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Donor and recipient CMV serostatus and antigenemia after renal transplantation: An analysis of 486 patients

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Abstract

Background: Cytomegalovirus infection in renal transplant recipients is a major clinical problem, with both short and long term sequelae. Infection can occur as a result of reactivation of latent virus or new infection from donor tissues. The impact of donor and recipient serostatus on viremia is well recognised, with seronegative recipients at greatest risk after transplantation of an organ from a seropositive donor. However, the impact of grafting such organs into seropositive recipients is less clear.
Objectives: To assess the impact of recipient serostatus on the risk of CMV antigenemia in a large renal transplant cohort.
Study design: We prospectively quantified CMV antigenemia over time in a cohort of 486 recipients. We analysed the antigenemia status according to donor and recipient serostatus.
Results: Antigenemia was most common in seronegative recipients of organs from seropositive donors (D+/R−). Nevertheless, we observed that even in CMV seropositive recipients, the impact of donor serostatus on CMV antigenemia is still substantial ($p = 0.006$; OR = 2.2).
Conclusions: In this large study, donor serostatus clearly plays a significant role in determining CMV risk, even in seropositive recipients.

Keywords: CMV; Transplant; Kidney; Reactivation; Superinfection

1. Introduction

Cytomegalovirus (CMV) is a significant problem in the immunosuppressed. In particular, renal transplant patients are at high risk of disease in the early post-transplant period. Long term survival of the graft may also be influenced by infection/reactivation (Schnitzler et al., 2003).

CMV may cause disease upon primary infection. Seronegative recipients are therefore at high risk, especially if the donor organ is from a seropositive individual (Brayman et al., 1988; Gjertson, 1992, 2003; Hirata et al., 1996; Ricart et al., 2005; Schnitzler et al., 2003; Warrell et al., 1980). Alternatively CMV may cause disease upon reactivation in immunosuppressed individuals, where immune surveillance is depressed as a result of disease or drug therapy (Rao et al., 2000; Warrell et al., 1980).

To analyse the role of pre-existing immunity in control of CMV post-transplant, we assessed antigenemia in a large cohort of renal transplant patients who had been carefully prospectively followed. The antigenemia assay is a robust quantitative measure of CMV reactivation which has been used in many previous studies (Pancholi et al., 2004). We analysed four patient groups, donor seropositive, recipient seropositive (D+R+), donor seronegative recipient seronegative (D−R−), and the mismatched D+R− and D−R+ groups. Specifically we analysed what the impact of donor serostatus was in recipients who exhibited prior immunity to CMV.

2. Methods

The patient cohort was taken from those individuals undergoing renal transplantation at the Churchill Hospital, Oxford. Individuals were routinely tested for CMV

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Table 1
Patient characteristics and CMV antigenemia

	D+R+	D−R+	D+R−	D−R−	Total
Patients	128 (26%)	107 (22%)	132 (27%)	119 (25%)	486
CMV detected	55	27	73	17	172 (35%)
CMV >5	29	12	40	8	89 (18%)
CMV >100	7	4	9	3	23 (4%)

serostatus pretransplant using CMV latex assays (BD, Pharmingen). Antigenemia levels were assessed regularly post-transplant up to 99 days, using a cytospin preparation of buffy coat cells from peripheral blood and direct pp65 analysis using APAAP immunochemistry (mouse anti-HCMV pp65 (CLONAB)). The immunosuppressive regimen varied little over this period—all patients received cyclosporin A (dosage adjusted according to levels), methylprednisolone and azathioprine conventional triple therapy. CMV seronegative donors received CMV negative blood products. Prophylaxis for CMV infection (ganciclovir or aciclovir/valaciclovir) was not used during the period studied.

Seven hundred and thirty-five patients were transplanted over the study period. These were divided according to pre transplantation serostatus into four groups—D+R+ (30%), D+R− (23%), D−R+ (24%) and D−R− (23%). Full follow-up data including details of the antigenemia testing up to 99 days were available on 486 patients (Table 1) and it was this group that was analysed in detail.

Statistical analysis was performed using Graphpad Prism software. Analysis of proportion was performed using Fisher's exact tests. To account for multiple comparisons, a p value of <0.05/8, i.e. <0.00625 has been used (Bonferroni correction).

3. Results

Overall, 35% of patients experienced antigenemia during the 99 day follow-up period, in about half of whom this reached a level of over 5/50,000 cells in blood (Table 1). A smaller fraction reached very high levels of antigenemia, although since this will be influenced by the treatment instituted and the response to therapy, it was not analysed further.

Amongst those with antigenemia, the frequencies varied widely between the four patient groups (Table 1 and Fig. 1). The extremes were seen in the seronegative recipient group. Amongst these, those receiving a kidney from a seropositive donor (D+R−) showed an antigenemia rate of 55%, while those receiving an organ from a seronegative donor had a basal rate of 14% (D−R−).

For seropositive recipients, the overall infection rate was 43% in those receiving an organ from a seropositive donor (D+R+), compared to 25% if the donor was seronegative (D−R+). Similarly, for antigenemia levels >5/50,000, the infection rates were 29% and 12%, respectively. The latter represents an odds ratio of 2.9 ($p = 0.002$). While the greatest rate of antigenemia >5/50,000 is seen in the D+R− group, the odds ratio compared to D+R+ is not significant (OR = 1.65; Table 2).

Overall, the risk of infection in R− recipients was 35%, compared to 36% in the R+ group (p = n.s.). When analysed by donor serostatus, D+ organs were associated with a 49% infection rate in the recipients, compared to 19% in D− organs ($p < 0.0001$, OR = 4.0). Similarly, when assessing the rate of infection >5/50,000, no significant difference was seen comparing R+ and R− groups (21% vs. 25%, p = n.s.), while D+ vs. D− groups showed a major effect (35% vs. 10%; $p < 0.0001$, OR = 4.9). Thus, donor status had a major impact on overall infection outcome, even in a group where about half the recipients were already seropositive.

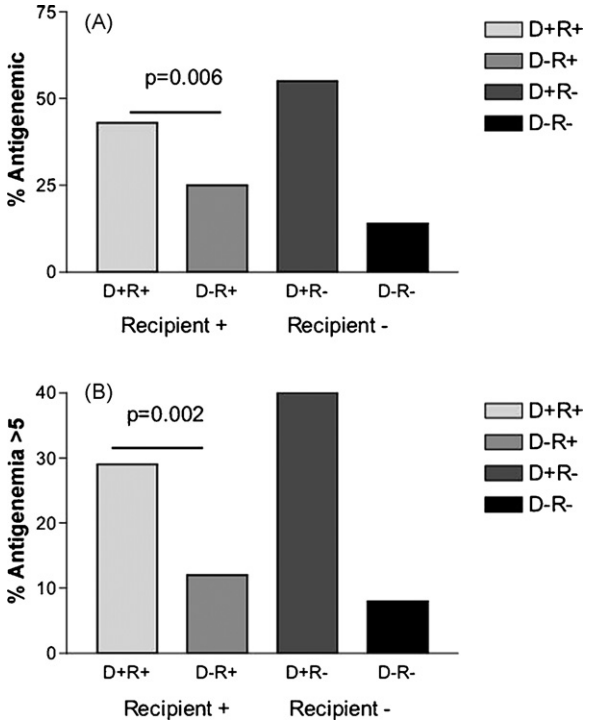

Fig. 1. Comparison of CMV antigenemia rates in different clinical risk groups. The upper panel (A) shows the proportion of individuals experiencing CMV antigenemia over the follow-up period in the four different clinical groups. The lower panel (B) shows the frequency of antigenemia at a level >5/50,000 over the same period. The mean onset of antigenemia did not differ between the different groups. The p value refers to the impact of donor serostatus in the seropositive recipient group. Other p values for these comparisons are shown in Table 2.