original research report

Early versus late outset of lymphoproliferative disorders post-heart and lung transplantation: The PTLD.Int Survey

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BACKGROUND AND OBJECTIVES: The presentation time of post-transplantation lymphoproliferative disorders (PTLD) are not well described because of the limited number of cases occurring at each center and lack of a reliable and unequivocal classification together with the absence of multi-institutional prospective studies. We gathered information on the histopathological and clinical features and prognosis of the disease in a very large number of heart and lung transplant recipients, with data from 27 previous reports, with an emphasis of time of presentation.

DESIGN AND SETTING: Retrospective analysis of data for individual patients from published studies, entered into a database and reanalyzed.

METHODS: A comprehensive review of the literature by PubMed and Google Scholar was performed to find all data available reports on PTLD after heart and lung transplantation.

RESULTS: Data from 288 PTLD patients after heart or lung transplantation from 27 reports were entered into analysis. Heart and lung recipients with early-onset PTLD compared with late-onset PTLD were significantly more likely to be of the B cell type (100% vs. 89.8%, respectively; *P*=.05). PTLD in patients with early onset was less likely to involve the skin (*P*=.05) and spleen (*P*=.015), but more frequently complications of the respiratory tract (*P*=.002). Morphology of PTLD lesions was significantly different between the two groups with a priority for late-onset PTLD to represent non-Hodgkin lesions (*P*=.009). No difference was found between the two groups in survival (*P*=.237). One and five-year survival rates for early-onset PTLD patients were 65% and 46%, respectively; compared to 53% and 41%, respectively, for the late-onset PTLD.

CONCLUSION: Due to a higher incidence of respiratory tract involvement in the early-onset PTLD patients and skin and spleen involvement in late-onset PTLD, we suggest that all heart/lung graft recipients should be evaluated for potential multiorgan disease based early or late presentation. Further multi-institutional prospective studies are needed to confirm our results.

Deficient cytotoxic T cell function due to pharmacologic immunosuppression in transplantation settings sensitizes these patients to post-transplantation lymphoproliferative disorders (PTLD) which represent a heterogeneous group of pathologic lymphoid hyperplasia and lymphoid neoplasia[1-3]— a challenging complication of organ transplantation, which is usually fatal if untreated.[4] Current evidence suggests that recipients of solid organ allograft are at a 25- to 500-fold greater risk for developing PTLD within the first year after transplantation.[5] The overall reported incidence of PTLD is 1% to 20%[6-9] but it depends on the type of allograft transplanted; the immunosuppression type and intensity; the occurrence of viral infections, particularly Epstein-Barr virus (EBV); underlying disease; and age.[9,10] The prevalence of PTLD in heart and lung transplant recipients is supposed to be at least twice that of recipients of other transplant types and up to 9.4%,[11,12] rising to 20% in pediatric series;[13-18] this rate ranges from 1.7% to 9% in liver recipients.[19-21]

Time of the malignancy onset is one of the most relevant characteristics of the PTLD, which can pre-

dict 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 represent distinct pathological and prognostic characteristics; and therefore may have different risk factors. For example, some authors have speculated that EBV-positive transplant patients represent early-onset PTLD than those with EBV negative serology;[3,22] evidence suggests that EBV–positive PTLD usually develops within 24 months post transplantation in organ recipients, whereas their EBV-negative counterparts have a median onset around 50 to 60 months after transplantation.[2] Other investigators have suggested that EBV-negative PTLD results in a worse prognosis compared with early-onset PTLD (the latter is more likely to present with EBV positive serology).[23-26] Moreover, the type and intensity of immunomodulation have also been shown as interfering factors.[27]

PTLD generally manifests during the first post transplantation year[28-30] and can present as early as less than a month to as late as several decades after transplantation. Although the general concept is that early-onset PTLDs have a favorable outcome, late-onset PTLD is thought to behave more alike aggressive lymphoma. Late-onset PTLD represents a distinct clinicopathological subset occurring more frequently in older patients with long latency period, often displays EBV negativity, responds poorly to treatment and has worse prognosis.[31] In our previous studies, we studied early- and late-onset PTLD in renal and liver transplant recipients.[17,18,22] The limited number of cases occurring at each center and lack of a reliable and unequivocal classification together with the absence of multi-institutional prospective studies makes it hard to have a reliable view of the different characteristics of the disease so as to develop preventive as well as treatment strategies. The present study, however, deals with different aspects of PTLD, including histopathological and clinical features and prognosis of the disease in a very large number of heart and lung transplant recipients, whose data were obtained from 27 previous reports, particularly with regard to presentation time (early vs late onset).

METHODS

We conducted a comprehensive search for the available data by PubMed and Google Scholar search engines for reports of lymphoproliferative disorders occurring in heart and lung transplant patients with regard to the disease presentation time. Keywords used for this purpose were "lymphoproliferative disorders + transplantation + heart + early onset" "lymphoproliferative disorders + transplantation + heart + late onset" "lymphoproliferative disorders + heart transplantation + presentation time" "lymphoproliferative disorder + transplantation + heart + time to PTLD" "PTLD + heart + early onset" "PTLD + heart + late onset" "lymphoproliferative disorders + transplantation + lung + early onset" "lymphoproliferative disorders + transplantation + lung + late onset" "lymphoproliferative disorders + lung transplantation + presentation time" "lymphoproliferative disorder + transplantation + lung + time to PTLD" "PTLD + lung + early onset" "PTLD + lung + late onset". In cases where we were unable to achieve the full text of the articles, emails were sent to correspondent authors requesting the article. We only included studies in which the data for each patient was presented separately, which was then entered data into a database; studies without data for each individual patient were excluded from analysis. To minimize selection bias, we only included studies reporting 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 with early- and late-onset PTLD 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[23,32-57] 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, depending on definitions in individual studies. Patients who presented with PTLD within the first 12 months post transplantation were considered as "early-onset PTLD" group, and heart and lung graft recipients who represented with the disease beyond this time period after transplantation were categorized as "late onset PTLD" patients.

Study population

Recipients of heart and/or lung grafts who developed PTLD through their treatment course were included in the analysis. Patient status regarding EBV infection was documented in 158 (54.9%) patients, of whom 114 (72.2%) were reported positive. Because data used for this study was from different studies with different methodologies, 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 three different organs (different lymph node areas were excluded from analysis due to lack of knowledge on how to categorize) were involved by PTLD, as reported in 35 (21.5%; 125 missing data)

patients. Multiorgan involvement defined as involvement of more than a unique organ as well as more than one lymphatic region was available in 78 (37.7%; 81 missing data) patients.

At lymphoma diagnosis, all patients were receiving and had received immunosuppressive regimens consisting of varying combinations of 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 clinical condition; data on PTLD response to treatment was reported by authors for only 49 (17%) patients, of whom 28 (57.1%) patients responded to anti-lymphoma therapy. However, we developed new criteria for defining remission rates for the study population. While the 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 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 patients who died at the first post-transplant month who were reported to have any remission episodes). According to this criteria, 143 (49.7%) patients represented data on remission of whom 95 (66.4%) had at least one response to treatment, irrespective of their future disease course. Overall mortality was 110 (38.2% of the study population and 58.2% of the reported cases; 99 patients had missing data) patients; death due to PTLD was defined if authors stated the fact, when patient died within 6 months post diagnosis, or when patients died due to PTLD treatment complications. Overall, 79 (41.8% of the reported data; 71.8% 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 chi-square and Fisher exact tests for proportions and the t test for continuous data. Survival analysis was done with life tables and Kaplan-Meier methods and log-rank test. All statistical tests were performed at the 0.05 significance level.

RESULTS

Overall, 288 patients with lymphoproliferative disorders after heart or lung transplantation were entered into the analysis. There were 180 (62.5%) heart transplant subjects and 108 (37.5%) lung graft recipients. Gender make up composed of 126 (68.9%) males and 57 (31.1%) female patients (missing data on 105). Mean (standard deviation) age at diagnosis of PTLD was 35.6 (22.6) years. The mean interval between transplantation and the diagnosis of PTLD was 40.8 (38.7) months whereas follow up time after diagnosis of PTLD was 25.0 (35.0) months.

Characteristics by onset time are summarized in **Table 1**. Heart and lung recipients with early onset PTLD were significantly more likely to be of the B cell type (100% vs. 89.8%, respectively; P=.05). Heart/lung transplant recipients with early-onset PTLD were comparable to their counterparts with late-onset disease as to rate of EBV infection rate (P=.2), total mortality rate (P=1.0), death due to PTLD (according to the defined criteria described in the methods section; P=.718), multiorgan involvement (according to the defined criteria; P=.645), disseminated PTLD (according to the defined criteria; P=.225). Gender make up was also different between the two patient groups with a trend toward a male predominance for late-onset PTLD (76% vs. 58%, respectively; P=.015). Heart/lung transplant patients with early-onset PTLD more frequently had remission episodes in their disease course (P=.041) and they also were more likely to be taking mycophenolate mofetil-based immunosuppression (vs. azathioprine based; P=.033).

Heart/lung transplant patients with early- or late-onset PTLD were comparable in age the time of transplantation (median age 42.0 versus 41.0 years; P=.763). Histopathological evaluations with regard to both the clonality (P=1.0) of specimen achieved from PTLD lesions in heart/lung transplant recipients showed comparable results in early- and late-onset PTLD patients; however, morphology of PTLD lesions was significantly different between the two groups, with more late-onset PTLD representing non-Hodgkin lesions (49% vs. 26%, respectively, P=.009). PTLD in patients with early onset was less likely to involve skin (P=.05) and spleen (P=.015) but more frequently in complications of the respiratory tract (P=.002) (**Table 2**).

At the last follow, 110 (58.2%) patients were dead (with 99 missing data). When death (irrespective of the reason) was used as the final outcome, the log-rank test showed no differences between the two groups in survival (P=.237; **Figure 1**); moreover, no statistically significant difference was seen between the two groups

when death only due to PTLD was used as the final outcome (based on the defined criteria in the methods section; P=.405). Separate reanalysis of data regarding basis of immunosuppression also did not show any survival preferences for any of the groups (P>0.4). One and five-year survival rates for early onset PTLD patients were 65% and 46%, respectively; compared to 53% and 41%, respectively, for the late onset PTLD.

DISCUSSION

Lymphoid tumors were first reported in organ transplant recipients in 1969 by Penn et al[58] and they are frequently termed as PTLD. PTLD are significant complications in solid organ transplant recipients with a broad range of clinical findings from self limited mononucleosis-type syndrome to rapidly progressive and disseminated disease.[59] PTLD commonly represents with uncontrolled B-cell proliferation with histopathologic features that range from plasmacytic hyperplasia to monomorphic large cell non-Hodgkin lymphomas. The reported incidence of the PTLD varies widely depending on the organ transplanted,[4, 60-65] with the highest incidence in the recipients of small bowel and heart and lung, viral infections and potency and length of immunosuppressive therapy.[62,64] Upon the introduction of highly potent immunosuppressive agents aiming at the prevention of graft rejection, the frequency of PTLD has dramatically increased[62] and the time interval between transplantation and the onset of PTLD has decreased.[62]

The highest reported rates of lymphomas were among graft recipients within the first 12 months post transplantation, so called early-onset PTLD with a slowly decreasing incidence rate over time.[66] In our series, 37% (106 patients) were early-onset PTLD and the remaining patients developed the disease beyond the first post transplant year. Nevertheless, we were not able to estimate the incidence of the PTLD after heart and lung transplantation because of methodological limitations: the first reason being the inclusion criteria, which excluded some studies from analysis; the second reason being that the existing literature does not represent the whole or even a comparable sample of the PTLD patients, because the literature does not include reports from all centers of the world.

The behavior and histopathological features of late-onset PTLD have been previously reported by different authors;[18,67,68] most of them focused on renal transplant recipients. The patients were older with lymphomas of the monomorph type with few responses to therapy. In our previous studies, we reported our findings on early- and late-onset PTLD in renal and liver transplant recipients;[17,18,22] in those studies, we also found that PTLD patients, despite all treatment strategies, had a high mortality rate.

In our study on heart and lung transplant recipients, we also found that histopathological features of PTLD have a trend toward the monomorph lesions in late-onset disease, but no difference in patient age regarding their PTLD onset time was found. Both of the above-mentioned findings were consistent with our previous study on liver transplant PTLD patients. On the other hand, we found that heart/lung transplant recipients who represent PTLD beyond the first year post-transplantation are more likely to be male; this finding contrasts with our study on liver transplant PTLD in which late onset disease was more frequently seen in females.

The PTLD presentation time is of particular interest as many authors believe that the time between graft and PTLD onset could be the main prognostic factor as well as the most important parameter to use in selecting therapeutic options.[8,68,69] In the current study,

Table 1. Characteristics of heart and lung transplant recipients with early and late onset post-transplant lymphoproliferative disorder.

Variables	Early onset	Late onset	*P*	Available data
Mean age (standard deviation) (y)	36.1 (21.9)	35.2 (23.1)	.763	279
Pediatric (<18 y)	28 (27.2)	54 (30.7)	.587	279
Gender male	45 (58.4)	81 (76.4)	.015	183
Mean (SD) time to PTLD development (mo)	6.3 (3.2)	60.9 (35.6)		288
Multiorgan involvement*	23 (34.8)	55 (39.0)	.645	207
Disseminated PTLD*	8 (15.4)	27(24.3)	.225	163
Morphology			.01	168
Early lesion (plasmacytic hyperplasia)	2 (3.2)	14 (13.3)		
Polymorphic B cell lymphoma	26 (41.3)	21 (20.0)		
Monomorphic PTLD	34 (54.0)	68 (64.8)		
Hodgkin lymphoma	1 (1.6)	2 (1.9)		
EBV status	44 (78.6)	70 (68.6)	.199	158
Remission episode	11 (22.0)	37 (39.8)	.041	143
Monoclonal lesions vs. polyclonal	15 (78.9)	37 (80.4)	1.0	65
Lymphoma cell type B cell	39 (100)	79 (89.8)	.05	127
Use of induction therapy	1(25)	16 (72.7)	.104	26

*according to the criteria defined in the methods section;
Data are n (%) or mean (standard deviation)

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

Involved organs	Early onset	Late onset	Sig.
Orbital	0	4(2.4)	0.311
Skin	0	8(4.9)	0.05
Stomach	1 (1.3)	6 (3.7)	0.437
Genitalia	1 (1.3)	3(1.8)	1.0
CNS	4 (5.3)	3 (1.8)	0.212
Skeleton	0	2 (1.2)	1.0
Spleen	1 (1.3)	16 (9.8)	0.015
Colon	5(6.6)	6(3.7)	0.331
Small intestine	3(3.9)	16(9.8)	0.197
Renal involvement	1(1.3)	7(4.3)	0.441
Liver involvement	5(6.6)	15(9.1)	0.620
Respiratory system	25(32.9)	24(14.6)	0.002
Bone marrow	2(2.6)	16(9.80)	0.06

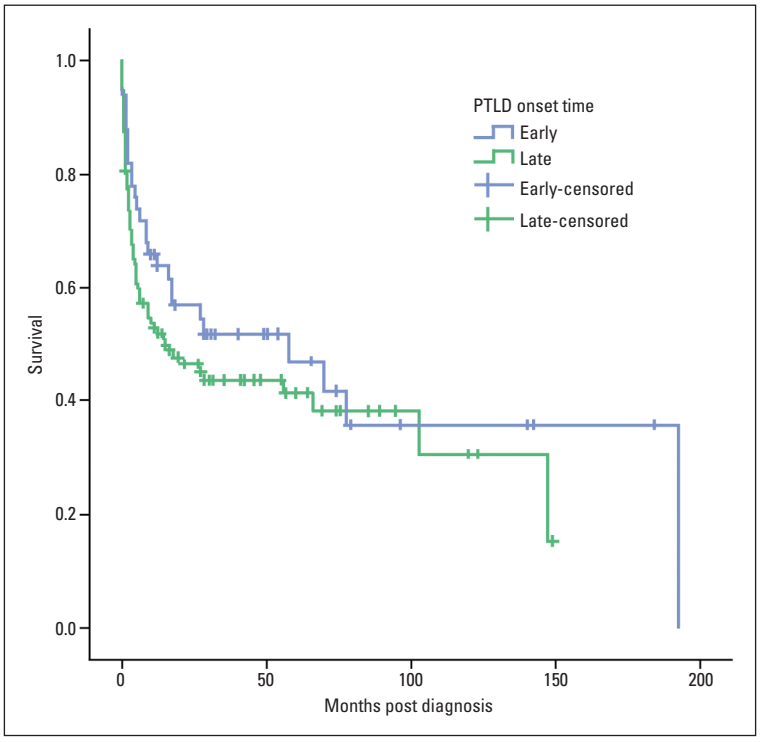

Figure 1. Survival curves of heart and lung transplant recipients with early and late onset disease.

we found no difference in the survival of patients with early- or late-onset PTLD. This finding differs from previous reports which suggest a superior outcome for early-onset PTLD in their centers but in concordance with our previous report on liver transplant patients.[22] Figure 1 might give the appearance that in the first years post transplantation, early-onset PTLD has a relatively higher survival, but reanalysis of the data did not show any significant difference.

Using the Collaborative Transplant Study database, investigators have found that treatment with ATG/ALG or OKT3 increased 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.[24] However, in the present study, presentation time of PTLD did not differ with regard to induction therapy.

It is generally accepted that immunosuppressive therapy favors both EBV infection (either primary or reactivation of latent infection) and growth and transformation of EBV-infected B-cells in an impaired cytotoxic T-cell function era. Previous studies have found several EBV-negative patients with late-onset PTLD.[6,69,70] In this study, however, we found no significant difference between early- and late-onset PTLD regarding EBV infection rates, which contrasts with our previous study on liver transplant PTLD subjects where we found a highly significant reduced EBV positive rates for late-onset PTLD compared to those with early-onset disease.

In our previous study on late-onset PTLD in renal allograft recipients, the major sites of PTLD were gastrointestinal tract and peripheral lymph nodes.[17] Another study of ours on early-onset PTLD in renal recipients, we found an allograft involvement preferential with 25% of the whole study population.[18] In another study on liver recipients, we however found that late-onset PTLD is more likely to involve colon and genitalia (the latter did not reach significance level), while early-onset PTLD more frequently complicates liver grafts. In the current study, however, we observed that the skin and spleen are the two preferred involvement organs in the late-onset PTLD whilst the respiratory tract is more frequently complicated by early onset disease in the heart/lung transplant recipients.

Potential criticisms of our study are, first, that our study population was gathered from different reports with inconsistent methodologies. 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. Another limitation might be due to the inconsistencies between studies because results were not presented in the same way. For example, response to treatment was presented very dissimilarly in different studies; while in one study partial and complete remission was used to translate the results, in another only "response to treatment" was used and in some others no specific terminology was employed. So we ought to invent new methods to accumulate the existing data for analysis.

In conclusion, we found that heart/lung transplant patients who develop PTLD have comparable patient outcomes both in the early and late onset disease. Due to a higher incidence of respiratory tract involvement in the early onset PTLD patients and skin and spleen involvement in late onset PTLD, authors suggest that all heart/lung graft recipients should receive enough evaluations for a potential multi organ disease regarding their presentation time. Further multi-institutional prospective studies are needed to confirm our results.

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