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Original Article

Small Intestinal Involvement by Lymphoproliferative Disorders Post-Renal Transplantation: A Report from the Post-Transplant Lymphoproliferative Disorder International Survey

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ABSTRACT. In this study, data on post-renal transplant lymphoproliferative disorders (PTLD) collected from the existing literature were pooled and analyzed to compare the characteristics, predictors and prognosis of small intestinal PTLDs. We performed a comprehensive search for the available data by Pubmed and Google scholar search engines for reports on this subject. Data from 18 previously published studies, comprising 120 renal allograft recipients, were included in the analysis. Renal transplant recipients with intestinal PTLD were significantly less likely to have Hogkin's and Hogkin's-like lesions (P = 0.044) and to be younger at the time of transplantation (P = 0.07). Except for Hodgkin's-like lesions, histopathological evaluations elsewhere were comparable between the group with PTLD in the small intestine and age- and sex-matched renal transplant recipients with PTLD in other sites. The overall mortality was relatively higher in the control group (P = 0.09). When death only due to PTLD was used as the outcome, a trend toward better outcome was seen for the intestinal PTLD group compared with the other localizations (P = 0.1). The 1- and 5-year survival rates for intestinal PTLD patients were 57% and 37%, respectively, compared with 54% and 21%, respectively, for the control group. According to our findings based on analysis of international data, renal transplant patients with small intestinal PTLD are more likely to be of younger age but less frequently represent Hodgkin's and Hodgkin's-like lesions. They also have better patient survival compared with transplant recipients with PTLD in other locations. Further multi-center prospective studies are needed to confirm our results.

Introduction

The entity of post-transplant lymphoproliferative disorder (PTLD) represents a major challenging diagnostic and therapeutic problem characterized by irregular proliferation of B- or T-cells in the lymphoid tissue. Penn et al[1] were the first investigators to publish a report on PTLD in a patient who had undergone living related kidney transplantation in 1969. Since then, several authors from all over the world have reported their experience with PTLD, indicating a high incidence of the disease among recipients of all types of organs.

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The reported rationale behind the observed predominance in the incidence of lymphoma among transplant recipients include use of immunosuppression, OKT3, anti-lymphoblast globulin (ALG), anti-thymocyte globulin (ATG) and Epstein-Barr virus (EBV) infection.[2-4]

Investigators have suggested that the incidence, time interval, prognosis and presentation of PTLD varies depending on the age of the patients, presence of viral infections, intensity of immunosuppression and the organ transplanted.[5-10] The frequency of PTLD has been reported to range from 1% to 10%, with significant variability based on the organ transplanted.[11-15] Walker et al[14] reported PTLD in 6.2% of patients after lung transplantation, 5.2% after kidney and pancreas transplantation, 2% after heart transplantation and 1.4% of patients after liver transplantation. The difference in the frequency of PTLD among these groups may be attributed to organ-specific immunosuppressive regimens. PTLD encompasses a spectrum of clinical manifestations, in addition to a wide range of histopathologic findings, from B-cell hyperplasia to lymphoma. Lesions primarily occur in the gastrointestinal tract, central nervous system and the allograft, and less commonly in the lymph nodes.[13,16] However, the reported number of renal transplant recipients who developed PTLD within the small intestine is limited and only a small number of cases with histologically proven PTLD have been previously reported. Because of the limited number of reports on the issue, data scarcity exists on various aspects of small intestine PTLD occurring in renal transplant patients. In this study, pooling data of lymphoproliferative disorders post-renal transplantation from the existing literature, we sought to analyze and compare the characteristics, predictors and prognosis of small intestinal PTLDs arising in renal allograft recipients.

Materials and Methods

Approach to the study

We conducted a comprehensive search for the available data by Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring within the small intestine in renal transplant recipients. Keywords used for this purpose were "lymphoproliferative disorders + transplantation + renal + intestine," "lymphoproliferative disorders + transplantation + renal + intestinal," "lymphoproliferative disorder + transplantation + renal + duodenum," "lymphoproliferative disorder + transplantation + renal + jejunum," "lymphoproliferative disorder + transplantation + renal + ileum," "PTLD + renal + intestinal," "PTLD + renal + duodenal," "PTLD + renal + jejunal" and "PTLD + renal + ileal." In situations where the full text of the articles was not available, e-mails were sent to the corresponding authors requesting for the article. We included only 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 multicenter populations, while studies with any specific selection criteria were excluded from the analysis; lymphoproliferative disorders occurring after transplantation within the small intestine were considered as our case group and renal transplant recipients developing PTLD in other sites were used as controls. Patients with isolated colo-rectal PTLD were excluded from the case group. A standard questionnaire was developed to collect data from different published studies. Finally, data from 18 previously published studies from various countries[17-34] were included in the analysis. The time between transplantation and onset of PTLD was defined as the period between placement of the graft and the first signs of PTLD or diagnosis, depending on the study approaches.

Study population

Overall, 120 renal graft recipients who developed PTLD during their treatment course were included in the analysis. Thirty (25%) patients from the study population were renal allograft recipients with intestinal PTLD while the remaining 90 patients (75%) had PTLD at other sites. The patients' status regarding EBV infection was available in 83 patients (69.2%), of whom 61 (73.5%) were reported positive.

Because data used for this analysis were from

different studies and they did not have any unique approaches, we were not able to get all the data needed from all the included patients. Disseminated lymphoma was diagnosed when it was declared by the authors or at least three different organs were involved by PTLD; this was reported in 17 patients (24.3%; 50 missing data). Multiple lymph node areas were excluded from analysis due to lack of knowledge on how to categorize them. Multi-organ involvement, defined as involvement of more than a unique organ as well as more than one lymphatic region, was reported in 40 patients (41.7%; 24 missing data).

At diagnosis of lymphoma, all patients were receiving or had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil (MMF) and anti-thymocyte/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 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 response to PTLD treatment was reported by authors for 38 patients (31.7%), of whom 26 (68.4%) responded to anti-malignancy treatment. However, we developed new criteria for defining remission rates for the study population. A remission episode was defined when patients were alive after their 24th month of diagnosis of PTLD and no remission was defined when a patient died within the first month post-PTLD. According to this criteria, 70 patients (58.3%) had remission, of whom 34 (48.6%) had at least one response to treatment, irrespective of their future disease manner. Overall, mortality was recorded in 65 patients (54.2% of the study population and 64.4% of the reported cases; 20 patients missing data); death due to PTLD was defined when (a) if the authors stated it, (b) when the patient died within six months post-diagnosis unless the authors stated other causes for death or (c) when the patient died due to PTLD treatment complications. Overall, 41 patients died due to the disease based on the above-mentioned criteria (44.6% of the reported data; 63.1% of the whole mortality rate).

Statistical Analysis

Software used for data analyses was SPSS version 13.0. Statistical differences between patients' sub-groups were performed by using χ^2 and Fishers' exact tests for proportions and the Students *t* test for continuous data. Survival analysis was made with life tables and Kaplan-Meier methods and log-rank test. Multivariate linear regression models were used to detect the independent association of various factors with time interval between transplantation and PTLD diagnosis. Because of the limited number of the study population, all statistical tests were performed at the 0.1 significance level.

Results

Overall, 120 patients with PTLDs were entered into the analysis. There were 75 male (68.2%) and 35 female patients (31.8%) (10, missing data). The mean age at diagnosis of PTLD was 39.8 ± 16.7 years. The mean interval between transplantation and the diagnosis of PTLD was 59.7 ± 58.8 months while the follow-up time after diagnosis of PTLD was 19.4 ± 24.3 months.

The characteristics of the patients regarding their site of malignancy are summarized in Table 1. Chi square test showed that renal recipients with intestinal PTLD were significantly less likely to represent Hogkin's and Hogkin's-like lesions (0% vs 13.3%, respectively; P = 0.044). Renal transplant recipients with small intestinal PTLD localization were comparable to their counterparts with PTLD localization elsewhere in their gender (70% vs 67% male, respectively; P = 1.0), lymphoma cell types

Table 1. Characteristics of renal transplant recipients with post-transplant lymphoproliferative disorder in the small intestine versus other localizations.

Variables	Intestinal PTLD	Control group	Sig. (*P*)	Available data
Age (years)	34.9 ± 16.1	41.35 ± 16.7	0.07	117
Pediatric; <18 years old (%)	5 (17.2)	10 (11.4)	0.522	117
Gender male (%)	19 (70.4)	56 (67.5)	1.0	110
Time to PTLD development (months)	62.4 ± 56.3	58.7 ± 60.1	0.779	130
Multi-organ involvement (%)*	12 (50.0)	28 (38.9)	0.351	96
Disseminated PTLD (%)*	6(37.5)	11 (20.4)	0.191	70
Hodgkin's disease (%)	0	6 (13.3)	0.044	57
EBV status (%)	14 (73.7)	47 (73.4)	1.0	83
Remission episode (%)	8 (47.1)	26 (49.1)	1.0	70
Azathioprine-based immunosuppression (vs MMF/FK-506)	1 (7.1)	12 (25)	0.264	62
Use of induction therapy	7 (53.8)	23 (69.7)	0.328	46
Early onset (within first 12 months post-transplantation)	8 (28.6)	22 (28.9)	1.0	104
Monomorphic lesions (%)	5 (45.5)	12 (32.4)	0.486	48
Lymphoma cell type B cell (%)	8 (88.9)	39 (97.5)	0.337	49

*According to the criteria defined in the methods section; PTLD: post-transplant lymphoproliferative disorders, EBV: Epstein Barr virus, IS: immunosuppression, MMF: mycophenolate mofetil, FK-506: Tacrolimus

(89% vs 97% B cell, respectively; *P* = 0.337), immunosuppression type (7% vs 25% MMF based, respectively; *P* = 0.264), presentation time (both 29% early onset; *P* = 1.0), multi-organ involvement (according to the defined criteria described in the methods section; 50% vs 39%, respectively; *P* = 0.351), disseminated PTLD (according to the defined criteria described in the methods section; 37% vs 20%, respectively; *P* = 0.191), author-defined diffuse PTLD (57% vs 56%, respectively; *P* = 1.0) and the EBV-positive rate (74% vs 73%, respectively; *P* = 1.0). The overall mortality rate was relatively more frequent in the control group (50% vs 68%, respectively; *P* = 0.09); moreover, death due to the PTLD was also more likely to occur in the control group (29% vs 50%, respectively; *P* = 0.09). Table 2 summarizes involvement of different organs by PTLD concomitantly with involvement of the intestine.

Patients with intestinal PTLD were significantly younger at the time of transplantation (*P* = 0.07) but had comparable time from transplantation to development of PTLD (*P* = 0.779). Histopathological evaluations were also comparable for PTLD occurring within the small intestine versus PTLD in other areas (45% vs 32% monomorph, respectively; *P* =

Table 2. Frequency of concomitantly involved organs in 120 renal transplant recipients with intestinal complicated post-transplant lymphoproliferative disorders.

Involved organs	Intestinal PTLD [n (%)]	Controls	Sig.
Skin	1 (3.3)	3 (3.3)	1.0
Stomach	1 (3.3)	3(3.3)	1.0
Genitalia	0	2(2.2)	1.0
CNS	0	10 (11)	0.116
Spleen	2 (6.7)	2(2.2)	0.260
Renal involvement	1 (3.3)	14 (15.6)	0.112
Respiratory system	4 (13.3)	6 (6.7)	0.266
Liver	3 (10)	14 (15.6)	0.557
Bone marrow	0	4 (4.4)	0.571

PTLD: Post-transplant lymphoproliferative disorders, CNS: central nervous system

0.486). Because of the very high number of missing data, we were not able to evaluate differences in clonality between the two studied groups.

When death irrespective of the reason was used as the outcome, log-rank test did not show any difference between the two groups in their survival (P = 0.260; Figure 1); however, when death only due to PTLD was used as the outcome (based on the defined criteria in the methods section), a trend toward better outcome was seen for the intestinal PTLD group compared with the other localizations (P = 0.1; Figure 2). The 1- and 5-year survival rates for intestinal PTLD patients were 57% and 37%, respectively, compared with 54% and 21%, respectively, for the control group.

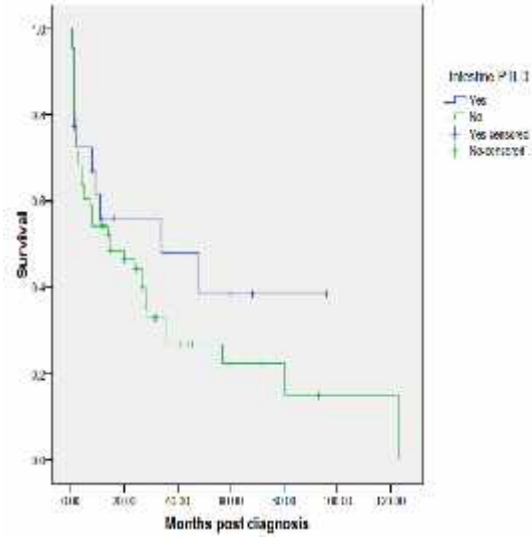

Figure 1. Survival curves of renal transplant recipients with and without post-transplant lymphoproliferative disorders affecting the intestine.

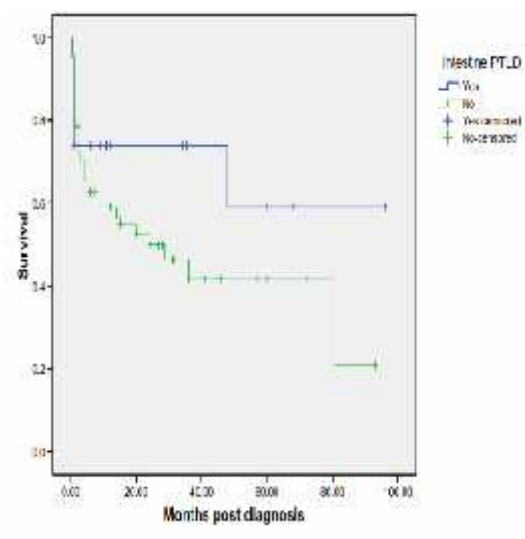

Figure 2. Survival curves of renal transplant recipients developing post-transplant lymphoproliferative disorders (PTLD) with and without intestinal involvement when death due to the PTLD was used as the outcome.

Discussion

PTLD represents a life-threatening disorder occurring after transplantation, ranging from a polyclonal mononucleosis-like illness to a monomorphic high-grade neoplastic disease with cytologic and histopathologic evidence representing a malignant lymphoma. The development of PTLD is described to be related to a deficient cellular immune response due to several interfering factors including immunosuppression administered to prevent graft rejection as well as EBV infection. The prevalence of PTLD ranges from 1% to 20% among all solid-organ transplants. Although the highest incidence of lymphoma has been observed during the first year after transplantation, the cumulative risk increases year by year. At ten years, the relative risk is 11.8-fold greater than in persons in the non-transplant population.[35] Among renal transplant recipients, the prevalence of PTLD is reported to be about 5%.[14] PTLD is considered as a potentially fatal complication among organ transplant recipients with mortality rates as high as 50-80%.[35-38] The number of reports on intestinal involvement by PTLD post-renal transplantation is limited in the literature. The PTLD International 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 existing data in the literature. To the best of our knowledge, this report deals with the largest ever population with PTLD involving the intestine aimed at discovering various characteristics of PTLD affecting the

small intestine and its histopathological features, including morphology, EBV infection status as well as prognostic factors.

In this study, we found that renal transplant recipients who present with intestinal PTLD are significantly more likely to be of younger age but less frequently develop Hodgkin's and Hodgkin's-like lesions. Moreover, we showed that intestinal PTLD is associated with superior survival when death due to PTLD is defined as the final outcome. This finding is of utmost relevance because reports have shown a poor outcome for individuals with intestinal lymphomas.[39] On the other hand, some investigators reporting a good survival for intestinal lymphomas have described this observation by the presence of MALT-derived lymphoma, which appears to have a favorable prognosis among patients with primary small intestinal lymphoma.[40] This may explain why our PTLD patients with intestinal involvement showed a superior outcome compared with those with other PTLD localizations. In our previous articles from the PTLD International Survey, we showed that PTLD, when it involves the adeno-tonsillar region (unpublished data), is also associated with better outcome than other localizations but found comparable survival for PTLD arising within renal[8] or liver allografts (unpublished data) as well as in patients with simultaneous renal-pancreas transplantation compared with renal-only recipients[41] and PTLD patients with EBV-positive results than those with negative EBV.[42]

Interestingly, we found no difference between the two patient groups regarding concomitant PTLD localizations. Although central nervous system (CNS) localization was not reported for the case group, 11% of the control group had CNS PTLD. However, the difference did not reach a significant level. Moreover, renal involvement was five-times more frequently seen in the control group. This observation may be due to a lack of precise reporting by the authors or limited number of patients.

This study has several limitations and criticisms may arise over our study. First, our study population was gathered from different reports with inconsistent approaches. We also believe that this is the unique major limitation for this study leading to substantial missing data for some of study variables and, thus, decreasing the power of our analyses. This limitation was most prominent for special data that are not typically included in reports on PTLD patients. On the other hand, inconsistencies available among the included studies have also resulted in weakening our study strength as results of different studies were not presented in the same way. For example, reports of any response to treatment were presented very dissimilarly in different studies; while in one study partial and complete remission was used to translate the results, in another study only "response to treatment" was used and in some others no specific terminology was employed. Thus, we had no choice but to invent new methods to cumulate the existing data for analysis. Finally, the significance level of 0.1, which was used for this survey, may raise criticisms on the reliability of the findings of this study. Despite all these limitations, we believe that our study presents with several advantages and its findings add valuable data to the existing literature. First, addressing a rare sub-classification of the PTLD population, this study deals with a relatively large renal transplant population who presented with PTLD within their small intestine and their data were compared with a best-possible matched population. Because of the rare frequency of the reviewed disease, we have a strong doubt that any single or even multicenter report can cumulate a larger and better matched patient population to have a better insight into the problem. Thus, although we do not debate that our article's methodology is so strong that it makes our findings nondoubtable, in the existing situation, we believe that we have presented some valuable data that can be used as a baseline for future studies.

In conclusion, when only death due to PTLD is considered as the outcome and death from unrelated reasons are censored, we found that renal transplant patients who develop PTLD within their small intestine are associated with better patient outcomes when compared with

those with other PTLD localizations. Moreover, renal transplant patients with small intestinal PTLD are more likely to be of younger age but less frequently represent Hodgkin's and Hodgkin's-like lesions. Further multi-institutional prospective studies are needed to confirm our results.

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