

Original Article

Epstein-Barr Viral Infection in Renal Allograft Recipients: a Single Center Experience

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ABSTRACT. In this study we attempted to identify the factors involved in Epstein-Barr viral (EBV) infection among renal allograft recipients. We studied 68 renal allograft recipients hospitalized at the Imam Khomeini Medical Center from 2001 to 2004. Blood samples were obtained from the patients before renal transplantation and repeated every 3 months during the first year after transplantation. Enzyme linked immunosorbant assay (ELISA) tests were performed on these samples to determine if antibodies to EBV antigens, such as viral capsid antigen (VCA) IgM, VCA IgG or Epstein Barr neoantigen (EBNA) IgG, were present. The types of prescribed immunosuppressive agents and the incidence of acute allograft rejection were closely observed to define their association with EBV. EBV infection developed in 58 (85.3 %) patients and active disease in 10 (14.7%). EBV was detected in 40 (58.8%) patients during the first year after transplantation. There was EBNA IgG seropositivity in 65 (95.6%) patients before transplantation; this number increased to 68 (100 %) after transplantation. In contrast, VCA IgG seropositivity increased from 92.6% before transplantation to 96.9% after transplantation; whereas VCA IgM seropositivity increased from 17.6% before transplantation to 58.8% after transplantation. There were no statistically significant differences in the reactivation of EBV infection between the different immunosuppressive regimens, between the groups of acute rejection and no acute rejection, or between the groups that received and did not receive anti-lymphocyte globulin (ALG). We conclude that most EBV activation after transplantation may represent a secondary form of a preexisting infection and we could not find a clear association with a specific immunosuppressive regimen, including the use of ALG. Further investigation is thus required to elucidate the factors involved in the reactivation of the EBV infection in the transplant population.

Key Words: Epstein Barr virus, Acute rejection, Transplantation, Renal, Immunosuppressive.

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Introduction

Epstein Barr virus (EBV) causes a disease that can be intensified by the immunosuppressive agents used to prevent rejection of allo-

grafts.¹⁻³ Furthermore, active EBV infection can result in a dysfunction of the immune system that manifests itself as rejection or post-transplant lymphoproliferative disease (PTLD).⁴

EBV is one of the most prevalent viral infections. Studies have demonstrated that EBV is detectable in 80% to 90% of transplant recipients during the first year.⁵

The purpose of this study was to identify the manifestations of the EBV infection among renal allograft recipients.

Methods and patients

We performed this study on 68 renal transplant recipients who were hospitalized at the Imam Khomeini Medical Center between 2001 to 2004. Blood samples were obtained prior to the operation and every three months during the first year post-transplantation. Enzyme linked immunosorbant assay (ELISA) tests were performed to determine if antibodies to EBV antigens, such as viral capsid antigen (VCA) IgM, VCAIgG or EBV neo-antigen (EBNA) IgG were present. The study patients' data included age, blood group, history of blood transfusion, and the cause of renal diseases. The immunosuppressive regimen and the episodes of allograft rejection were closely monitored.

Primary EBV infection was defined as seropositivity for VCAIgM; whereas previous EBV infection was defined as seropositivity for VCAIgG or EBNAIgG. Reactivation of EBV was defined as seropositivity for all VCA IgG, VCA IgM, and EBNA IgG.

Statistical Analysis

We analyzed the collected data using the statistical package for social sciences software (SPSS). The X square values were compared and the statistical significance was set at $P < 0.05$.

Results

Patient ages ranged from 20 to 56 years old. The immunosuppressive regimens included cyclosporine (CSA), azathioprine (AZA), prednisolone (PRE) and mycophenolate mofetil (MMF).

EBV infection developed in 58 (85.3 %) of the patients and active EBV disease developed in 10 (14.7%). EBV infection was detected in 40 (58.8%) patients during the first year after transplantation.

Sixty-five (95.6%) patients were EBNA IgG seropositive and the remaining 3 (4.4%) were seronegative prior to transplantation. During the first year after transplantation, all patients became seropositive.

Prior to transplantation, 63 (92.6%) recipients were VCAIgG seropositive and 5 (7.6%) were seronegative. However, during the first year after transplantation, 66(97%) recipients became seropositive and the remaining 2 (3%) remained seronegative.

Prior to transplantation, 12 (17.6%) recipients were VCAIgM seropositive, while 56 (82.4%) were seronegative. One year after transplantation, 40 (58.8%) recipients became seropositive, while 28(41.2%) remained seronegative.

The increase in VCAIgM seropositivity, from 17.6% to 58.8%, within the 12 month period indicates the recent activity of the infection.

There were 35 (51.4%) study patients on a CSA+PRE+AZA immunosuppressive regimen, 8 (11.8%) on CSA+PRE+MMF, and 25 (36.8%) on CSA+PRE. Table 1 shows the distribution of seropositivity to EBV among these groups. There were no statistically significant differences between the different immunosuppressive regimens in the incidence of active EBV infection.

Nineteen patients developed acute rejection during the first year after transplantation. Table 2 compares the EBV infection rates in these patients with those who did develop

Table 1. Prevalence of EBV infection prior to and one year after transplantation according the immunosuppressive regimen used. N= 68 patients.

	Group 1 (%) [*]	Group 2 (%) ^{**}	group 3 (%) ^{**}	Total (%)
EBV infection prior to transplantation	12 (43.2)	5 (66.7)	11 (42.1)	28 (41.1)
EBV infection active cases during the first year after transplantation	23 (65.8)	3 (33.3)	14 (57.9)	40 (58.8)
Total	35 (100)	8 (100)	25 (100)	68 (100)

* Cyclosporine + Prednisolone + Azathioprine, ** Cyclosporine + Prednisolone + Mycophenolate Mofetil, *** Cyclosporine + Prednisolone.

Table 2. EBV infection and acute rejection occurrences during the first year of transplantation.

	EBV infection prior to Transplantation (%)	Active EBV during the first year of Transplantation (%)	Total (%)
In patients with acute Rejection	6 (31.5)	13 (68.5)	19 (27.9)
In patients with no acute Rejection	22 (44.8)	27 (55.2)	49 (72.1)
Total	2 (41.2)	40 (58.8)	68 (100)

develop acute rejection. There was no statistically significant difference between the two groups.

ALG was administered to 26 (38.2%) patients. Table 3 shows the rate of EBV infection in relation to ALG administration. There were no statistically significant differences in the incidence of EBV of active cases in relation to ALG administration.

Discussion

The results of our study on the prevalence and incidence of EBV infection in the renal allograft recipients are similar to other reports from Iran,⁴ Europe,^{6,7} and the U.S.A.⁸

Secondary active EBV infection was detected in 58.8% of our patients, which was higher than the 24.4% reported by Hornef et al,⁸

the 27.7% reported by Rostamzadeh et al.⁶ or the 17.7% reported by Kenagy et al.⁹

EBNAIgG, VCAIgG and VCAIgM were respectively positive in 95.6%, 92.6%, 17.6% of our patients prior to transplantation, and 100%, 96.9%, 58.8% during the first year after transplantation. Other studies detected a similar profile of antigens and antibodies.^{6,8,9} Our results thus corroborate studies from other countries that indicate that EBV infection develops mostly as a secondary active disease after transplantation.

No particular immunosuppressive regimen was found to be responsible for the reactivation of EBV in our study, again in agreement with other studies.⁶

We did not find a statistically significant association between the incidence of infection and the occurrence of acute rejection in our

Table 3. Prevalence of EBV infection in patients who had ALG during the first year after transplantation.

	EBV infection prior to Transplantation (%)	Active EBV infection during the first year of Transplantation (%)	Total (%)
In patients who had ALG	12 (46.1)	14 (53.9)	26 (38.2)
In patients who had no ALG	15 (35.7)	27 (64.3)	42 (68.1)
Total	27 (39.7)	41 (60.3)	68 (100)

study. The results of other similar studies^{6,8,10} also indicate that acute rejection does influence EBV reactivation.

Furthermore, our results indicate that administration of ALG after transplantation also did not influence EBV reactivation, again in agreement with other studies.^{6,8,11}

In conclusion, our study suggests that most post-transplantation EBV activation is a secondary form of a previously existing infection. We could not detect a clear relationship with a specific immunosuppressive regimen or with the use of biological agents such as ALG. Further investigation is still needed to elucidate the factors involved in the reactivation of the EBV infection in the transplant population.

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