Original Paper

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Significance of Epstein-Barr virus infection in the outcome of renal transplant patients with lymphoproliferative disorders

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Summary

Background: The impact of EBV infection on the incidence of post-transplant lymphoproliferative disorders (PTLDs) is well established, but scant data exists on the significance of such an infection on organ transplant recipients who develop lymphoproliferative disorders. In the present study, we investigated the epidemiology of EBV infection in renal transplant recipients developing post-transplant lymphoproliferative disorders and its potential impact on these patients.

Material/Methods: International data from 5 different studies were included in the analysis. Complete remission (CR) was defined as no evidence of disease by different diagnostic methods. Partial remission was defined as a substantial decrease in measurable known lesions without the appearance of new ones.

Results: Overall 45 PTLD patients were included into analysis. Remission rate was significantly higher in EBV negative patients (p=0.010). Patients with EBV infection had significantly lower patient survival rate (p=0.06). Incidence of early onset PTLDs was significantly related to EBV infection (p=0.02).

Conclusions: This study demonstrates EBV infection is a major complication in post-transplant lymphoproliferative patients. Physicians should more intensively follow their EBV-infected transplant patients who have lymphoproliferative disorders.

Key words: **post-transplant lymphoproliferative disorders • outcome • PTLD • Epstein Barr Virus**

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Background

Epstein-Barr virus (EBV) is an opportunistic pathogen that substantially affects survival of immunocompromised patients [1–4]. *In vitro*, EBV infects resting B cells, transforming them into proliferating blasts, resulting in unregulated polyclonal expansion of latently infected lymphoblasts [5,6]. In the absence of an appropriate EBV-specific cytotoxic T-cell response, probably caused by the immunosuppressive regimen after transplantation, the proliferative transformed cells increase the incidence of malignancies in these patients. Post-transplant lymphoproliferative disorder (PTLD) is one of the morbidities shown to be related to EBV infection in solid organ recipients. Since transplant recipients usually receive aggressive immunosuppressive medication to control rejection episodes, they are especially at risk for PTLDs [7–9].

As mentioned above, the impact of EBV infection on the occurrence of PTLDs is well illustrated both epidemiologically and on a molecular basis. However, there is little data on the significance of such an infection in organ transplant recipients who develop lymphoproliferative disorders. In the present study, we examined the epidemiology of EBV infection in renal transplant recipients developing post-transplant lymphoproliferative disorders, and its potential impact on these patients.

Materials and Methods

We conducted a comprehensive search for the available data by Pubmed and Google scholar search engines on post-transplant lymphoproliferative disorders. A standard questionnaire was developed to collect data from different published studies. Finally, data from 5 different previously published studies from different countries were included in the analysis [10–14]. We focused on EBV infection and its epidemiology and potential impact in renal transplant recipients.

The time between allografting and PTLD onset was defined as the period between the graft and the first signs of PTLD. Early-onset PTLDs were defined as PTLDs occurring less than 1 year after transplantation and late-onset PTLDs were defined as PTLD occurrence more than 1 year post-transplantation.

Because the various studies included in this analysis used different approaches, we were not able to get all data we needed from all of the included patients. Initial malignancy site was available for all patients: 16 (36%) represented gastrointestinal involvement, in 14 (31%) patients peripheral lymph nodes were the primary site of involvement, brain involvement existed in 6 (13%) patients, kidney allograft was the initial presentation site of PTLD in 5 (11%) patients, and palatine and lung involvement were seen in 2 (4.4%) patients. Pre-transplantation EBV serologic status was documented in all the patients; 32 (71%) were seropositive. Data for potential metastases was available for 18 (40%) patients; 12 (67%) patients did not develop metastasis, while 6 (33%) patients had metastases at the time of PTLD diagnosis or during their follow-up period.

At lymphoma diagnosis, all patients were receiving and had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, and antithymocyte/lymphocyte globulin (ATG/ALG) and OKT3.

A uniform approach to treatment was used to manage all PTLD patients in the different reports studied. Upon diagnosis of lymphoproliferative disorders, the first step in the majority of patients was to decrease or discontinue immunosuppressive therapy. Complete remission (CR) was defined as no evidence of disease by clinical examination, radiographic, endoscopic, and/or histopathologic results. Partial remission was defined as a substantial decrease in measurable known lesions without the appearance of new ones.

Statistical analysis

Software used for data analyses was SPSS v.13.0. Statistical differences between patients' subgroups were performed by using χ^2 and Fishers' exact tests for proportions and the Student's *t* test for continuous data. Non-parametric analysis did not change the results. Survival analysis was done with life tables, Kaplan-Meier methods and the Breslow test. Because of the limited number of included subjects, we were not able to perform multivariable analyses; as well, for the same reason, all statistical tests were performed at the 0.07 significance level.

Results

Overall, 45 real transplant patients who developed PTLDs reported by 5 international studies with

Table 1. characteristics of PTLD patients regarding their EBV test result.

Variables		EBV infection		Sig.
		Positive	Negative	
N		32 (71%)	13 (29%)	
Gender (m%)		19 (59%)	7 (54%)	0.5
Age		39±13	47±10	0.03
Time to PTLD (mo)		58±57	114±73	0.02
Extranodular involvement		25 (78%)	6 (46%)	0.04
Remissions	Any remission	11 (48%)	11(100%)	0.003
	Complete remis.	10 (44%)	7 (64%)	–
	Partial remis.	1 (4%)	4 (36%)	–
Mortality		18 (56%)	6 (50%)	0.7

at least 1 EBV test result for each of the patients regardless to the method of detection were included into analysis. There were 26 (58%) male and 19 (42%) female patients. Mean age at diagnosis of PTLD was 41.3±12.8 years. The mean interval between transplantation and the diagnosis of PTLD was 74.5±66.2, and follow-up time after diagnosis of PTLD was 23.9±40.6 months.

Despite discontinuation or reduction of immunosuppressive agents, surgical therapy, chemotherapy, and radiotherapy, 24 (53.3%) of the patients died (1 was lost to follow-up). At the last follow-up, 20 (44.4%) patients were alive. EBV infection in the PTLD patients was significantly associated with peripheral lymph node involvement as the initial neoplasm site (p=0.043), while other neoplasm localizations were not related to EBV infection (p>0.1 for all).

PTLD remission data was available in 34 (76%) patients: complete remission was observed in 17 (37.8%) patients, while 5 (11.1%) patients experienced partial remission and no remissions were reported in the remaining 12 (26.7%) patients. The remission (either partial or complete) rate among EBV-negative patients was 100%, while it was 48% in EBV-positive patients (Table 1). Kaplan-Meier survival analysis showed a significant relationship between EBV infections and remissions (p=0.010, Figure 1). Patients with EBV infection had a significantly lower patient survival rate within the first 30 months after diagnosis of PTLDs (p=0.06; Figure 2). Incidence of early onset PTLDs was significantly related to EBV infection, with 10 (100%) of early-onset PTLD subjects infected with EBV infection, compared to 22 (63%) for late-onset PTLD patients (p=0.02).

Discussion

In the present era of solid organ transplantation, when potent immunosuppressants form the backbone of transplant anti-rejection therapies, post-transplant lymphoproliferative disorder (PTLD) has emerged as a progressively more imperative complication of transplantation, significantly affecting graft and patient survival [15,16]. The disease can present various features with different localizations, including peripheral lymph node involvements, as well as extra-nodal diseases and early and late onset presentations.

EBV infection has been implicated as a major cause of lymphoproliferative disorders based on serologic evidence, EBNA staining, and molecular hybridization [17–19]. Since EBV induces polyclonal activations of B cells bearing EBV receptors [18] *in vitro* [21] and *in vivo* [22], the combined immunologic and virologic evidence strongly implicates EBV as the causative agents in these patients. Since absence of anti-EBV antibody production in seronegative PTLD patients may reflect their impaired humoral immunity system [23,24], the impact of EBV infection on the incidence and complications related to the PTLDs is probably underestimated.

In our analysis, however, we did not aim to evaluate EBV infection and its role in the development of PTLDs; thus, analysis of our international data showed that EBV infection is significantly associated with early onset PTLD occurrence. This finding is in accordance with the current concept [25,26] that lymphomas arising early after transplantation are almost all EBV-positive. Experimental evidence also suggests cytogenetic abnormalities

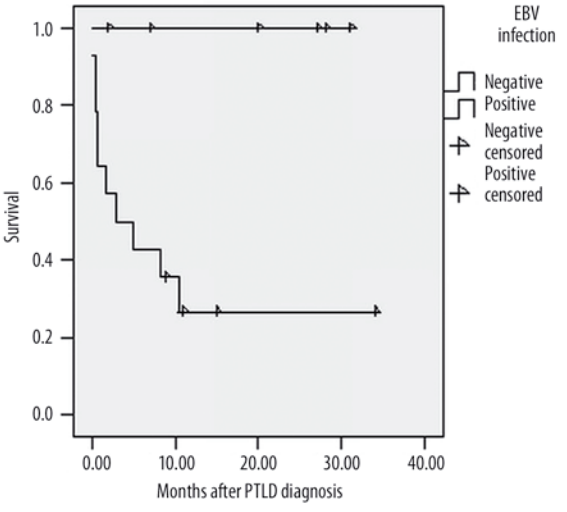

Figure 1. Remission rates (either partial or complete) in PTLD patients regarding their EBV infection status.

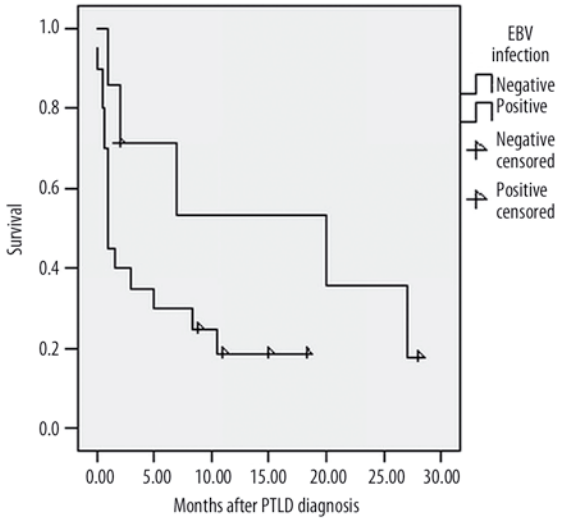

Figure 2. 30 months survival of PTLD patients regarding EBV test results.

in EBV-transformed cells are related to distorted cellular growth patterns. These altered functions can lead to monoclonal cytogenetic abnormalities resulting to malignancies, especially in the early period after transplantation, when anti-rejection therapies are at their highest levels.

We also found that EBV infection in PTLD patients is associated with lower patient survival rates, as well as remission of the PTLD. Hanto et al. [27] demonstrated that EBV infection is significantly associated with lethal feature for PTLD, and showed that the clinical course of young patients presented early after transplantation with an infectious mononucleosis-like illness characterized by fever, pharyngitis, and lymphadenopathy, in the untreated patients, was a rapidly progressive and lethal lymphoproliferative disorder. In patients with adequate immunologic response, a polyclonal B-cell proliferation after EBV infection was demonstrated.

This study revealed that EBV infection is significantly associated with less extra-nodal localization of the PTLDs as the initial site of the disorder, compared to EBV-negative patients. Previous studies are in contrast with this finding, suggesting that EBV infection is more likely to involve allograft as the initial site of PTLDs [28]. Our results suggest that EBV-infected PTLD patients have more progressive and lethal disease. One explanation for this observation is that our analysis was only performed based on the initial site of the infection and did not include metastases. Future studies should explore whether initial localization of the PTLDs may significantly affect patient survival.

Conclusions

This study showed that EBV infection is a major complication in post-transplant lymphoproliferative patients. EBV-infected transplant patients with lymphoproliferative disorders should receive more intensive follow-up.

References:

1. Cohen JI: Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. Medicine (Baltimore), 1991; 70: 137–60
2. Craig FE, Gulley ML, Banks PM: Posttransplantation lymphoproliferative disorders. Am J Clin Pathol, 1993; 99: 265–76
3. List AF, Greco FA, Vogler LB: Lymphoproliferative diseases in immunocompromised hosts: the role of Epstein-Barr virus. J Clin Oncol, 1987; 5: 1673–89
4. Preiksaitis JK, Cockfield SM: Epstein-Barr virus and lymphoproliferative disorders after transplantation. In: Bowden RA, Ljungman P, Paya CV (eds.), Transplant infections. Philadelphia: Lippincott-Raven Publishers, 1998: 245–63
5. Diehl V, Henle G, Henle W, Kohn G: Demonstration of a herpes group virus in cultures of peripheral leukocytes from patients with infectious mononucleosis. J Virol, 1968; 2: 663–69
6. Pope JH, Horne MK, Scott W: Transformation of foetal human leukocytes *in vitro* by filtrates of a human leukaemic cell line containing herpes-like virus. Int J Cancer, 1968; 3: 857–66

7. Nalesnik MA, Jaffe R, Starzl TE et al: The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A – prednisone immunosuppression. Am J Pathol, 1988; 133: 173–92
8. Newell KA, Alonso EM, Whitington PF et al: Posttransplant lymphoproliferative disease in pediatric liver transplantation: interplay between primary Epstein-Barr virus infection and immunosuppression. Transplantation, 1996; 62: 370–75
9. Penn I: The role of immunosuppression in lymphoma formation. Springer Semin Immunopathol, 1998; 20: 343–55
10. Pourfarziani V, Taheri S, Lessan-Pezeshki M et al: Lymphoma after living donor kidney transplantation: an Iranian multicenter experience. Int Urol Nephrol, 2008; 40(4): 1089–94
11. Avolio AW, Agnes S, Barbarino R et al: Posttransplant lymphoproliferative disorders after liver transplantation: analysis of early and late cases in a 255 patient series. Transplant Proc, 2007; 39(6): 1956–60
12. Koike J, Yamaguchi Y, Hoshikawa M et al: Posttransplant lymphoproliferative disorders in kidney transplantation: histological and molecular genetic assessment. Clin Transplant, 2002; 16(Suppl.8): 12–17
13. Mamzer-Bruneel MF, Lomé C, Morelon E et al: Durable remission after aggressive chemotherapy for very late post-kidney transplant lymphoproliferation: A report of 16 cases observed in a single center. J Clin Oncol, 2000; 18(21): 3622–32
14. Jain M, Badwal S, Pandey R et al: Post-transplant lymphoproliferative disorders after live donor renal transplantation. Clin Transplant, 2005; 19(5): 668–73
15. Khedmat H, Taheri S: Late onset post transplantation lymphoproliferative disorders: analysis of international data from 5 studies. Ann Transplant, 2009; 14(4): 80–85
16. Khedmat H, Taheri S: Early onset post transplantation lymphoproliferative disorders: analysis of international data from 5 studies. Ann Transplant, 2009; 14(3): 74–77
17. Cockfield SM: Identifying the patient at risk for posttransplant lymphoproliferative disorder. Transpl Infect Dis, 2001; 3: 70
18. Hanto D, Frizzera G, Purtilo DT et al: Clinical spectrum of lymphoproliferative disorders in renal transplant recipients and evidence for the role of Epstein-Barr virus. Cancer Res, 1981; 41: 4253–61
19. Hanto D, Frizzera G, Gajl-Peczalska K et al: Epstein-Barr virusinduced B-cell lymphoma after renal transplantation. N Engl J Med, 1982; 306: 913–18
20. Jondal M, Klein G: Surface markers on human B and T lymphocytes. II. Presence of Epstein-Barr virus receptors on B lymphocytes. J Exp Med, 1973; 138: 1365–78
21. Rosen A, Gergely P, Jondal M et al: Polyclonal Ig production after Epstein-Barr virus infection of human lymphocytes *in vitro*. Nature (London), 1977; 267: 52–54
22. Hanto D, Sakamoto K, Purtilo DT et al: The Epstein-Barr virus in the pathogenesis of posttransplant lymphoproliferative disorders. Surgery, 1981; 90: 204–13
23. Penn I, Hammond W, Brettschneider L, Starzl TE: Malignant lymphomas in transplantation patients. Transplant Proc, 1969; 1: 106–12
24. Khedmat H, Alavian SM, Taheri S: Significance of human leukocyte antigen typing in kidney transplantation: time to revisit old strategies? Iran J Kidney Dis, 2009; 3(3): 176–77
25. Armitage JM, Kormos RL, Stuart RS et al: Posttransplant lymphoproliferative disease in thoracic organ transplant patients: ten years of cyclosporine-based immunosuppression. J Heart Lung Transplant, 1991; 10: 877–86
26. Dotti G, Fiocchi R, Motta T et al: Epstein-Barr virus-negative lymphoproliferate disorders in long-term survivors after heart, kidney, and liver transplant. Transplantation, 2000: 69: 827
27. Hanto DW, Gajl-Peczalska KJ, Frizzera G et al: Epstein-Barr virus (EBV) induced polyclonal and monoclonal B-cell lymphoproliferative diseases occurring after renal transplantation. Ann Surg, 1983; 198: 356–69
28. Bakker NA, Van Imhoff GW, Verschuuren EA et al: Early onset post-transplant lymphoproliferative disease is associated with allograft localization. Clin Transplant, 2005; 19: 327–34