original research report

Very late onset lymphoproliferative disorders occurring over 10 years post-renal transplantation: PTLD.Int. Survey

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BACKGROUND AND OBJECTIVES: Knowledge of the significance of post-transplant lymphoproliferative disorders (PTLD) that occur "very late" or more 10 years after renal transplantation is limited. Thus, we analysed and compared characteristics and prognosis of the disease in renal transplant patients with very late onset PTLD vs. early- and late-onset PTLD.

DESIGN AND SETTING: Retrospective study of data obtained from comprehensive search of medical literature

PATIENTS AND METHODS: We searched for available data using the Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring in renal transplant patients by disease presentation time.

RESULTS: We analyzed data from 27 studies that included 303 patients with lymphoproliferative disorders after renal transplantation. Renal graft recipients with very late onset PTLD were significantly less likely to be under mycophenolate mofetil (MMF)- and/or tacrolimus (FK-506) (vs. azathioprine) -based immunosuppression (P=.035) and less likely to have a history of antibody induction immunosuppression (P<.001). Compared to "early onset" disease, "very late" onset PTLD is more likely to develop in older patients (P=.032). Survival analysis did not show any difference in outcome (P=.5). No organ involvement priority was found for this patient group (P>.1 for all).

CONCLUSIONS: Older renal transplant patients are at increased risk for development of very late onset PTLD, and should be strictly followed. Further multi-institutional prospective studies are needed to confirm our results.

The introduction of highly potent, T-cell specific immunosuppressive drugs such as cyclosporine in the late 1980s revolutionized the practice of transplantation due to its substantial impact in preventing rejection episodes and enhancements in both patient and allograft survival. However, after a while, it emerged that these agents have some side effects, which can adversely affect transplantation outcome. Deficient cytotoxic T cell function due to pharmacologic immunosuppression in transplantation settings sensitizes these patients to post-transplantation malignancies including lymphoproliferative disorders (PTLD), which represent a heterogeneous group of pathologic lymphoid hyperplasia and lymphoid neoplasia.[1,2] PTLD is a challenging complication of organ transplantation and is usually fatal if untreated.[3] Current evidence suggests that recipients of solid organ allografts are at a 25- to 500-fold greater risk for developing PTLD with an overall reported incidence of about 1% to 20%.[4-8] The incidence of PTLD is reported to be dependent on factors, including the type of allograft transplanted, the immunosuppression type and intensity, the occurrence of viral infections, particularly Epstein-Barr virus (EBV), underlying disease, and patient age.[9-16] The prevalence of PTLD in renal transplant recipients is the least compared with most other organ recipients and is about 1%,[8,17] with higher rates in the pediatric setting,[18,19] possibly due to a lower rate of EBV positivity before transplantation.[20]

The time of the malignancy onset is one of the most relevant characteristics of the PTLD and can predict the behavior and features of the disease. Early onset

(occurring within the first year post-transplantation) and late-occurring PTLD (developing more than one year after transplantation) each have distinct pathological and prognostic characteristics, and therefore may have different risk factors. PTLD generally manifests during the first post-transplantation year[21-23] and can present from less than a month to as late as several decades later. Late-onset PTLD represents a distinct clinicopathological subset, occurring more frequently in older patients with a long latency period, often displays EBV negativity, responds poorly to treatment and has a worse prognosis.[24] Some investigators have introduced a new category for the onset time of the PTLD: "very late onset" disease, which indicates PTLD with a time interval of longer than 10 years between transplantation and PTLD appearance. Due to the very limited number of "very late onset" PTLD diagnosed in the individual and multicenter transplantation databases, current knowledge of the significance of this new category is limited. In our previous studies, we studied early and late onset PTLD in renal and liver transplant recipients.[15,25,26] The present study, however, aims to clarify specific aspects of PTLD, including its histopathological and clinical features, predictors and prognosis, when it occurs beyond the tenth year post-transplantation. The study includes the largest number of renal transplant recipients whose data have been analyzed and reported in the current literature.

PATIENTS AND METHODS

We conducted a comprehensive search for available data using the Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring in renal transplant patients with regard to the disease presentation time. Keywords were "lymphoproliferative disorders + transplantation + renal + late onset" "lymphoproliferative disorders + transplantation + kidney + very late onset" "lymphoproliferative disorders + renal transplantation + presentation time" "lymphoproliferative disorder + renal transplantation + time to PTLD" "PTLD + renal + late onset" "PTLD + renal + very late onset" "lymphoproliferative disorders + renal transplantation + onset". When we were not able to achieve the full text of an article, emails were sent to correspondent authors requesting the article. Then we only included studies in which data for each patient was presented separately. To minimize selection bias, we only included studies reporting a series of patients from single or multicenter populations. Studies with any specific selection criterion were excluded from the analysis; moreover, only studies that had patients in the "very late" group and at least one of the remaining two groups (early- and late-onset) were included in this analysis. A standard questionnaire was developed to collect data from different published studies. Finally, data from 27 previously published studies from various countries[5,27-52] were included in the study. 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 each study's approach. Patients who presented with PTLD within the first 12 months post-transplantation were considered the "early-onset PTLD" group; renal recipients presenting with the disease beyond this time but less than 10 years after transplantation were categorized as "late onset" PTLD patients. "Very late onset" PTLD was diagnosed when it occured after the tenth year post transplantation.

Because data from the studies varied in methodology, we were not able to get all the data we needed for all patients. Disseminated lymphoma was diagnosed when the authors stated it was present or when at least three different organs (different lymph node areas were excluded from analysis due to lack of knowledge on how to categorize) were involved in PTLD, which was reported in 27 (17.4%) patients (151 patients had missing data). Multiorgan involvement was defined as involvement of more than a one organ as well as more than one lymphatic region, which was available in 62 (32.8%) patients (117 had missing data).

At the time of lymphoma diagnosis, all patients were receiving or had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, and antithymocyte/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 also used for some of patients.

Response to treatment was defined as any favorable change in the cancer measures as well as patient clinical condition. Data on response to treatment was reported by authors for only 148 (48.4%) patients of whom 98 (66.2%) patients responded to anticancer treatment. However, we developed new criteria for defining remission rates for the study population. A remission episode was defined when patients were alive at their 24th month since PTLD diagnosis (since all reported cases meeting 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 reported cases there were no pa-

tients who died at the first post-transplant month and none reported any remission episode). For patients who died between these two time periods, no modification was made. According to this criteria, 213 (69.6%) had data on remission of whom 77 (36.2%) had at least one response to treatment, irrespective of their future disease course. Overall mortality was 154 patients (50.8% of the study population and 55.4% of the reported cases; 25 had missing data); death due to PTLD was defined when if authors stated it or when the patient died within 6-months postdiagnosis, or when patients died due to PTLD treatment complications. Overall 101 patients (37.7% of the reported data; 65.6% of the whole mortality rate) died due to the disease based on the abovementioned criteria.

Software used for data analyses was SPSS v.13.0. Statistical differences between subgroups were performed by using $\chi 2$ and Fisher exact tests for proportions and the *t* test for continuous data. One-way ANOVA was used for comparing continuous data between the three patient groups. The Bonferroni test was used for multiple comparisons. Survival analysis was done with life tables and Kaplan-Meier methods and the log-rank test. All statistical tests were performed at the P=.05 significance level.

RESULTS

Data on 303 patients who developed lymphoproliferative disorders after renal transplantation were included in the analysis. EBV infection was documented in 176 (57.5%) patients, of whom 121 (68.8%) were reported positive. There were 171 (62%) males and 105 (38%) females (30 patients had missing data). Mean (SD) age at diagnosis of PTLD was 43.1 (16.9) years. The mean (SD) interval between transplantation and the diagnosis of PTLD was 77 (67.3) months whereas follow-up time after diagnosis of PTLD was 23.7 (30.7) months.

Renal graft recipients with very late onset PTLD were significantly less likely to be under mycophenolate mofetil (MMF) and/or tacrolimus (FK-506) (vs. azathioprine)-based immunosuppression (P=.035) and less likely to have a history of antibody induction immunosuppression (P<.001) (**Table 1**). Renal transplant recipients with very late onset PTLD had other characteristics comparable to their counterparts with late onset disease. No priority for organ involvement was found for very late onset PTLD compared to other patients (**Table 2**). Age at the time of transplantation was not different when the very late group was compared to others together, but a post hoc analysis of the three patient groups showed that the "very late" onset PTLD was more likely to develop in older patients (P=.032).

At the last follow, 154 (50.8%) patients were dead (25 had missing data). When death for any reason was used as the final outcome, the log-rank test did not show any difference between the two groups in survival (P=.497; **Figure 1**); moreover, no statistically significant difference was seen between the two groups when death due only to PTLD was used as he final outcome (based on the defined criteria in the methods section; P=.266). A separate reanalysis of the data when all the three patient groups were entered into analysis did not change the results (P=.714; **Figure 2**). One and five-year survival rates for the very late onset PTLD patients were 56% and 29%, respectively; compared to 62% and 35%, respectively, for the controls.

DISCUSSION

After the recent improvements in the production and use of highly potent immunosuppressants, a substantial improvement has been observed in the overall survival of patients who receive organ grafts, including renal transplants. This trend of longer survival time as well as the special impact of the newly introduced immunosuppressive agents has increased the possibility of very late occurrence of PTLD.[53,54]

Lymphomas are more likely to develop among graft recipients within the first 12 months post-transplantation, which is usually termed as early-onset PTLD, but the incidence rate has declined over the years; this fact, along with the substantially higher rate of mortality in the early period post-transplantation leaves a limited number of PTLD cases occurring after the tenth post-transplant year. Therefore, we compared our results with studies reporting both late onset and very late onset PTLD. In our series, 23% (71 patients) were in the "very late" onset PTLD group and the remaining patients developed the disease before the tenth post-transplant year. Nevertheless, we were not able to draw a firm conclusion on the incidence of the very late onset PTLD after renal transplantation through this study, because of the methodological limitations, including the need to exclude some studies from the analysis and because the reported data does not represent the whole or even a comparable sample of the PTLD patients (i.e., it does not include data from all centers of the world).

An EBV positive serology might be associated with the time of PTLD appearance with a significant trend toward a longer time between transplantation and PTLD for EBV-negative patients (reviewed by Thomas Lowe et al [55] and Daniela Capello et al [56]). In this study of 303 patients, we detected a significantly lower rate of EBV infection for the very late onset PTLD com-

Table 1. Characteristics of renal transplant recipients with early and late onset PTLD.

Variables	Time to PTLD			*P* (two-sided)		Available data (number of patients)
	Early onset (n=52)	Late onset (n=180)	Very late onset (n=71)	Very late vs. others	Three groups comparison	
Mean (SD) age (years)	37.6 (18.3)	43.6 (16.4)	46 (17)	.119	.032	286
Pediatric (%)	7 (15.2)	13 (8)	5 (8.3)	1.0	.314	269
Gender male (%)	22 (52.4)	102 (61.4)	45 (69.2)	.189	.211	273
Time to PTLD development (months)	6.2 (3.5)	59.7 (30.9)	172.7 (57.5)	-	-	-
Time from diagnosis to death (monoths; dead patients included only)	31.6 (6.9)	16.3 (1.8)	12.4 (2.2)	.67	.203	139
Multiorgan involvement (%)[a]	11 (31.4)	38 (31.7)	13 (31)	1.0	.996	197
Disseminated PTLD (%)[a]	8 (26.7)	13 (13.4)	6 (15.4)	1.0	.224	166
Immunosuppression (azathioprine-based) (%)[b]	21 (53.8)	75 (67.6)	28 (82.4)	.044	.035	184
Cell types (% B cell)	22 (88)	57 (70.4)	22 (68.8)	.505	.179	138
Morphology				.650	.249	162
Early lesion (plasmacytic hyperplasia)	0	6 (6.3)	2 (5.4)			
Polymorphic B cell lymphoma	12 (41.4)	21 (21.9)	6 (16.2)			
Monomorphic PTLD	14 (43.8)	61 (63.5)	25 (67.6)			
Hodgkin lymphoma	3 (10.3)	8 (8.3)	4 (10.8)			
EBV status (%)	20 (90.2)	72 (67.3)	27 (61.4)	.259	.044	173
Mortality rate (%)	25 (54.3)	95 (56.9)	34 (52.3)	.572	.810	278
Remission episode (%)[c]	16 (58.6)	60 (65.2)	21 (77.8)	.184	.301	148
Remission episode (%)[a]	22 (61.1)	86 (64.7)	28 (63.6)	1.0	.925	213
Monoclonal lesions vs. polyclonal (%)	5 (41.7)	24 (77.4)	8 (100)	.088	.010	51
Lymphoma cell type B cell (%)	22 (88)	57 (70.4)	22 (68.8)		.179	138
Use of induction therapy (%)	19 (61.3)	62 (66)	9 (26.5)	<.001	<.001	159

[a]According to the criteria defined in the methods section; [b]versus under MMF and/or FK-506-based immunosuppression; [c]author reported.

pared to early onset disease; although the difference was not significant when early and late onset PTLD were pooled and compared with the very late PTLD.

Potent immunosuppressive agents have been associated with an earlier development of lymphomas post-transplantation. A major study from the Collaborative Transplant Study database reported that treatment with antibody induction therapy increases the risk of lymphoma only during the first year after transplantation, whereas the risk was similar to that in non-antibody-treated patients in subsequent years.[57] In the current study, we found that patients under more potent immunosuppressants (MMF and/or FK-506) were significantly more likely to develop early PTLD while azathioprine-based therapy was more frequently observed in the very late onset PTLD. Moreover, use of antibody

Table 2. Frequency of involved organs in 168 renal transplant recipients with early or late onset PTLD.

Involved organs	Time to PTLD			*P*		Available data (number of patients)
	Early onset	Late onset	Very late onset	Very late vs. others	Between three groups	
Skin	3 (8.6)	36 (27.5)	14 (26.9)	.711	.060	218
Stomach	0	5 (4.5)	2 (4.7)	.662	.446	187
Genitalia	0	2 (1.8)	0	1.0	.493	187
CNS	14 (33.3)	22 (17.9)	10 (20.8)	1.0	.109	213
Spleen	0	5 (4.5)	2 (4.5)	.665	.415	189
Colon	1 (2.9)	3 (2.7)	1 (2.3)	1.0	.985	187
Small intestine	1 (2.9)	17 (15.2)	5 (11.6)	1.0	.160	189
Renal involvement	9 (26.5)	13 (11.6)	4 (9.3)	.453	.05	189
Liver involvement	2 (5.9)	14 (12.5)	3 (7)	.572	.397	189
Respiratory system	11 (39.3)	14 (15.4)	8 (21.6)	1.0	.025	156
Heart	2 (9.5)	2 (2.5)	0	.424	.306	133
Bone marrow	2 (5.9)	6 (5.5)	11 (5.9)	.717	.937	187

induction in the very late onset disease was significantly less common than that in the other two groups.

Evidence suggests that very late onset PTLD is more frequently of the monoclonal type while early onset disease is mostly polymorphic. Webber et al[58] have reported that almost three-quarters of patients developing PTLD less than 3 years from transplantation were polymorphic in nature, while more than half of the late onset cases were monomorphic. Moreover, early-onset PTLDs, occurring within 1 year after transplantation, are supposed to be mainly polyclonal; however, most late-onset PTLDs are monoclonal lymphoid malignancies (reviewed by Daniela Capello et al[56]). In the current study, although very late onset PTLD had a trend toward monomorphic lesions, it did not reach statistical significance. Nevertheless, PTLD lesions in all of the reported cases in the very late onset group were monoclonal and the difference was significantly higher than those in the other two groups.

Based on the current literature, late-onset PTLD more frequently represents extra-graft localization and widespread disease with involvement of multiple nodal and extranodal sites.[17,56] Moreover, a lesser incidence of graft involvement in the late-onset PTLD has been reported compared to that in the early-onset PTLD.[59-61] However, in the current study, we found no difference between the groups with regard to multiorgan involvement and disseminated disease. On the other hand, the rate of renal allograft involvement was significantly lower in the patients developing very late onset PTLD. In our previous reports on allograft localization of the PTLD in renal, liver and lung transplantation, we showed that PTLD presenting in the graft are significantly more likely to develop within the first year after transplantation.[9,15] About half of the heart allograft PTLD cases were also in the early onset PTLD group, although statistical significance was not achieved (unpublished data).

Wasson et al speculated that PTLD occurring in late post-transplantation might be associated with poor survival.[37] The evidence suggests a higher rate of mortality among late-onset than that in early-onset PTLD;[17] Armitage et al described their observation that an increased duration of immunosuppression contributes to a more severe and possibly advanced clonal evolution.[62] Moreover, it is reported that late onset PTLD less frequently responds to treatment.[63] However, in the current study of international data, we found no survival difference between different PTLD groups based on presentation time, and survival curves were fairly similar. This finding raises doubts on current speculation over the prognosis of late onset PTLD. Our study population with very late onset PTLD were under immunosuppression over 10 years, but had survival rates comparable with early and late onset PTLD.

Potential criticisms of our study are that the study

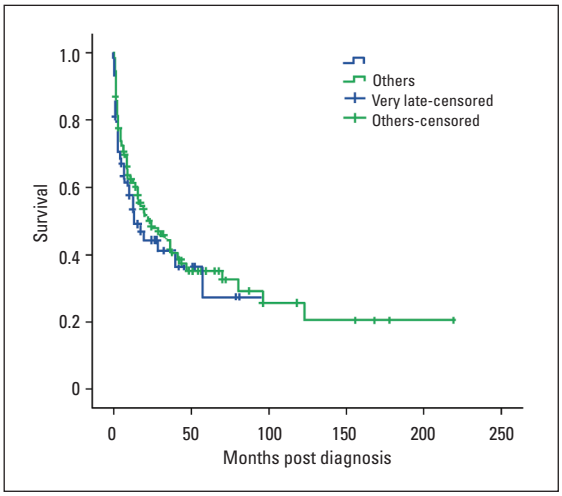

Figure 1. Survival curves of renal transplant recipients developing "very late" PTLD versus other onset times (*P*=.497).

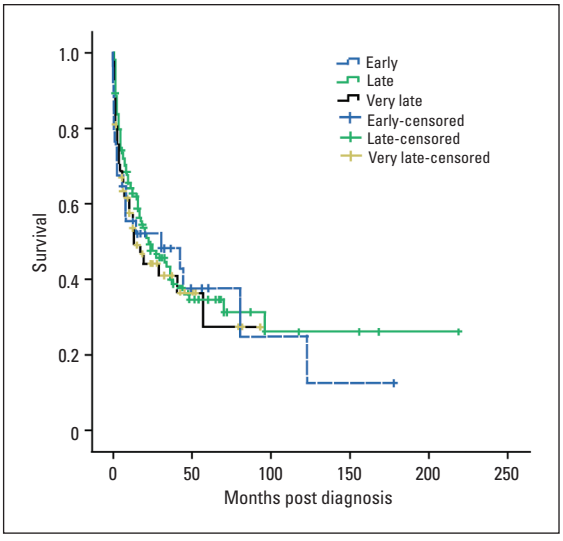

Figure 2. Survival curves with all three patient groups (*P*=.714).

population was gathered from different reports with inconsistent approaches. We believe that this is the 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. Another limitation is that the results of different studies were not presented in the same way. For example, the report of response to treatment was presented very dissimilarly: as partial or complete remission in one, while only "response to treatment" in another. Better methods are needed to accumulate the existing data for analysis.

In conclusion, we found that renal transplant patients who develop PTLD in the very late post-transplantation period have comparable patient outcomes to those with earlier onset disease. They also had similar rates of multiorgan involvement and disseminated disease. On the other hand, very late onset PTLD was associated with monoclonal lesions and use of less potent immunosuppressants. Further multi-institutional prospective studies are needed to confirm our results.

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