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Original Article

Post-Transplantation Lymphoproliferative Disorders in Renal vs. Simultaneous Renal–Pancreas Allograft Recipients: A Survey and Analysis of Data from the Literature

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ABSTRACT. The epidemiology and other aspects of post-transplantation lymphoproliferative disorders (PTLD) are different in different transplant populations. In this study, we sought to determine the clinical, histopathological and various other features of PTLD in recipients of pancreas–renal allografts and to compare their data with renal-only transplant patients, based on the current available literature. We conducted a comprehensive search for the available data using the Pubmed and Google scholar search engines for reports of lymphoproliferative disorders after renal and simultaneous pancreas–renal (SPR) transplantations. A total of 229 recipients of renal and pancreas–renal allografts were included in the analysis. Localizations for SPR recipients were significantly higher than renal recipients in the pancreas (P <0.0001), skin (P = 0.035), liver (P = 0.043) and bone marrow (P = 0.022). Involvement of lymph nodes was more prevalent in renal recipients (P = 0.046). The occurrence of metastasis was more common among SPR recipients (P = 0.005). Hodgkin's and Hodgkin's-like PTLD were also more prevalent among SPR transplant patients (P <0.0001). Time to development of PTLD was significantly shorter among recipients of SPR (P <0.0001). In this study of international data, we found that PTLD in SPR transplant recipients have various characteristics in their site of involvement, disease presentation time and histopathological features. However, no difference in outcome was detected in these groups of PTLD patients. Future studies with larger study populations are needed for confirming and extending our study results.

Introduction

Post-transplant lymphoproliferative disorders (PTLD) are one of the most common malignancies complicating solid-organ recipients, including simultaneous renal and pancreas (SPR) transplant (Tx) recipients.[1-6] PTLD represent a spectrum of heterogeneous pathologic lymphoid proliferations developing due to an abnormal response by the lymphoid system to Epstein-Barr virus (EBV) infection in hematological cells, chronic immunological response to the allograft antigens and pharmacologic immunosuppression after organ trans-

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plantation.[7,8] PTLD are generally considered to be more prevalent and extremely more aggressive diseases compared with malignant lymphomas in the general population.[8-13] The epidemiology and other aspects of PTLD are different in different transplant populations.[14,15] Recipients of some allograft types are at higher risk of developing PTLD, and the features of PTLD are quite different between them. Previous reports on PTLD occurring in SPR Tx recipients are on limited patient population without comparing the results with other Tx populations. Thus, we do not have a reliable view on the characteristics of PTLD occurring after SPR Tx. In this study, we sought to determine the clinical, histopathological and various other features of PTLD in recipients of SPR allografts and to compare their data with renal-only transplant recipients.

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 after renal and SPR Tx. Keywords used for this purpose were "lymphoproliferative disorders + renal transplantation," "lymphoproliferative disorders + pancreas + renal transplantation," "PTLD + renal transplantation," "PTLD + pancreas + renal transplantation" and "PTLD + simultaneous pancreas + renal transplantation." In cases where we were not able to access the full text of the articles, an email was sent to the correspondent authors requesting for the article. We only included studies in which data of each patient was presented separately, and excluded the others. To minimize selection bias, we only included studies reporting their series of patients from single or multi-center populations; studies with any specific selection criterion were excluded from the analysis; SPR allograft recipients were considered as the case group and renal transplant patients were used as controls. A standard questionnaire was developed to collect data from different published studies. Finally, data from 23 previously published studies from various countries[4,7,14-34] were included in the analysis. The time between transplantation and onset of PTLD was defined as the period between the date of transplantation and the first signs of PTLD or diagnosis, depending on the studies.

Study population

Overall, 229 recipients of SPR allografts were included in the analysis. Twenty (9%) patients the study population were recipients of SPR allografts and the remaining 209 (91%) patients were recipients of renal transplants. Because data used for this study were from different studies, and they had no unique approaches, we were not able to get all the data needed from all the included patients. Thus, data for sites of malignancy were available for 189 patients (82%) only. Renal allograft localization was seen in 47 patients (25%), thyroid in three (2%), bone (including vertebrae) in seven (4%), heart in three (2%), pancreas in six (3%), retroperitoneal tumor in nine (5%), adrenal gland in two (1%), skin in eight (4%), spleen in six (3%), lymph nodes in 71 (38%), central nervous system in 22 (12%), pharynx in 11 (6%), liver in 21 (11%), gastrointestinal tract (including stomach and small and large intestines) in 70 (37%), stomach in 10 (5%), genitalia in four (2%), bone marrow in 12 (6%) and lung in 18 (9%). Disseminated lymphoma was reported in six patients (3%). Multi-organ involvement was noted in 75 patients (40%), while 114 (57%) were reported to have only one PTLD localization site. Table 1 shows the localization of malignancy according to the allograft types. At diagnosis of lymphoma, all patients were receiving immunosuppressive regimens including varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, anti-thymocyte/lymphocyte globulin (ATG/ALG) and OKT3. More or less, a rather uniform approach was used to manage all PTLD patients in the included reports. On diagnosis of PTLD, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; different regimens of chemotherapy, with or without surgical interventions, were used for some

Table 1. Characteristics of the study population regarding their allograft type.

Variable	Renal graft	Renal–pancreas graft	Significance	Data availability
Gender male (%)	110 (64)	16 (80)	0.21	192
Age at PTLD	41 ± 16	40 ± 7	0.53	220
Months from Tx* to PTLD	72 ± 66	29 ± 37	0.001	115
PTLD of T-cell type (%)	2 (3)	5 (26)	0.005	87
Hodgkin's and Hodgkin's-like PTLD (%)	29 (36)	13 (87)	<0.0001	96
Cancer site				
Renal allograft	40 (23)	7 (37)	0.26	189
Thyroid	3 (2)	0	1.0	189
Bone and spine	6 (3)	1 (5)	0.53	189
Heart	2 (1)	1 (5)	0.27	189
Pancreas	1 (1)	5 (26)	<0.0001	189
Retroperitoneal tumors	9 (5)	0	0.60	189
Adrenal	1 (1)	1 (5)	0.19	189
Skin	5 (3)	3 (16)	0.035	189
Spleen	5 (3)	1 (5)	0.47	189
Lymph nodes	68 (40)	3 (16)	0.046	189
CNS*	19(11)	3 (16)	0.47	189
Pharyngeal region	11 (6)	0	0.6	189
Liver	16 (9)	5 (26)	0.043	189
Gastrointestinal tract	59 (35)	11 (58)	0.07	189
Stomach	8 (5)	2 (10)	0.26	189
Genitalia	4 (2)	0	1.0	189
Bone marrow	8 (5)	4 (21)	0.022	189
Lung	16 (9)	2 (10)	0.69	189
Metastasis	68 (40)	14 (74)	0.005	189
Disseminated disease	6 (3)	0	1.0	189
EBV sero-positivity	85 (73)	11 (73)	1.0	132
Relapse episodes	11 (26)	0	1.0	44
Initial response to drug	77 (54)	2 (22)	0.09	151
Total mortality	100 (53)	13 (65)	0.52	210
Death due to PTLD	65 (35)	6 (30)	0.81	207

Tx: Transplantation, PTLD: Post-transplant lymphoproliferative disorders, CNS: Central nervous system, EBV: Epstein-Barr virus

of the patients.

Laboratorial findings and disease progression

The EBV serologic status was documented in 132 patients (58%), of whom 96 (73%) were sero-positive. For categorizing a parameter for defining "metastasis," we considered all subjects with more than one PTLD localizations as having metastatic disease; patients with over one PTLD localization that were defined as having non-metastatic disease by the authors were considered non-metastatic. With this definition criteria, in addition to patients in whom metastasis was definitely documented by the authors (31 patients), 82 patients (36%) presented with metastatic disease while 18 patients (8%) were documented as having no metastases by the authors.

Response to treatment

Response to treatment was defined as any favorable change in the cancer measures as well as patients' clinical condition; data of PTLD response to treatment was reported for 119 patients (52%), of whom 75 patients (68%; 65 patients completely remitted) responded to anti-malignancy treatment while 12 (of the 45 reported cases; 27%) experienced

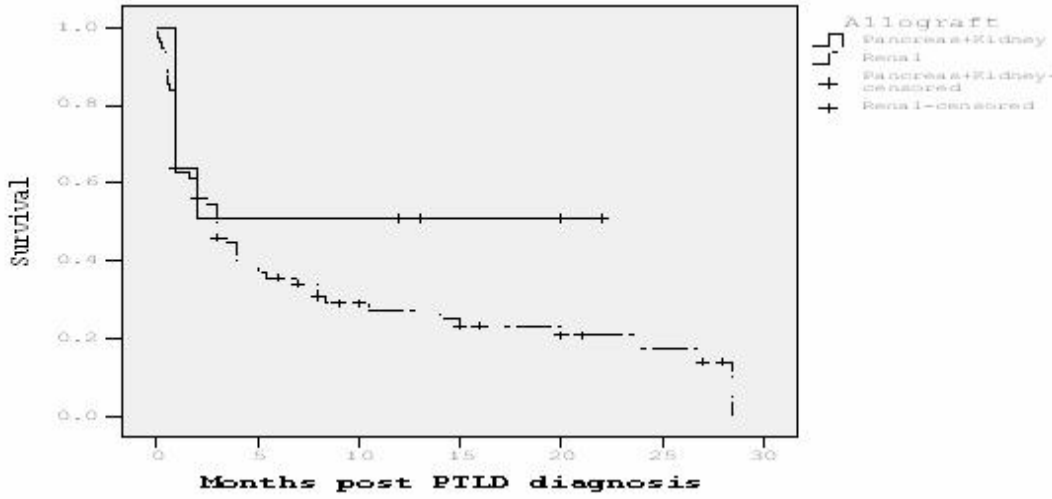

Figure 1. Survival curves for renal transplant patients and simultaneous pancreas-renal recipients after PTLD diagnosis

episodes of relapse. Overall, 116 patients (51%) died; death due to PTLD was defined when (a) if authors stated it or (b) when patient died within six months post-diagnosis and (c) when patients died due to complications related to PTLD treatment. Overall, 71 patients (63%) died of the disease based on the above-mentioned criteria.

Statistical Analysis

The software used for data analyses was SPSS v.13.0. Statistical differences between patients' sub-groups were performed using χ^2 and Fisher's exact tests for proportions and the Student's *t* test for continuous data. Survival analysis was performed with life tables and Kaplan-Meier methods and log-rank test. All statistical tests were performed at the 0.05 significance level.

Results

Overall, 229 patients with lymphoproliferative disorders after renal transplantation were enrolled in the analysis. There were 126 male (65%) and 66 female (34%) patients (37 missing data). Mean age at diagnosis of PTLD was 41 ± 15 years. The mean interval between transplantation and the diagnosis of PTLD was 61 ± 67 months, while the follow-up duration after diagnosis of PTLD was 26 ± 62 months. The characteristics of the patients regarding their allograft types are summarized in Table 1. Chi square test showed that PTLD localizations for SPR recipients were significantly higher than in renal recipients as follows: (a) pancreas [five (26%) vs. one (1%), respectively; P <0.0001]; (b) skin [three (16%) vs. five (3%), respectively; P = 0.035]; (c) liver [five (26%) vs. 16 (9%), respectively; P = 0.043]; and (d) bone marrow [four (21%) vs. eight (5%), respectively; P = 0.022]; while renal recipients were significantly more likely to develop PTLD within lymph nodes [68 (40%) vs. three (16%), respectively; P = 0.046]. Multi-organ involvement was more likely to occur in SPR recipients [13 (68%) vs. 62 (36%), respectively; P = 0.012]. The occurrence of metastasis was also significantly more prevalent among SPR recipients compared with renal transplant recipients [14 (74%) vs. 68 (40%), respectively; P = 0.005]. SPR recipients were more likely to develop PTLD of T-cell type than renal recipients [five (26%) vs. two (3%), respectively; P = 0.005]. Hodgkin's and Hodgkin's-like PTLD were also more prevalent among SPR Tx patients compared with renal recipients [13 (87%) vs. 29 (36%), respectively; P <0.0001; 133 missing data].

Because of the lack of data for histological patterns, including clonality and morphology for SPR PTLD patients, we were not able to compare these parameters between the two groups. Time to PTLD development was significantly shorter among recipients of SPR (26 ± 35 vs. 64 ± 69 months, respectively; P <0.0001); EBV sero-positivity was equal between the two transplant groups [85 (73%) for renal recipients vs. 11 (73%) for SPR transplant patients; P = 1.0]. At last follow-up, 94 patients (45%) were alive (19 missing data). One-year survival rates for renal transplant and SPR recipients with PTLD were 45% and 29%, respectively (P = 0.7). Bivariate analysis did not show any difference in patient survival between renal transplant patients and SPR recipients (P = 0.2), although after the first six months post-diagnosis, the survival curve dropped for SPR recipients (Figure 1). Similar results were found when death due to PTLD (excluding other reasons) was used as the end point (P = 0.2).

Discussion

PTLD is an important complication in allograft recipients who are treated with immunosuppression that mainly targets the T-cell response;[35-37] this disorder is also one of the interfering factors that restricts the long-term outcome of transplantation. Until now, several studies have been published on PTLD occurring in organ transplant recipients. Renal transplant patients are the most commonly investigated transplant population on the epidemiology, features and prognosis of PTLD. However, there is shortage of data on PTLD occurring after SPR Tx and its potential differences with PTLD in renal-only transplant recipients. Because most studies in the existing literature deal with a limited number of PTLD patients, analyses may not properly demonstrate specific features of the disease in different populations. In this study, we attempted summation of data from different studies to have a larger population in which analyses may represent a more accurate result. Our analyses on the pooled data from 23 international studies have demonstrated several new pieces of information on PTLD occurring after SPR transplantation. We found that SPR recipients have comparable patient survival to recipients of kidney-only allografts despite their diverse characteristics, including occurrence of metastasis and multi-organ involvement. SPR recipients had a significantly shorter time to PTLD development. This finding is in contrast to a previous report in which no difference was seen between different allograft recipients.[15] Histopathological features were also significantly different between the two transplant groups, with SPR transplant recipients significantly more likely to develop PTLD of T-cell type and Hodgkin's disease. Paraskevas et al[15] also reported that T-cell PTLD was more prevalent in their series of pancreas transplant patients; however, to our knowledge, our study is the first reporting a higher incidence of Hodgkin's and Hodgkin's-like diseases among SPR recipients. Localization of PTLD was also significantly different between SPR recipients and renal transplant patients. We found that PTLD was more likely to involve the pancreas, skin, liver and bone marrow in SPR recipients, while lymph nodes were the predominant involvement site in renal allograft recipients. Gastrointestinal tract localization was also more prevalent among SPR recipients, although it did not reach a significance level (P = 0.07). Additionally, the initial response to treatment was relatively lower among SPR recipients (P = 0.09). Moreover, occurrence of metastasis was more prevalent among SPR recipients than in renal transplant patients. We are aware of the limitations of our study protocol. First, our study population was gathered from different reports with inconsistent approaches. Also, another major limitation of this study is the substantial missing data for some of study variables thus decreasing the power of some of our analyses. This limitation was most prominent for special data that are not typically included in all reports on PTLD patients. On the other hand, we studied different series of patients from 23 studies in this analysis. Some studies were simple series reported from individual centers while others

focused on graft involvement or other specific criteria. Thus, we were not able to globalize our observation on the incidence or frequencies in our study population. Another limitation was that results of different studies were not presented in the same way. For example, report of response to treatment was presented in different ways in different studies. In one study, "partial and complete remission" was used to describe the response to treatment, while in some other studies, "response to treatment" was used and in yet other studies, no specific terminology was employed. Hence, we ought to invent new methods to cumulate the existing data for analysis.

In conclusion, in this study of international data, we found that PTLD arising in SPR Tx recipients have various characteristics in their involvement site, disease presentation time and histopathological features. However, no outcome difference was detected in these groups of PTLD patients. Future studies with larger study populations are needed for confirming and extending our study results.

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