samples taken for detection of CMV infection ($n = 172$). Results from the same patient population have been published previously [5,11]. Samples for the detection of CMV were obtained only when infection was suspected. No anti-viral prophylaxis for CMV or other herpesviruses was routinely given postoperatively. Clinically significant symptomatic CMV infections were treated with i.v. ganciclovir. Primary immunosuppression therapy at the time of transplantation consisted mainly of cyclosporin A, azathioprine and methylprednisolone. Diagnosis of acute rejection was based on fine-needle aspiration biopsy and/or biopsy histology [12] and on clinical criteria. Clinically significant acute rejections were treated with high-doses of intravenous methylprednisolone, OKT3 or plasmapheresis. Altogether 1451 adult renal transplantations were performed between years 1992 and 2000, and 394 of these patients remained at follow-up at the Helsinki University Hospital Division of Nephrology.

Demonstration of CMV infection

The diagnosis of CMV infection was based on the standard CMV pp65 antigenemia test and rapid shell vial cultures from blood and urine. Specimens for detection of CMV antigenemia and viral cultures from blood and urine were obtained only, when clinical signs of CMV infection were suspected (fever, unexplained increase of serum creatinine, leukopenia, trombocytopenia, hepatopathy, gastroenteritis and pneumonia).

Demonstration of CMV in the biopsies

For the purpose of this study, CMV antigens were detected in kidney allograft biopsies with monoclonal antibody against CMV specific protein pp65 (Biotest, Dreieich, Germany) and indirect immunoperoxidase staining. The biopsy material was snap-frozen, and 3–4 μm thick sections were cut, acetone fixed, and stored at −20 °C until used. Before staining, the sections were treated with chloroform to avoid unspecific reactions with endogenous peroxidase. The presence of CMV in kidney allograft biopsies was also demonstrated by DNA hybridization *in situ* using a biotinylated probe (Enzo Biochem Inc., New York, NY, USA) prepared from a mixture of two clones of CMV sequences in the *Bam*HI site of pBR22 as described previously [9]. All the biopsies used for the detection of CMV were taken after CMV infection and were either 6-month protocol biopsies or biopsies taken for clinical indications (suspicion of rejection or deterioration of graft function). As no extra biopsy or blood samples were taken for the purpose of this retrospective study, approval of the ethics committee was not required.

Clinical variables

The following baseline data at the time of transplantation were obtained from patient files: recipient age and gender, donor age and gender, primary renal disease, number of HLA-A, B and DR mismatches, cold ischemia time, and delayed graft function (as defined by the need of postoperative dialysis during the first week after transplantation). Systolic and diastolic blood pressure and the following laboratory values were obtained from the patient files annually after transplantation: blood trough level of cyclosporin A, glycosylated haemoglobin, and total serum cholesterol.

Demonstration of kidney function

Function of the kidney allograft was measured as the level of serum creatinine (μmol/l), and creatinine clearance (ml/min/1.73 m^2) was calculated with the Cockcroft–Gault formula [13].

Statistical analyses

All data are expressed as mean ± 1 standard deviation, unless otherwise indicated. Difference in the distribution of continuous variables was assessed using the nonparametric Mann–Whitney *U*-test, and differences between three groups were evaluated by the nonparametric Kruskal–Wallis one-way analysis. Nonparametric tests were chosen because all distributions were not normal. Graft survival probabilities were estimated by the Kaplan–Meier method, and differences between two or more groups were determined by the log rank test. Univariate Cox regression analysis was used to calculate relative risks (RR) and 95% confidence intervals (CI) of graft failure. Graft survival was analysed both uncensored for death, i.e. death with a functioning graft was considered as an event, and censored for death, i.e. deaths with functioning grafts were censored. For logistic regression analyses,

creatinine clearance values were converted to binary and used as outcome variables. The median was used as a cut point to obtain two categories. At 1 year post-transplantation the cut-off values were <61 ml/min ($n = 32$) and ≥61 ml/min ($n = 31$), and at 2 years <59 ml/min ($n = 31$) and ≥59 ml/min ($n = 31$). Based on the recommendation not to include more than one variable per 10 events in multivariate analysis [14,15], we included at maximum three variables in logistic regression analyses at the same time, and only one variable in Cox regression analysis. For multivariate analyses, the three most significant variables in univariate analysis were chosen. The calculations were performed with SPSS statistical software (version 12.0.1; SPSS Inc., Chicago, IL, USA). Two-tailed *P*-values <0.05 were considered statistically significant.

Results

CMV infections

In 172 renal transplant recipients, CMV was diagnosed in 82 patients. Frozen biopsy material from biopsies taken after CMV infection were only available from 48/82 patients for the demonstration of CMV antigens by immunohistochemistry and DNA by hybridization *in situ*. Frozen biopsy material was available for the demonstration of CMV also from 15 patients with no evidence of previous CMV infection, despite several samples taken for the detection of CMV at different time-points after transplantation. These 63 patients were further analysed. In the 48/82 CMV patients CMV was diagnosed mean 61 ± 62 days (SD) after transplantation by positive pp65-antigenemia test and viral cultures from blood and urine ($n = 44$), or by a positive viral culture from urine only ($n = 4$). Several CMV infection episodes developed in 19/48 patients. All except four patients received gancyclovir treatment. These four patients demonstrated occasional low level CMV antigenemia (<10/50 000) only, which subsided during follow-up period of a few days.

In 17 of the 48 patients with a history of CMV infection, CMV persisted in the kidney allograft, as CMV antigens or DNA or both were demonstrated in the biopsy 2–12 months after the last positive CMV finding in blood or urine (persistent CMV). In 14 patients both CMV antigens and DNA were found in the biopsy, and in three patients only CMV DNA was found in the biopsy. No CMV DNA or antigens were demonstrated in the biopsies of 31/48 patients with previous CMV infection (nonpersistent CMV) or in the biopsies from 15 patients with no history of CMV infection. Of the biopsies analysed, 12/17 were protocol biopsies in the persistent CMV group, 22/31 in the nonpersistent CMV group, and 9/15 in the no CMV group. Biopsies for the demonstration of CMV were obtained mean 267 ± 187 days after transplantation in the persistent CMV group, mean 303 ± 286 days after transplantation in the nonpersistent CMV group, and mean 243 ± 216 days after transplantation in the group with no previous CMV (P = nonsignificant, NS). No differences were recorded in the baseline characteristics of these three groups, i.e. persistent CMV, nonpersistent CMV, and no CMV groups (Table 1).

Acute rejections

Acute rejection developed in 11/17 patients with persistent intragraft CMV mean 43 ± 49 days after transplantation and in 17/31 patients with nonpersistent CMV infection mean 32 ± 18 days after transplantation. Of the 15 patients with no CMV, 10 suffered from acute rejection mean 51 ± 65 days after transplantation (P = NS). Most of the acute rejection episodes were mild and fully reversible. One patient with persistent CMV, one patient with nonpersistent CMV, and two patients with no CMV suffered from steroid-resistant acute rejection and were successfully treated with OKT3. In addition, one patient with persistent CMV and two patients with nonpersistent CMV suffered from grade II vascular rejection and were successfully treated with plasmapheresis and OKT3.

Survival

Follow-up data 5 years after transplantation was analysed from all the 63 patients. Of these, 12 died or returned to dialysis during the follow-up. In the group of patients with persistent CMV in the graft, three patients died with a functioning graft (causes of death were cardiovascular in two, and ischemic colitis in one patient), and two patients returned to dialysis because of graft failure during the 5 years follow-up. One patient died with graft failure before dialysis was started (cause of death was renal insufficiency). In the nonpersistent CMV group two patients died with a functioning graft (causes of death were cardiovascular and lymphoma) and one patient returned to dialysis because of graft failure. In the group with no CMV two patients died with a functioning graft (causes of death were cardiovascular and unknown) and one patient returned to dialysis. Graft survival (uncensored for death) in patients with persistent CMV was significantly reduced compared with patients with nonpersistent CMV and no CMV ($P = 0.049$) (Fig. 1a). A similar trend was seen in death-censored graft survival ($P = 0.11$, NS; Fig. 1b). When the study population was divided into two groups, comparing patients with persistent CMV in the graft with patients with no evidence of CMV in the graft (i.e. both the other groups combined), significantly reduced graft survival (uncensored for death) was recorded in the persistent CMV group ($P = 0.020$;

Table 1. Baseline characteristics of the three study groups*.

	No CMV ($n = 15$)	Nonpersistent CMV ($n = 31$)	Persistent CMV ($n = 17$)
Primary renal disease [*n* (%)]			
Diabetic nephropathy	4 (27)	5 (16)	6 (35)
Glomerulonephritis	0	10 (32)	2 (12)
Others	11 (73)	16 (52)	9 (53)
Serological CMV status [*n* (%)]			
R–/D–	1 (7)	0	0
R–/D+	4 (27)	9 (29)	4 (24)
R+/D–	1 (7)	3 (10)	1 (6)
R+/D+	9 (60)	19 (61)	12 (71)
Donor age (years)	36 ± 16	37 ± 15	44 ± 15
Recipient age (years)	46 ± 11	49 ± 11	48 ± 11
Donor gender (male/female)	7/8	15/16	11/6
Recipient gender (male/female)	9/6	22/9	9/8
HLA-A, -B, and -DR-mismatch	2.3 ± 1.2	2.2 ± 1.0	2.8 ± 0.8
Cold ischemia time (h)	22 ± 8	22 ± 4	22 ± 5
Delayed graft function [*n* (%)]	5 (33)	14 (45)	8 (47)
Acute rejection episodes [*n* (%)]	10 (66)	17 (57)	11 (65)
Systolic blood pressure (mmHg)†	148 ± 26	145 ± 19	148 ± 16
Diastolic blood pressure (mmHg)†	90 ± 9	84 ± 9	84 ± 10
Total serum cholesterol (mmol/l)†	6.0 ± 1.2	6.0 ± 1.3	6.4 ± 1.3
GHbA1C (%)†‡	7.0 ± 1.6	6.6 ± 1.4	7.6 ± 1.7
B –CyASPES (μg/l)†§	119 ± 19	110 ± 27	111 ± 34

*All differences are nonsignificant.
†Determined 1 year after transplantation.
‡GhbA1c, glycosylated haemoglobin A1c.
§B-CyASPES, blood trough level of cyclosporin A.

Fig. 2a). Death-censored graft survival was also significantly reduced in patients with persistent CMV compared with the other patients analysed ($P = 0.041$; Fig. 2b).

Cox regression analysis

The risk of graft loss (uncensored for death) associated with the following variables was investigated by univariate analysis: persistent CMV in the graft (compared with both the other groups combined), acute rejection episodes, delayed graft function, donor age, mismatch, cold ischemia time, and recipient age (Table 2a). Persistent intragraft CMV was the only significant risk factor for poorer graft survival (RR: 3.5, $P = 0.030$). When the risk of the same variables were studied with regard to death-censored graft survival, HLA-ABDR mismatch was a risk factor for reduced graft survival (RR: 5.0, $P = 0.028$), and borderline increased relative risk was seen with persistent CMV and longer cold ischemia time (RR: 5.3 for persistent CMV, $P = 0.068$, Table 2b). As the patients with no previous CMV do not represent true control patients due to possible selection bias (suspicion of CMV and biopsy material available for the demonstration of CMV), all these analyses were also performed comparing only patients with persistent CMV to patients with nonpersistent CMV. In these analyses, persistent intragraft CMV was similarly a risk factor for poorer graft survival (uncensored for death; RR: 4.7, 95% CI: 1.2–18.8, $P = 0.03$). The risk associated with CMV with regard to death-censored graft survival was statistically nonsignificant (RR: 7.1, $P = 0.09$).

Creatinine clearance

Creatinine clearance values 1 and 2 years after transplantation were significantly lower in patients with persistent CMV in the graft compared with the nonpersistent or no CMV groups (at 1 year 53 ± 19 vs. 70 ± 19 and 63 ± 16 ml/min respectively, $P = 0.018$ and at 2 years 50 ± 19 vs. 67 ± 19 and 59 ± 21 ml/min, $P = 0.012$). When the study population was divided into two groups, comparing patients with persistent intragraft CMV to patients with no evidence of persistent CMV, significantly lower clearance was recorded in the persistent CMV group at 1 and 2 years after transplantation (at 1 year 53 ± 19 vs. 67 ± 18 ml/min, $P = 0.007$ and at 2 years 50 ± 19 vs. 65 ± 21 ml/min, $P = 0.007$). For logistic regression analysis, the creatinine clearance values were converted to binary values and used as outcome variables. In univariate analysis, persistent CMV and higher donor age showed to be the only significant risk factors for lower clearance 1 year after transplantation (OR: 7.69 for

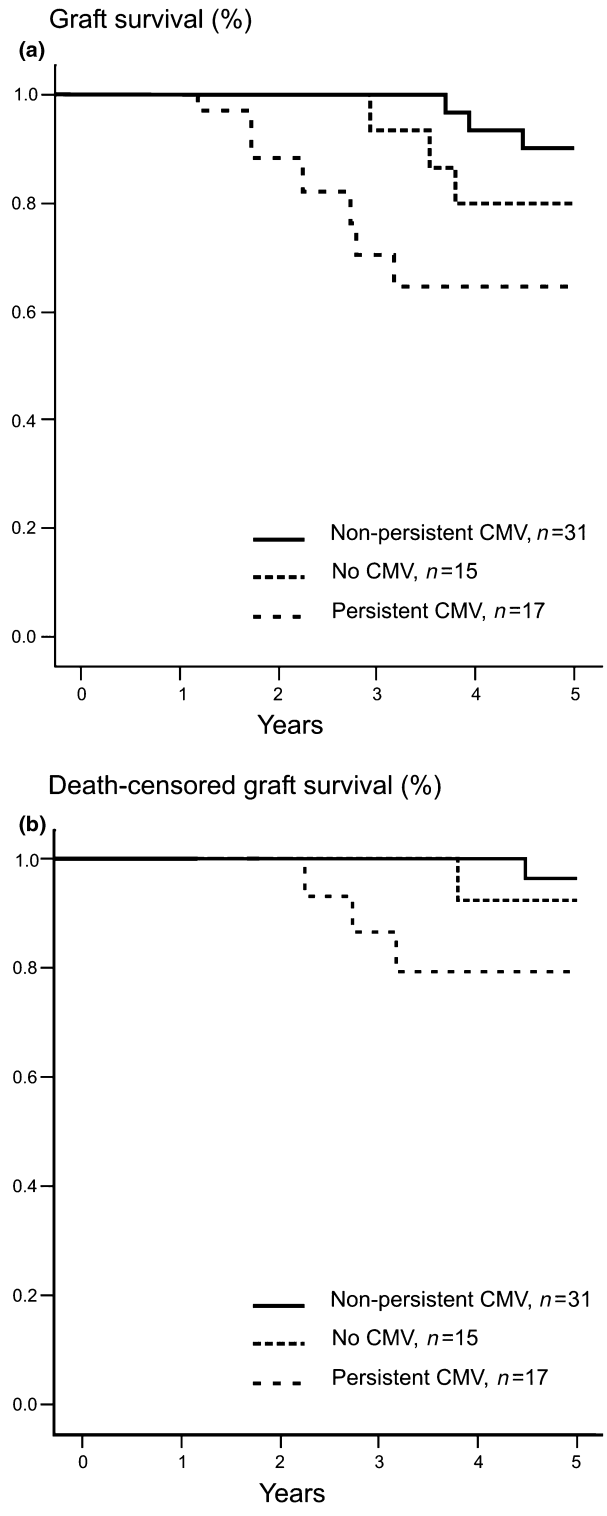

Figure 1 (a) Graft survival (uncensored for death; $P = 0.049$) and (b) death-censored graft survival (P = NS) in the three study groups (persistent CMV, nonpersistent CMV, no CMV).

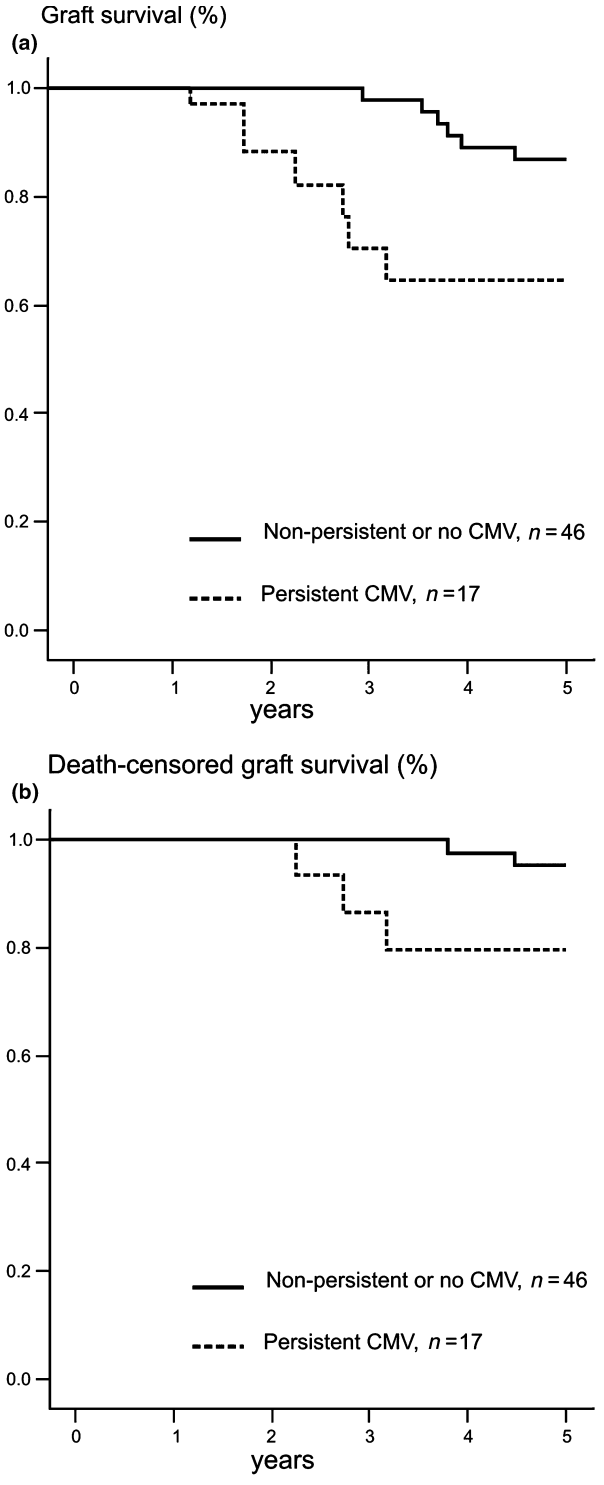

Figure 2 (a) Graft survival (uncensored for death; $P = 0.020$) and (b) death-censored graft survival ($P = 0.041$) in patients with persistent CMV compared with patients with nonpersistent or no CMV.

Table 2. Univariate Cox regression analysis of the risk factors for graft loss: (a) uncensored for death and (b) death-censored.

Variable	Relative risk for graft loss (uncensored)	Confidence interval 95%	*P*-value
(a)			
Persistent CMV	3.5	1.1–10.9	0.030
Acute rejection	0.47	0.13–1.7	0.467
DGF*	1.4	0.47–4.5	0.552
Donor age (years)	1.02	0.98–1.1	0.393
ABDR-mismatch†	2.1	0.95–4.6	0.063
CIT‡	1.1	0.94–1.2	0.383
Recipient age (years)	1.001	0.95–1.1	0.972
(b)			
Persistent CMV	5.3	0.89–31.8	0.068
Acute rejection	0.93	0.15–5.5	0.93
DGF*	2.2	0.36–13.0	0.40
Donor age (years)	0.99	0.94–1.1	0.85
ABDR-mismatch†	5.0	1.2–21.1	0.028
CIT‡	1.2	0.99–1.4	0.056
Recipient age (years)	1.02	0.94–1.1	0.62

*DGF, delayed graft function.
†ABDR-mismatch, HLA-A, B, and DR mismatch.
‡CIT, cold ischemia time (h).

CMV, $P = 0.004$, OR: 1.06 for 1 year increase in donor age, $P = 0.014$, Table 3a). Similarly, in multivariate analysis (persistent CMV, donor age, and cold ischemia time), persistent intragraft CMV and higher donor age appeared as independent risk factors for lower clearance 1 year after transplantation (OR: 4.4 for CMV, 95% CI: 1.2–16.6, $P = 0.027$, and OR: 1.04 for 1 year increase in donor age, 95% CI: 1.00–1.09, $P = 0.049$). Persistent CMV appeared as the only significant risk factor for lower clearance at 2 years in univariate analysis (OR: 4.3, $P = 0.026$, Table 3b). In multivariate analysis (persistent CMV, cold ischemia time, and recipient age), persistent CMV showed as the only significant independent risk factor for lower clearance 2 years after transplantation (OR: 4.9, 95% CI: 1.3–18.9, $P = 0.020$). In the demographic data of the study population, some degree of differences, although not statistically significant, was recorded in donor age and HLA-mismatches between the groups. When tested in multivariate analyses (persistent CMV, HLA mismatch, donor age), the risk of lower renal function associated with persistent CMV was independent of donor age and HLA mismatches both 1 and 2 years after transplantation (OR: 6.1, 95% CI: 1.5–24.6, $P = 0.01$, and OR: 4.1, 95% CI: 1.1–15.5, $P = 0.03$ respectively). Similarly, donor age was an independent risk factor at 1 year after transplantation (OR: 1.05 for 1 year increase, 95% CI: 1.01–1.09, $P = 0.02$). As acute rejection is one of the strongest risk factors for poor graft outcome, all these variables were also tested together with acute rejection in multivariate analyses; the risks associated with persistent CMV at 1 and 2 years, and the risk associated with donor age at 1 year were independent of acute rejection episodes (data not shown).

Table 3. Univariate logistic regression analysis of risk factors for creatinine clearance (a) <61 ml/min 1 year and (b) <59 ml/min 2 years after transplantation.

	OR for lower clearance at 1 year	95% CI	*P*-value
(a)			
Persistent CMV	5.1	1.4–18.0	0.012
Acute rejection	0.62	0.23–1.7	0.36
DGF*	1.6	0.57–4.3	0.38
Donor age (years)	1.1	1.01–1.1	0.014
ABDR-mismatch †	0.95	0.57–1.6	0.83
CIT‡	0.96	0.87–1.1	0.38
Recipient age (years)	1.003	0.96–1.1	0.89
(b)			
Persistent CMV	4.3	1.2–15.2	0.026
Acute rejection	1.1	0.41–3.2	0.80
DGF*	1.3	0.47–3.6	0.61
Donor age (years)	1.02	0.98–1.1	0.33
ABDR-mismatch†	1.3	0.76–2.1	0.37
CIT‡	1.1	0.95–1.2	0.29
Recipient age (years)	1.04	0.99–1.1	0.085

*DGF, delayed graft function.
†ABDR-mismatch, HLA-A, B, and DR mismatch.
‡CIT, cold ischemia time (h).

Because of the limitations in the control group of patients with no previous CMV, all these analyses were also performed comparing only patients with persistent CMV to patients with nonpersistent CMV. In these analyses, persistent CMV was similarly a risk factor for reduced graft function at 1 and 2 years (OR: 6.8, 95% CI: 1.4–34.3, $P = 0.02$, and OR: 5.0, 95% CI: 1.2–21.4, $P = 0.03$ respectively), independent of donor age, HLA-mismatches and acute rejections. No differences were recorded in the creatinine clearance values at 3–5 years after transplantation between the persistent CMV and the other groups (data not shown).

Discussion

Persistent CMV in the kidney allograft predicted inferior kidney allograft survival and function. Patients with CMV DNA or proteins found in the allograft after viremia or viruria had reduced renal function 1 and 2 years after transplantation, and their graft survival was decreased. The effect of persistent CMV on both graft survival and function sustained even when adjusting for the effect of several other pre- and post-transplant factors.

Considerable controversy exists as to the role of CMV in chronic allograft nephropathy. Evidence suggests that

CMV is associated with acute rejection episodes [2], and graft loss [16,17], whereas a study by Dickenmann *et al.* [7] found no association between CMV and acute rejection episodes or long-term graft function. We have shown that the presence of CMV proteins or genome in the kidney allograft together with a previous history of acute rejection episodes was associated with increased vasculopathic changes in 6 month protocol biopsies [5]. Similar results of the impact of CMV on chronic rejection only in the presence of previous acute rejection have also been presented [6].

Some evidence shows that CMV genome is able to persist in the kidney allograft several months and that this persistence can be associated with the chronic changes in the graft [10]. Persistent expression could be found in various tubular, glomerular and vascular structures of the graft during a period without a positive CMV finding in blood or urine for several weeks or even months after a systemic infection. We found CMV antigen expression and especially CMV-DNA in tubular epithelial cells, in endothelial cells as well as in interstitial inflammatory cells in the kidney allografts.

Our findings show persistent cytomegalovirus infection in the allograft as a new possible risk factor for poorer early kidney allograft function and survival. Previous studies have only analysed the association of CMV infection or disease with rejections or graft function and survival, and the presence of intragraft CMV has not been recorded. Our results suggest that it could be particularly the persistence of CMV in the graft that is associated with the inferior outcome after transplantation. This could be an explanation of why this association has been difficult to demonstrate, and why previous studies have presented controversial long-term results about the effect of CMV on kidney allograft.

In the baseline characteristics of the three study groups, patients with persistent CMV had a higher number of HLA-A, B, and DR mismatches and also somewhat higher donor age; both factors that increase the immunogenicity of the allograft. Increased alloimmune response early after transplantation could trigger CMV, and the virus may persist more easily in allografts with more immunogenic activation. The persistence of CMV in organ allografts has been examined only in a few studies [8–11], and no data about the factors that might favour the persistence of CMV are available. Moreover, animal models show that CMV is able to increase the immunogenicity of the allograft by several mechanisms [18,19]. Indirectly via inflammatory response to infection, but also directly, persistent CMV could possibly induce the expression of adhesion molecules and production of cytokines, which result in growth factor response and contribute to the early development of chronic changes in the graft and finally, to the deterioration of graft function. Our recent findings support this hypothesis [5,11].

Graft function or survival was not reduced in the nonpersistent CMV group in any of the analyses, compared with patients with no previous CMV. Therefore, to increase the power of the statistical analyses, we combined these two groups with no evidence of persistent CMV for further analyses. Of known risk factors for chronic allograft nephropathy, we found HLA-mismatch as a risk factor for death-censored graft loss, but other risk factors had no impact on graft survival. Our material, however, comprised only patients with CMV infection or a suspicion of CMV infection after transplantation and does not represent normal kidney transplant recipient population. For instance, 60% of the patients in this material underwent acute rejection episodes, whereas the normal acute rejection rate is much lower [20]. The control group in this study was not ideal; patients in our centre are not regularly monitored for CMV, and only patients with a suspicion of CMV (and samples taken for detection of CMV) could be included in the study. These patients do not represent true control patients due to other post-transplant complications that have raised the suspicion of CMV. Despite the material being selective for patients with complications after transplantation, the effect of persistent intragraft CMV on graft function and survival was clearly recorded. Due to this possible selection bias in the group of patients with no previous CMV, all the analyses were also performed comparing only recipients with persistent CMV to recipients with nonpersistent CMV, with similar results. The groups differed slightly in the baseline data with regard to donor age and the number of HLA-mismatches; the risk of poor graft function associated with persistent intragraft CMV was, however, independent of donor age, HLA-mismatches, or acute rejection. Unfortunately, the small number of events did not allow us to calculate multivariate Cox regression analyses of the risk factors for graft loss. Despite the lack of true control group due to the retrospective nature of this study, in our opinion it clearly demonstrates a novel association of persistent CMV with poor outcome after transplantation, especially compared with recipients with previous transient CMV infection.

In conclusion, the results of this study show that cytomegalovirus persisting in the kidney allograft after viremia is associated with significantly reduced graft survival and inferior graft function 1 and 2 years after transplantation. On the basis of these results and those of our earlier studies, we hypothesize that persistent CMV infection in the graft might cause continuous damage to graft, contributing to the early histopathological changes that lead to graft dysfunction and ultimately to graft failure [5,11]. Our novel findings bring new insights into the association

of CMV and chronic allograft nephropathy. However, prospective studies with larger materials are needed to confirm this new observation.

Funding

This study was supported by grants from Biomedicum Helsinki Foundation, The Kidney Foundation Finland, The Finnish Medical Society Duodecim, The Finnish Society of Transplant Surgeons, from Helsinki University Hospital Research Funds (EVO to I.L.) and from a special governmental subsidy for health sciences research (EVO to I.H.).

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