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Original Article

Post-Transplantation Lymphoproliferative Disorders (PTLD) Localized in the Central Nervous System: Report from an International Survey on PTLD

Hossein Khedmat[1], Saeed Taheri[2]

[1]Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Baqiyatallah University of Medical Sciences; [2]Dr. Taheri Medical Research Group, Tehran, Iran

ABSTRACT. Post-transplantation lymphoproliferative disorders (PTLD) localized to the central nervous system (CNS) is a rare but potentially fatal side-effect of immunosuppression for organ transplantation. Till now, to the best of our knowledge, the total number of such cases reported worldwide is less than 100. In this survey, we collected the data of PTLD localized to the CNS (CNS-PTLD) and compared this data with other PTLD patients with localizations to other areas serving as the control group. A comprehensive search was performed for studies reporting CNS-PTLD data in the Pubmed and Google scholar search engines. Finally, international data from 21 different studies were included in the analysis. Overall, 367 patients were entered into analysis. Organ recipients with CNS-PTLD had comparable gender make up, lymphoma cell types, Epstein-Barr virus infection rate, remission and mortality rates, with PTLD patients having other localizations. Multiorgan involvement as well as disseminated lymphoma were significantly more prevalent in the control group (P <0.05). At the last follow-up, 192 (60%) patients were dead (47 missing data). Irrespective of whether the overall death or only death due to PTLD was used as the final outcome, we found that the survival rates were similar for patients of the two groups (P = 0.895). Renal transplant recipients are at greater risk for developing CNS involvement by PTLD, while heart and liver recipients represent significant lower risks for the same. This study showed that PTLD patients who had CNS presentation have quite a comparable outcome compared with those with other areas of localization. However, further prospective studies are needed for reaffirming our findings.

Correspondence to:

Dr. Hossein Khedmat,
Professor and Chief,
Department of Internal Medicine,
Baqiyatallah University of Medical Sciences,
Tehran, Iran
E-mail: Khedmat.h@gmail.com

Introduction

Post-transplantation lymphoproliferative disorder (PTLD) is a well known complication of organ transplant recipients that produces a high amount of burden to these patients as well as to the health care system. The pathogenesis is presumed to be associated with impairment occur-

ring in the cellular immunity, leading to proliferation of the lymphoid system in immunocompromised patients.[1,2] PTLD occurs with increased frequency in patients who are immunologically suppressed, such as those who have undergone organ transplants or those having acquired immune deficiency syndrome (AIDS).[3,4] Intense immunosuppression is one of the most widely established factors that stimulate PTLD in organ-transplanted patients.[5,6] Epstein-Barr virus (EBV) is another demonstrated relevant factor that plays causative and prognostic roles in PTLD patients, and a great majority of tumors are associated with this virus.[7]

PTLD localized to the central nervous system (CNS) is a rare but potentially fatal complication of immunosuppression for organ transplantation.[8] The first report on CNS involvement by PTLD (CNS-PTLD) was published in 1970 by Schneck and Penn.[9] Since then, a number of studies have reported their individual experiences from different transplant centers around the world on CNS-PTLD. However, the number of reported patients was quite limited and a recent article published in 2010 claimed that the whole number of reported series on CNS-PTLD was only 45 patients reported by three case series through three decades.[10] This shows that this disease is an uncommon condition and our knowledge on its various aspects, including epidemiology, clinical and laboratorial presentations, treatment strategies and prognosis, is extremely limited. We performed this survey to collect the data of studies reported by various international authors on CNS-PTLD and to compare this data with data from other PTLD patients reported by similar studies on CNS sparing lymphomas, to have a view on the various aspects of the disease, including epidemiology, prognosis and predictors of prognosis.

Materials and Methods

Approach to the study

We conducted a comprehensive search for the available data using the Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring within the CNS among organ transplant patients. Keywords used for this purpose were "lymphoproliferative disorders + transplantation + brain", "lymphoproliferative disorders + transplantation + central nervous system", "PTLD + brain" and "PTLD + CNS". In cases that we were not able to achieve the full text of the articles, an e-mail was sent to the correspondent authors requesting for the article. We included only the studies in which data of each patient was presented separately. Furthermore, to minimize any selection bias, those studies with any specific selection criterion were excluded from the analysis. Lymphoproliferative disorders occurring after transplantation within the CNS were considered as the case group and other PTLD patients with localizations to other areas served as the control group. Patients in the control group with scalp and/or vertebral involvements were excluded from the analysis (two subjects) due to the ambiguous localization of the PTLD in these patients. A standard questionnaire was developed to collect data from different published studies. Finally, data from 21 previously published studies from various countries[1,11-30] were included in the 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. Because the data used for this study was from different studies, and because they did not have unique approaches, we were not able to get all the data we needed from all the included patients.

Disseminated lymphoma, diagnosed if it was stated by the authors or when at least three different organs (excluding different lymph node areas) were involved by PTLD, was reported in 86 (23.4%) patients. Multiorgan involvement was defined as involvement of more than one unique organ as well as having more than one lymphatic region, and was seen in 123 (33.5%) patients.

Response to treatment was defined as any favorable change noticed in the lesion as well as in the patients' clinical condition. However, we also analyzed the data by a new criteria developed for defining remission rates for the

study population. By this, remission episode was defined as patients being alive after their 24th month of PTLD diagnosis (because all reported cases having this criterion had at least one confirmed remission episode) and no remission was defined when a patient died within the first month post PTLD diagnosis (because, among the reported cases, there were no patients dying at the first post-transplant month and reported to have any remission episodes).

Death due to PTLD was defined when (1) the authors stated it, (2) the patient died within six months post diagnosis and (3) patients died due to the complications of PTLD treatment.

Statistical Analysis

The software used for data analyses was SPSS v.13.0. Statistical differences between patients' subgroups were performed by using the χ^2 and the Fishers' exact tests for proportions and the Students t test for continuous data. Survival analysis was performed 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.

Result

Overall, 367 patients with lymphoproliferative disorders after organ transplantation were identified and were included in the analysis. Ninety (24.5%) patients of the study population were patients with CNS-PTLD, while the remaining 277 (75.5%) patients represented PTLD in other sites. There were 210 (64.4%) male and 116 (35.6%) female patients (41 missing data). Mean age at diagnosis of PTLD was 39.9 ± 19.6 years. The mean interval between transplantation and the diagnosis of PTLD was 46.1 ± 53.0 months, whereas follow-up time after diagnosis of PTLD was 20.3 ± 28.1 months. EBV serologic status was documented in 207 (56.4%) patients, of whom 153 (74%) were seropositive.

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

Characteristics of the patients regarding their malignancy site are summarized in Table 1. Chi square test showed that organ recipients with CNS localization of PTLD had comparable gender make up, lymphoma cell types, EBV infection rate, remission, and mortality rates when compared with PTLD patients with other localizations. Multiorgan involvement as well as disseminated lymphoma (defined according to the criteria described in the methods section) were significantly more prevalent in the control group; however, when we only considered metastatic disease as defined by the authors, both groups represented an equal prevalence for metastasis.

Hodgkin and Hodgkin-like PTLD were statistically equal for the two PTLD groups. Overall, 129 patients had data on their PTLD clonality condition, of whom 100 (77.5%) had monoclenal lesions while 24 (18.6%) had polyclonal disease and five (%1.4) had oligoclonal PTLD. As categorization of patients regarding morphological characteristics of the disease was based on different references in different studies, we were not able to include all of them into a unique analysis; therefore, we extracted data for mono- and polymorphic lesions; data from 132 patients showed that 56 (42.4%) patients were monomorphic while 76 (57.6%) patients were polymorphic. Clonality and morphological features were not different between PTLD patients regarding CNS involvement.

Data of response to treatment of PTLD was reported by authors for 105 (28.6%) patients, of whom 70 (66.7%) had response to anti-malignancy treatment. Sixty-one (58.1%) patients had complete remission. However, using the new cri-

Table 1. Characteristics of PTLD patients with and without CNS involvement.

Variables	CNS PTLD	Controls (CNS spared PTLD)	Sig.	Available data
Age (year)	42.1 ± 17.4	39.1 ± 20.3	0.195	355
Gender male (%)	50 (58)	160 (67)	0.189	326
Time to PTLD development (mo)	40 ± 53	47.8 ± 52	0.254	352
Multiorgan involvement (%)	14 (21)	109 (41)	0.004	330
Disseminated PTLD (%)	10 (15)	76 (28)	0.028	330
Author defined metastasis (%)	9 (54)	64 (61)	0.598	122
Remission episode (%)	33 (43)	71 (47)	0.672	226
Relapse rate (%)	6 (12)	7 (13)	1.0	100
Monoclonal lesions vs. polyclonal lesions (%)	8 (80)	92 (77)	0.802	129
Monomorphic lesions (%)	11 (55)	45 (40)	0.230	132
Lymphoma cell type B cell (%)	25 (86)	165 (93)	0.268	207
EBV infection	36 (80)	117 (72)	0.341	207
Allograft types				328
All together			<0.0001	
Renal (%)	50 (66)	93 (37)	<0.0001	
Liver (%)	6 (8)	44 (17.5)	0.045	
Heart (%)	6 (8)	68 (27)	<0.0001	
Lung (%)	2 (3)	23 (9)	0.082	
Pancreas (%)	7 (9)	17 (7)	0.457	
Bone marrow (%)	5 (7)	7 (3)	0.158	

teria that we developed for defining remission rates for the study population, the overall mortality was 192 patients (52.3% of the study population and 60% of the reported cases). Overall, death due to PTLD was 124 patients (33.8% of the study population; 71.7% of the whole mortality rate) based on the above-mentioned criteria.

At the last follow-up, 192 (60%) patients were dead (47 missing data). When death, irrespective of the reason, were used as the final outcome, the log-rank test did not show any diffe-

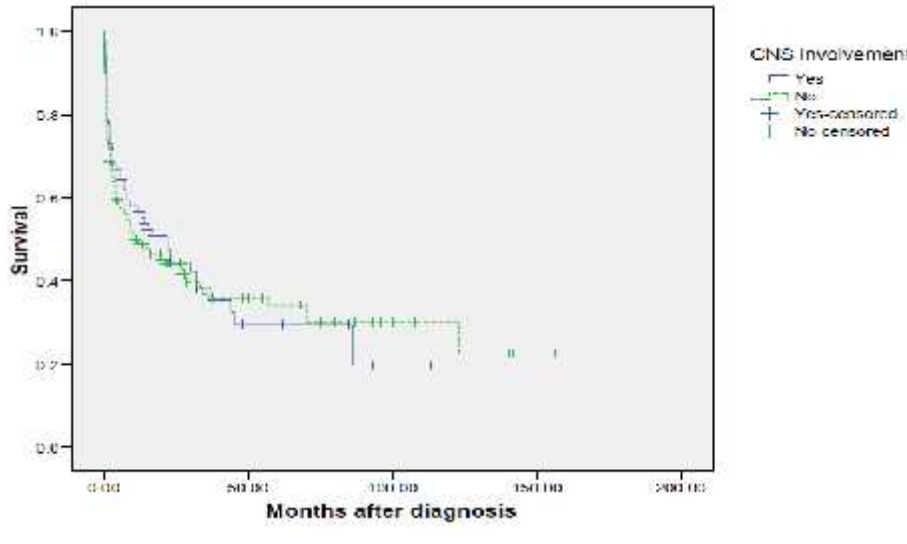

Figure 1. Survival curves for PTLD patients with or without central nervous system involvement, when death from any reasons was used as the final outcome.

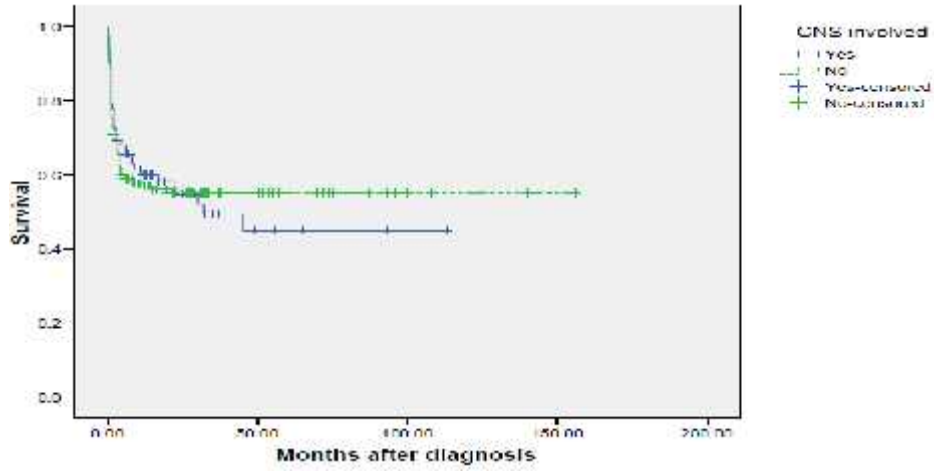

Figure 2. Survival curves for PTLD patients with or without central nervous system involvement, when death due to PTLD was used as the final outcome.

rence between the two groups in their survival (P = 0.456; Figure 1). The 1 and 5 years survival rates for CNS-involved PTLD patients were 57% and 30%, respectively, and 49% and 34%, respectively, for the control group. On the other hand, when death specifically due to PTLD was used as the final outcome, again, we found similar survival rates for patients representing PTLD involving either CNS or other localizations (P = 0.895; Figure 2).

Discussion

PTLD is one of the most common malignancies among adult solid organ transplantation recipients.[31] PTLD involving the CNS, the most sensitive organ of the human body, is of extreme relevance and is supposed to be an uncommon site for localization for this disease. The incidence of CNS involvement in typical lymphomas is reported as 1%.[22] However, a report from the Israel Penn International Transplant Tumor Registry claims that CNS involvement complicates about 15% of all PTLD patients.[32] On the other hand, Schneck and Penn[9] reported a CNS-PTLD prevalence of 50% for renal transplant recipients. In this survey, we collected and analyzed data of 90 PTLD patients who developed CNS involvement, which is, undoubtedly, the largest series of CNS-PTLD whose data was pooled and analyzed, ever.

CNS lymphoma is known to be associated with ocular involvement.[22] However, in this study, we found no relation between CNS-PTLD and orbital localization of the disease. In contrast to our study, Buell et al[32] in their report from the Israel Penn International Transplant Tumor Registry found that pancreas transplant recipients are in obviously greater risk for development of PTLD within the CNS. As mentioned, we found no relation between pancreas transplantation and CNS-PTLD. However, we found that renal transplant recipients are in greater risk for the disease. This finding is consistent with our previous knowledge from the first report of CNS involvement by PTLD, where 50% of all the renal recipients with PTLD had CNS involvement. On the other hand, we surprisingly found that heart transplant patients as well as liver allograft recipients are significantly less likely to develop CNS-PTLD (Table 1), an observation for which we have no explanation.

Previous studies have demonstrated that PTLD complicating CNS impose a high burden to the morbidity and mortality rates of organ transplant patients. It is postulated that CNS localization of lymphomas occurring post transplantation is the most fatal form of the disease.[8] However, in this study, when we analyzed sur-

vival of our patients regarding their PTLD localization, we found no statistically significant difference. This was quite an unexpected finding; therefore, we hypothesized that there might be some interfering factors that induced this result. Because several deaths among PTLD patients are not due to the PTLD itself, e.g. due to sepsis and heart conditions, we extracted data of reasons of death for each patient where it was available and re-analyzed the data for a potential different finding. However, the new approach to survival analysis did not change the result. This finding is in contrast with our previous presumption that PTLD patients with CNS involvement have quite a poor outcome than PTLD with other localizations.[8,33,34] However, in accordance with our finding, Cavaliere et al[10] (whose data were not included in this analysis due to its different style of data presentation, making it impossible to be compared), in their large case series, found similar results to those of ours. The median survival time for their series of primary PTLD involving CNS was 47 months, which is an obviously excellent outcome, comparable or even better than other PTLD patients.[35]

Radiotherapy is generally considered as the initial therapeutic modality in the management of CNS-involved lymphomas,[36,37] although the existing literature indicates poor results for radiotherapy and survival of these patients.[10,38,39] Moreover, Gonzalez and Schuster-Uitterhoeve found no relationship between total radiation dose and survival.[37] In this study, we also found no significant impact of radiotherapy on the survival of our PTLD patients with CNS involvement. The finding was the same when analysis was repeated including chemotherapy, and surgery although these could have been potential interfering factors affecting the outcome. This finding is also in keeping with some previous studies reporting similar results.[10] An interesting observation in this article is that despite the lack of response to treatment, CNS-PTLD patients had comparable patient survival as the control group, for which we have no explanation.

Multiorgan involvement as well as disseminated lymphoma was significantly more prevalent in the control group than in the CNS-PTLD patients. This may be due to a simple bias related to a less-distinct report on patients whose CNS was involved. For example, in some studies, authors only declared that all their patients had CNS involvement, with no further description on possible involvement of other organs. This assumption comes more into view as we found no difference between the two patient groups when only author-defined metastasis/disseminated diseases were entered into analysis compared with those that reported the number of other PTLD involvement sites.

The present study has some limitations. First, it is the retrospective nature of data collection from different institutions. As mentioned before, due to the different approaches employed by the 21 included series, we were unable to gather all data of the variables for any individual to have a perfect view on the whole population. For example, categorization of histological features of the PTLD was not based on the same method; therefore, we had to evolve some new methods to maximize inclusion of patients from various studies. On the other hand, data presentation was not perfect in all the articles; for example, while some series have reported very distinct data on their treatment methods or PTLD involvement sites, others represented very limited and ambiguous data, or even nothing. Methods of data ascertainment were also different between different reports. For example, for evaluation of EBV infection status, some of the studies have used simple serological evaluations while some other used polymerase chain reaction methods. However, despite all these limitations, we think that our study has several advantages over single-center reports as it uses data from several centers around the world, which strengthens our results by decreasing selection bias and/or inter-institutional disparities in the access to procedures and high-cost treatments as well as elevating potential inter-racial diversities in response to treatment.

In conclusion, in this study, we found that renal transplant recipients are at greater risk for developing CNS involvement by PTLD, while

heart and liver recipients represent significant lower risks for the same. Moreover, PTLD patients who represent CNS presentation have quite a comparable outcome compared with those with other disease localizations. We feel that these findings should be further evaluated with prospective studies with a larger number of patients.

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