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Review Paper

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Significance of *in situ* hybridization results for EBV-encoded RNA in post-transplantation lymphoproliferative disorder setting: Report from the PTLD.Int Survey

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Summary

Background: Epstein–Barr virus (EBV) encodes 2 small nonpolyadenylated noncoding RNAs termed EBERs. EBERs are the most common viral transcripts found in EBV-infected cells. In the present study we aimed to examine various aspects of EBER positivity in PTLD patients.

Material/Methods: We conducted a comprehensive search for the available data by Pubmed and Google Scholar search engines for reports indicating results of EBERs in PTLD patients. Data from 27 previously published studies were included into analysis. Finally, 243 recipients of allograft were included into analysis.

Results: One and 5 years survival rates for PTLD patients with EBER-positive results were 61% and 50%, respectively, compared to 55% and 49%, respectively, for EBER-negative PTLD patients. When death specifically due to PTLD was used as the final outcome, EBER-positive PTLD patients had relatively superior outcome; although p-value did not reach the significance level (p=0.09). EBER-positive patients were significantly more likely to develop PTLD lesions of B cell types (vs. T cell type; p=0.018); and early onset PTLD (p<0.001). EBER-positive PTLD patients were significantly more likely to be polymorphic versus monomorphic (p=0.05). EBER-negative PTLD patients were more likely to develop non-Hodgkin PTLD lesions (p<0.001).

Conclusions: We found that PTLD patients with positive results for EBER represent relatively better histopathological features than those in EBER-negative PTLD patients, and the survival rate of EBER-positive PTLD patients is not inferior to that of the EBER-negative subjects. Moreover, they were more likely to represent early onset PTLD of B cell type with polymorphic and Hodgkin-like lesions; and biopsy specimens from different organs were significantly different regarding EBER test results. Future studies with large PTLD populations are needed to confirm our findings.

Key words: **post transplant lymphoproliferative disorders • EBV-Encoded RNA • EBER • *in situ* hybridization • ptld**

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Background

Post-transplantation lymphoproliferative disorder (PTLD) is a well known complication of organ transplant recipients, occurring in 2–10% of organ recipients [1–5]. The pathogenesis is presumed to be associated with impairment occurring in the cellular immunity, leading to proliferation of lymphoid system in immunocompromised patients [6]. There are 2 major risk factors associated with the high incidence of the disease: first; immunocompromised patients, such as patients with acquired immune deficiency syndrome (AIDS) and organ transplant recipients, are at highest risk for developing post transplant lymphomas [7,8]; the second major risk factor is Epstein-Barr virus (EBV) infection, which plays both causative and prognostic roles in PTLD patients, and a great majority of tumors are associated with this virus [9].

Epstein-Barr virus (EBV) is a human gammaherpesvirus that creates a consistent dormant infection in B lymphocytes after the initial exposure [10]. *In vitro*, EBV infects resting B cells, transforming them into proliferating blasts, resulting in unregulated polyclonal expansion of latently infected lymphoblasts [11,12]. In the absence of an appropriate EBV-specific cytotoxic T-cell response, probably caused by the immunosuppressive regimen after transplantation, the proliferative transformed cells enhance the incidence of malignancies in these patients. EBV is demonstrated to be related to several malignancies, including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, gastric carcinoma, and lymphoproliferative diseases in immunocompromised patients [13].

Epstein-Barr virus (EBV) encodes 2 small nonpolyadenylated noncoding RNAs termed EBERs. EBERs are the most common viral transcripts found in EBV-infected cells. There are 2 recognized EBERs: EBER1 and EBER2. Due to their very high availability and their conservative nucleotide sequence preservation, EBERs are strongly suspected to have important biological functions. EBERs are shown to have growth-stimulatory functions [14,15].

In the present study, aggregating data from different international reports, we aimed to examine the clinical and histological relevance of EBER-positivity in organ transplant recipients who developed post-transplantation lymphoproliferative disorder.

Material and Methods

Approach to the study

We conducted a comprehensive search for the available data by Pubmed and Google scholar search engines for reports indicating results of EBERs in patients representing lymphoproliferative disorders after organ transplantation. Keywords used for this purpose were "lymphoproliferative disorders + transplantation + EBER" "lymphoproliferative disorders + transplantation + EBV-encoded RNA" "PTLD + EBER" "PTLD + EBV + RNA". In cases that we were not able to achieve the full text of the articles, an email was sent to correspondent authors requesting the article. Then we only included studies in which data of each patient was presented separately and excluded others. To minimize selection bias, we only included studies reporting their series of patients from single or multi center populations and studies with any specific selection criterion were excluded from the analysis. A standard questionnaire was developed to collect data from different published studies. Finally, data from 27 previously published studies from various countries [16–42] were included into analysis. The time between transplantation and PTLD onset was defined as the period between the graft and the first signs of PTLD or diagnosis, based on the studies approaches.

Study population

Overall, 243 recipients of allografts were included into analysis; 185 (76.1%) of the study population were patients with at least 1 EBER-positive report from any EBER type, while the remaining 58 (23.9%) patients had EBER-negative test results.

Because data used in this study was from different studies, and they did not have unique approaches, we were not able to get all data we needed from all the included patients. Disseminated lymphoma was diagnosed when it was declared by the authors, or at least 3 different organs (excluding different lymph node areas) were involved by PTLD, reported in 15 (11.3%; 110 missing data) patients. Multi-organ involvement defined as involvement of more than a unique organ as well as more than 1 lymphatic region was available in 52 (30.8%; 74 missing data) patients.

At lymphoma diagnosis, all patients were receiving and had received immunosuppressive regimens consisting of varying combinations of

Table 1. Characteristics of PTLD patients with EBER positive and negative results.

Variables		EBER positive		EBER negative		Sig.	Available data
Age (yr)		26.5±24.1		37.5±23.7		0.004	207
Gender male (%)		80	(71.4)	32	(66.7)	0.575	160
Time to PTLD development (mo)		32.2±42.2		79.4±58.4		<0.001	224
Multi organ involvement (%)*		40	(31.5)	14	(31.8)	1.0	171
Disseminated PTLD (%) *		13	(13.1)	4	(11.1)	1.0	135
Hodgkin disease (%)		12	(11.8)	0		<0.001	123
Remission episode (%)		75	(75.8)	22	(52.5)	0.05	136
Azathioprine based IS** (vs. MMF/FK-506)		17	(56.7)	8	(53.3)	0.238	45
Use of induction therapy		12	(36.4)	3	(33.3)	1.0	42
Early onset (within first 12 months post TX)		82	(48%)	4	(7%)	<0.001	228
Monoclonal lesions vs. polyclonal (%)		15	(62.5)	6	(100)	0.2	30
Monomorphic lesions (%)		39	(40.6)	14	(66.7)	0.05	117
Lymphoma cell type B cell (%)		51	(92.7)	20	(71.4)	0.018	83
Allograft types	All together					0.281	235
	Renal (%)	33	(18)	12	(23.1)	0.428	
	Liver (%)	84	(45.9)	24	(45.3)	1.0	
	Heart (%)	41	(22.4)	5	(9.4)	0.047	
	Lung (%)	5	(2.7)	1	(1.9)	1.0	
	Pancreas (%)	3	(1.6)	2	(3.8)	0.313	
	Bone marrow (%)	14	(7.7)	4	(7.5)	1.0	

* According to the criteria defined in the methods section; ** IS; immunosuppression.

azathioprine, prednisone, cyclosporine, mycophenolate mofetil, and antithymocyte/lymphocyte globulin (ATG/ALG) and OKT3. A rather uniform approach was used to manage all PTLD patients in the included reports. On diagnosis of PTLDs, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; different regimens of chemotherapy with or without surgical interventions were also used for some of patients.

Response to treatment

Response to treatment was defined as any favorable change in the cancer measures, as well as patients' clinical condition. Data on PTLD response to treatment was reported by authors for 65 (26.7%) patients, of whom 52 (80%; 43(66.2%) represented complete remission. However, we developed new criteria for defining remission rates for the study population; while remission episode was defined when patients were alive after their 24th month of PTLD diagnosis (since all reported cases having this criterion had at least 1 confirmed remission episode) and no remission was defined when a patient died within the first month after PTLD diagnosis (because among reported cases there were no patients dying at the first post-transplant month and reported to have any remission episodes). Overall mortality was 93 (38.3% of the study population and 50% of the reported cases) patients. Death due to PTLD was defined when: 1) authors stated it, 2) the patient died within 6 months post-diagnosis, or 3) the patient died due to PTLD treatment complications. Overall, 67 (27.6% of the study population; 72% of the whole mortality rate) patients died due to the disease based on the abovementioned criteria.

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

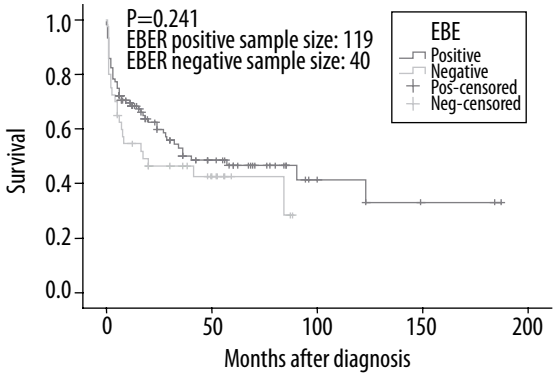

Figure 1. Survival curves of PTLD patients with positive and negative results for any of the EBER tests when death irrespective of the reason is used as the outcome.

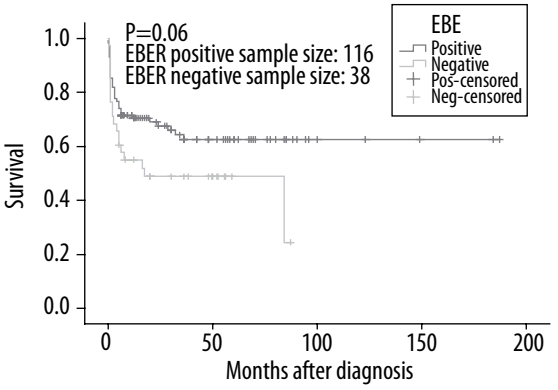

Figure 2. Survival curves of PTLD patients with positive and negative results for any of the EBER tests when only death due to PTLD is used as the outcome.

continuous data. Survival analysis was done with life tables and Kaplan-Meier methods and log-rank test. Cox regression models were used for multivariate analysis. All statistical tests were performed at the 0.05 significance level.

Results

Overall, 243 patients with lymphoproliferative disorders after organ transplantation were entered into analysis. There were 109 (69.9%) males and 47 (30.1%) female patients (87 missing data). Mean age at diagnosis of PTLD was 29.4±24.4 years. The mean interval between transplantation and the diagnosis of PTLD was 43.9±50.9 months, whereas follow-up time after diagnosis of PTLD was 28.5±34.6 months.

Characteristics of the patients regarding their malignancy site are summarized in Table 1. Chi square test showed that EBER-positive test results were relatively equal between males and females (p=0.575). To detect any potential disparity between different transplant groups respecting their EBER test results, we compared EBER positivity rates between different transplant groups (RT vs. Others; LT vs. others; etc.). The only transplant population who had a significantly higher EBER-positive rate when compared to other allograft type recipients was heart transplant recipients (p=0.047). Other transplant populations did not have different EBER-positive rates compared to others (p>0.2, for all).

Transplant patients with EBER-positive results were comparable with EBER-negative patients regarding their immunosuppression types (p=0234), multi-organ involvement (p=1.0) and disseminated PTLD (p=1.0) rates. EBER-positive patients were significantly more likely to develop PTLD lesions of B cell types (vs. T cell type; p=0.018); and early onset PTLD (PTLD occurring within the first post-transplantation year; p<0.001). PTLD histopathological features were also diverse regarding their EBER results. EBER-positive PTLD were significantly more likely to be polymorphic versus monomorphic (p=0.05); moreover, EBER-negative PTLD patients were more likely to develop non-Hodgkin-like lesions (p<0.001).

At the last follow-up, 93 (50.0%) patients were dead (57 missing data). When death irrespective of the reason was used as the final outcome, log-rank test did not show any difference between the 2 groups in their survival (p=0.241; Figure 1); however, when death specifically due to PTLD was used as the final outcome and deaths with non-related reasons were excluded, patients with EBER-positive test results had a relatively superior outcome compared to EBER-negative patients, although p-value did not reach significance level (p=0.06; Figure 2). Due to the number of missing data for each variable and its inconsistency in different patients as well as the weak p-value, we were not able to employ multivariate survival analysis. One and 5 years survival rates for PTLD patients with EBER-positive results were 61% and 50%, respectively; compared to 55% and 49%, respectively, for EBER-negative PTLD patients.

Discussion

Infectious diseases are one of the most relevant factors that adversely affect lives of both general populations as well as patients with impaired

immune systems, and efforts have been made to discover, prevent and rehabilitate morbidities due to the infectious diseases [44–46]. The PTLDint survey was an attempt at gathering international data from PTLD patients to conduct analyses on the largest possible patient population to discover new perspectives on the disease, based on the existing data in the literature. In this study, we analyzed one of the largest ever series of PTLD patients to discover their histopathological features, including morphology and clonality, as well as prognostic factors in patients who have at least 1 documented test result for *in situ* hybridization for EBER.

Transplant patients are at increased risk for developing lymphoproliferative disorders. The proposed major risk factors responsible for the disease are the potency of immunosuppression and Epstein-Barr virus infections [47–50]. The presence of latent virus in the involved tissues of PTLD lesions has been investigated in several studies, and is commonly termed as EBV-associated PTLD. Although EBV infection is a well known risk factor for the development of the PTLD, the way that the virus plays its role in the pathogenesis or maintenance of the proliferation remains obscure. Observations have been reported from different research protocols that complicate explanation for PTLD occurring after EBV infection. For example, it is known that allograft recipients who are seronegative before transplantation are at much higher risk for PTLD development [51–53]. On the other hand, significance of EBV infection in organ recipients who currently have developed PTLD is even less known. In a previous study, we showed that EBV seropositive PTLD patients not only represent inferior survival than those with negative EBV serology, they are also significantly more likely to develop early onset PTLD. In the present study, we confirmed our previous finding that PTLD patients whose EBER test was positive were significantly more likely to develop early onset PTLD. However, some inconsistent results in our previous study have also been achieved in this study.

The most unexpected finding of this study is the relatively superior outcome for EBER-positive PTLD patients compared to PTLD patients who had a negative result for the EBER test. To understand this observation, we should consider the characteristics and relevance of EBER test result for detection of the EBV genome. It is demonstrated that EBERs are not consistently expressed in cells permissively infected by EBV; however, an EBER result is generally considered quite reliable when used in latently infected cells. However, several studies have presented uncertainty on this conclusion about the reliability of EBER test results in latently infected tissues. Sugawara et al. [54], in their study on hepatocellular carcinoma, Bonnet et al. [55], in invasive breast cancers, and Yao et al. [56] in nasopharyngeal carcinoma have shown that despite very high levels of EBV viral load in the tissue specimen, even highly sensitive EBER assays failed to detect EBV infections in the biopsy specimen. Considering these studies, we cannot be sure that, using EBER, we can detect all latent EBV infections and EBER-negative latent infection. So, interpreting the observed relatively better survival for EBER-positive patients than those of EBER-negative PTLD, we should consider that this does not exactly mean the same for EBV-infected patients. Even an adverse explanation is possible, and EBV infection in its active phase might not be detectable by the EBER. In fact, Greifenegger et al. [57], in their study using nuclear run-on assays, demonstrated that EBER transcription was down-regulated during the switch from latent infection to lytic replication of the virus. This probably can explain why EBER-negative PTLD patients may represent inferior outcome than their EBER-positive counterparts.

In this study, we also found that an EBER-positive result for PTLD lesions was less likely to be represented in colon, small intestine, and skin PTLD specimen, and relatively more likely to be established in stomach tissue; although the significance level was not achieved in the latter case (Table 2). Due to the limited number of patients included in this analysis, the significant relationships found could be simply explained by potential biases. However, one may assume that different organs may represent inconsistent susceptibility to EBV infection; moreover, it is also possible that some organs may represent different EBER results despite an EBV infection, due to unknown reasons. In fact, previous studies support this conclusion. Gilligan et al. [58] failed to detect EBV infection in specimens from patients with AIDS leukoplakia [58]; the same findings were achieved in patients with Sjogren's syndrome [59], in salivary gland tumors [60], and in oral papilloma [61].

We also found that PTLD patients who undergone transplantation at younger ages are significantly more likely to have positive EBER test results; moreover, PTLD from EBER-positive patients were more likely to be polymorphic in their

Table 2. PTLD organ involvement with respect to their EBER test result from a total 204 PTLD patient population.

Organ involved by PTLD	EBER positive		EBER negative		1-sided sig.	Two sided Sig.
Skeleton (%)	1	(0.7)	1	(1.9)	0.446	0.446
Spleen (%)	2	(1.3)	1	(1.9)	0.588	1.0
Colon (%)	4	(2.6)	5	(9.6)	0.049	0.049
Small intestine (%)	20	(13.2)	13	(25.0)	0.041	0.05
Kidney (%)	3	(2.0)	1	(1.9)	0.731	1.0
Liver (%)	23	(15.1)	3	(5.8)	0.060	0.094
Respiratory system (%)	20	(13.2)	6	(11.5)	0.488	1.0
Bone marrow (%)	7	(4.6)	3	(5.8)	0.491	0.717
Orbit (%)	2	(1.3)	0		0.554	1.0
Skin (%)	1	(0.7)	3	(5.8)	0.05	0.05
Stomach (%)	10	(6.6)	0		0.049	0.068
Genitalia (%)	2	(1.3)	0		0.554	1.0
Central nervous system (%)	9	(5.9)	5	(9.4)	0.275	0.358

histopathologic evaluation. Both of the abovementioned findings may explain the superior outcome observed in the EBER-positive PTLD group. For evaluating any potential independent association between EBER positivity and outcome, we need to conduct multivariable analyses; however, due to the limited size of the study population, in addition to the amount of missing data and its inconsistency between the 2 variables, conducting a multivariable survival analysis was not useful. Remission was also more frequent among EBER-positive patients, confirming a better outcome for this group of PTLD patients. Time interval between transplantation and PTLD development was also shorter among EBER-positive patients. This finding is in accordance with our previous findings on the impact of EBV infection on transplant recipients.

Conclusions

In conclusion, we found that PTLD patients with positive EBER test results represent relatively better histopathological features as well as survival rate than those in EBER-negative PTLD patients. Moreover, they were more likely to represent early onset PTLD of B cell type with polymorphic and Hodgkin-like lesions; and biopsy specimens from different organs were significantly different based on EBER test results. Future studies with large PTLD populations are needed to confirm our findings.

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