Cytomegalovirus as a Risk Factor in Living-related Renal Transplantation

A Prospective Study

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Forty-four living-related donor kidney (LRD) recipients (19 HLA-identical and 25 haploidentical) were followed prospectively to determine the posttransplant incidence and sequelae of cytomegalovirus (CMV) infection as they relate to the CMV status of recipients and donors. CMV titers were measured in all patients before transplantation by an immunofluorescent assay (IFA). Recipients similarly had CMV titers measured at selected intervals after transplant and during febrile episodes. Appropriate viral cultures were simultaneously performed. Laboratory evidence of infection was correlated with symptoms and signs of active CMV disease. Mean follow-up period was 20 ± 12 months with a range of 3–51 months. Three patients were excluded due to early acute rejection resulting in graft loss. Twenty-eight of 41 donors (68%) and 22 of 41 recipients (54%) had positive CMV titers before transplantation. Six of 41 recipients (15%) subsequently developed clinical and laboratory evidence of CMV infection: three of 19 seronegative recipients and three of 22 seropositive recipients. All six patients received kidneys from seropositive donors. Four patients had severe CMV disease (2 seronegative, 2 seropositive), whereas two patients had leukopenia and fever only. Two patients with severe CMV infections subsequently lost their grafts due to unrelated causes. Overall, actual patient and graft survival of the entire group is 95% and 82%, respectively. In conclusion, individuals who receive LRD kidneys from seronegative individuals are unlikely to develop CMV infection, and transplantation of seropositive LRD kidneys may be associated with transmission of CMV in susceptible recipients regardless of their serologic status. With appropriate management of CMV illness in the posttransplant period, LRD kidney donation is safe and efficacious and should not be discouraged on the basis of pretransplant CMV serology in any donor-recipient pairing.

CYTOMEGALOVIRUS (CMV) infection is ubiquitous in the normal population as well as in the renal transplant recipient population.[1] Furthermore, CMV infection may cause serious and sometimes fatal illnesses in the immunocompromised host.[2,3] Thus, recommendations have been made regarding the prevention of viral transmission as well as drug prophylaxis, especially in cadaveric donor situations where the CMV status of the donor may be unknown.[4] Evidence from a number of large collected series has implicated the transplanted donor kidney as the vehicle for the transmission of the virus to previously uninfected or seronegative recipients.[1] The issue of whether patients with chronic end-stage renal disease are at increased risk for CMV infection after receiving kidneys from living-related donors (LRD) who are seropositive for CMV remains controversial.

We have followed prospectively a group of LRD kidney recipients to determine the posttransplant incidence and sequelae of CMV infection, specifically with respect to the CMV status of the LRD. Our data reveals that regardless of the serologic status of the recipient, transplantation of kidneys from seropositive LRDs may increase the risk of CMV infection but does not increase the risk of lethal viral illness or of graft loss.

Materials and Methods

Forty-four LRD renal transplants were performed between January 1982 and December 1985 at the University of Illinois Medical Center in Chicago. Nineteen were HLA-identical and 25 were haploidentical donor-recipient pairs. The basic immunosuppressive protocol consisted of azathioprine and steroids for all HLA-identical recipients. Before January 1984, haploidentical recipients were treated with an additional course of 14 days of antilymphocyte globulin (ALG) in the immediate posttransplant

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period as previously described.[5] Thereafter, haploidentical recipients received cyclosporine and steroids with no prophylactic ALG use. Donor-specific pretransplant blood transfusions (DSBT) were used routinely in all haploidentical donor-recipient pairs, and were administered under azathioprine coverage as previously described.[6]

All donors had serum CMV titers measured by immunofluorescent antibody assays (IFA) (Electro Nucleonics Inc., Columbia, MD).[7] Recipients similarly had pretransplant CMV titers measured by IFA or complement fixation. Thereafter, at the time of admission, at 6 and 12 weeks after transplant and during any febrile episode, the serologic studies, as well as sputum, blood, and urine viral isolation and culture studies, were performed. A positive serologic titer was defined as >1:8 dilution, and active infection by CMV was serologically defined as a four-fold increase or seroconversion of the CMV antibody titer in the posttransplant serum. Positive culture of the virus from a body cavity or from specimens of urine, sputum, or blood (growth on a human fibroblast cell line, WI38) was also considered as evidence of new infection where these cultures had been negative previously. Clinical symptoms and signs of active CMV disease were correlated with the laboratory evidence.

Mean follow-up period was 20 ± 12 months with a range of 3–51 months.

Results

Three patients were excluded from the study due to early acute graft loss as a result of accelerated rejection, leaving 41 patients available for long-term follow-up. Twenty-eight of 41 donors (68%) and 22 of 41 recipients (54%) had positive CMV titers before transplantation. Six recipients (15%) subsequently developed clinical and serologic evidence of CMV infection: three of 19 seronegative recipients and three of 22 seropositive recipients (Table 1). Seroconversion or an increase in antibody titers did not occur in the absence of a clinical manifestation of infection. The six patients who developed CMV infection received kidneys from 28 seropositive donors (21%). One patient was a seronegative recipient of an HLA-identical kidney, whereas five patients were from a group of 25 recipients who received a series of pretransplant donor-specific blood transfusions from their haploidentical donors (20 seropositive and 5 seronegative). Two of these five patients were seronegative and three were seropositive before transplant.

Severe CMV illness that required hospitalization occurred in four recipients, whereas two patients manifested only fever and leukopenia. The clinical episodes developed at a mean of 5 weeks (range: 3–6 weeks) after transplantation. No allografts were lost concurrent with the acute CMV infections, but two recipients with severe CMV disease did ultimately lose their kidneys. One patient developed recurrent membranous glomerulonephritis with a severe nephrotic syndrome, necessitating graft nephrectomy 18 months after the initial infection. The other patient died after an intracranial hemorrhage with a functioning kidney 4 months after recovery. One additional patient in the study died of a myocardial infarction with a functioning kidney. Thus, the actual patient survival for the entire group was 95% (42 of 44 patients). Three additional kidneys were lost due to chronic rejection consequent on noncompliance with the immunosuppressive regimen, for an actual graft survival of 82% (36 of 44 grafts).

TABLE 1. *Relationship between Donor and Recipient CMV Serology Before Transplant and Subsequent Infection with CMV in the Post Renal Transplant Period*

	Donor	
Recipient	Seropositive N = 28	Seronegative N = 13
Seropositive (N = 22)		
No. of patients	17	5
CMV infection	3	—
Seronegative (N = 19)		
No. of patients	11	8
CMV infection	3	—

Discussion

Our study confirms the excellent long-term patient and graft survival results from living-related donor renal transplantation regardless of the CMV serologic status of the donor-recipient pair.[8] The serologic status of the recipients was not predictive of the likelihood of clinical CMV illness since seronegative and seropositive recipients were at equal risk. Thus, recipient seronegativity is not a contraindication to transplantation from a seropositive donor. Seropositive patients were not protected against reinfection or reactivation of latent CMV if they received transplants from seropositive donors. However, infection and clinical manifestations of CMV are more likely to appear in recipients of kidneys from seropositive donors, as recipients of seronegative donor kidneys did not develop CMV infection. These findings support the contention that transmission of the virus by the donor kidney is an important factor in the development of CMV infection of the recipient.[1] Adding weight to this argument is the demonstration, using DNA recombinant techniques, of transmission and expression of identical CMV viral strains between donor and recipient.[9] Furthermore, in seropositive recipients, "reactivation" of CMV would appear to represent rather reinfection with a different strain of the virus, in fact carried in the transplanted kidney.[9]

The incidence of CMV infection in this study was 15%: a figure that might underestimate the true infection rate since up to 60% of patients may develop an asymptomatic

carrier state at long-term follow-up.[1] This latter figure may decrease significantly to 8–10% if the kidney donor is CMV seronegative. Seroconversion, or a rise in posttransplant CMV titers, was usually associated with some form of clinical illness, a feature previously noted by Simmons et al.[10]

Fewer recipients of HLA-identical LRD kidneys developed CMV infection than in those recipients of mismatched LRD kidneys. This observation was confirmed by others.[1] This difference might be explained on the basis of the use of less immunosuppression in the HLA-identical recipient.[8] An alternative explanation might be the use of DSBT in the mismatched pairs. The risk of transmission of CMV by blood or blood products has been previously reported to be about 2.7%/unit.[11] This risk is small but may increase the chances of CMV infection in the immunocompromised recipient. However, only five of 25 recipients transfused from their seropositive donors acquired CMV infection. Thus, DSBT does not seem to diminish the safety of the overall transplant procedure when the blood originates from a CMV seropositive donor.

No patients suffered the loss of life or allograft as a result of infection with CMV. This favorable outcome is partially due to the recognition that CMV infection enhances the immunosuppressed state, leading to routine withdrawal of all immunosuppressive agents for the duration of the illness (except for steroids at a low maintenance dose).

The correlation between the type or degree of chemical immunosuppression and severity of CMV illness has recently been demonstrated with the introduction of protocols using cyclosporine, low-dose steroids, and, specifically, a reduction in the use of antilymphocyte globulin. These protocols have been associated with a decrease in the incidence and the severity of CMV illness.[12–14]

Thus it appears from our study and other published reports that at least three factors may be operational in the development of CMV infection in the LRD transplant recipient: (1) the CMV status of the donor, (2) the degree of immunosuppression used, and (3) the CMV status of the recipient. We conclude from our study that (1) individuals who receive LRD kidneys from seronegative individuals are unlikely to develop CMV infection in the posttransplant period, (2) the transplantation of seropositive LRD kidneys may be associated with transmission of CMV in susceptible recipients, and (3) CMV infection occurs with equal frequency in seropositive and seronegative LRD kidney recipients. With careful management, serious morbidity and loss of life can be avoided in those individuals in whom CMV infection develops in the posttransplant period. Thus, living-related kidney donation should not be discouraged on the basis of pretransplant CMV serology alone in any donor-recipient pairing.

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