Original Article

Bone marrow involvement by lymphoproliferative disorders after renal transplantation: PTLD. Int. Survey

ABSTRACT

Context: Renal graft recipients who develop post-transplant lymphoproliferative disorders (PTLD) that complicate bone marrow (BM).

Aims: To investigate features, predictors and prognosis of BM involvement by PTLD in renal transplant patients.

Settings and Design: A comprehensive search for the available data though PubMed and Google Scholar for reports of PTLD localization in BM in renal allograft recipients.

Materials and Methods: Data of 168 PTLD cases in renal transplant context who have developed bone marrow PTLD gathered from 18 studies and were pooled and analyzed.

Statistical Analysis Used: Chi-square test, Student's t test and fissure's exact test were employed.

Results: Chi-square test showed that renal recipients with BM PTLD were significantly more likely to represent multi-organ disease ($P<0.001$), and disseminated PTLD ($P<0.001$). BM PTLD was also more frequently seen among pediatric renal recipients who had developed PTLD ($P=0.016$). PTLD, in BM PTLD renal recipients more significantly complicated liver ($P=0.008$), but less commonly affected skin ($P=0.045$). BM PTLD lesions were relatively more likely to be of monomorph phenomenon ($P=0.06$).

Conclusions: Renal recipients with BM PTLD represent worse outcome and more unfavorable histopathological phenomenon than in other organ involvements. Moreover, a concomitant PTLD involvement site in liver was found which necessitates full hepatic evaluation for a potential complication by the disease in renal recipients whose BM is involved.

KEY WORDS: Bone marrow disease, post-transplant lymphoproliferative disorder, renal transplantation

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INTRODUCTION

The development of post transplant lymphoproliferative disorder (PTLD) remains a challenging diagnostic and therapeutic problem characterized by neoplastic lymphoid proliferation of B- or T-cell origins. The first evidence on this entity was provided in 1969 by Penn *et al.*[1] in a patient who had undergone living related kidney transplantation. Since then, several reports from different centers throughout the world showed a high incidence of PTLD among recipients of all types of organs including the kidney. A wide range of 1–20% incidence of PTLD after organ transplantation has been reported,[2-5] representing a 10 to over 100 fold higher risk compared to that in the general population;[6,7] with renal transplant patients representing one of the lowest rates.

PTLD emerges in a wide spectrum from a limited disease to quite a disseminated neoplasm. Bone marrow (BM) examination is an integral part of non-Hodgkin lymphomas evaluations, since its involvement indicates stage IV disease, which is an adverse prognostic factor independently associated with a worse outcome.[8] The frequency of BM involvement by the lymphoma varies according to the disease subtype with higher frequency in patients with low grade non-hodgkin's lymphoma, ranging from 30% for marginal zone lymphomas to almost 100% for chronic lymphocytic leukemias[9,10] than in diffuse large B cell lymphomas (8–35%).[9-13]

Differences in the incidence of BM complication by PTLD with regard to their histopathological phenotype or association with Epstein–Barr virus (EBV) infection are currently not known. Although general belief is that BM involvement by monomorphic PTLD is uncommon, gradually emerging evidence indicates several individual reports on the occurrence of BM infiltrations in the PTLD population of this phenotype. On the other hand, no study with substantial number of patients has been conducted to investigate different characters, predictors and prognosis including changeable prognostic factor in renal transplant

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recipients. Knowing these factors, we can design preventive and screening methods that potentially decrease the incidence of the disease or promote its diagnosis in earlier stages which can result in survival advantages both for the graft and the patients.

Considering the above mentioned factors, in the current study we aimed to search the existing literature to find reported cases of renal recipients developing PTLD within their BM, and to compare their demographic data, histological phenomena and survival with renal recipients who represented PTLD in other organs to find potential predictive and prognostic factors which play major roles in this patient population.

MATERIALS AND METHODS

Approach to the study

We conducted a comprehensive search for the available data though PubMed and Google Scholar for reports of PTLD localization in BM in renal allograft recipients. Search terms used were "lymphoproliferative disorders + renal transplantation + BM," "lymphoproliferative disorders + kidney transplantation + BM localization," "lymphoproliferative disorder + renal transplantation + marrow infiltration". In cases where we were not able to obtain the full text of the article, emails were sent to the correspondent authors requesting the article. Of the full texts obtained, we enrolled subjects from studies in which data of each patient was presented separately. To minimize selection bias, we only included studies reporting their series of patients from single- or multi-center populations, and studies with any specific selection criterion were excluded from the analysis. Control patients were renal recipients whose PTLD localization organ was not BM. For minimizing interfering factors including center-selection bias, control patients were also enrolled from the same studies reporting BM PTLD renal recipients. A standard questionnaire was developed to collect data from different published studies. 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 the study's approach.

Study population

Eighteen international published studies[14-30] were found that met our criteria. A total of 168 renal recipients with a documented PTLD site were included in the analysis; of whom 31 (18.5%) had BM PTLD and the remaining 137 (81.5%) patients had developed non-BM PTLD. EBV status was documented in 108 (64.3%) patients, of whom 75 (69.4%) were reportedly positive.

Because of different methodologies employed in the published studies enrolled into the current survey, some of our measures were not available for all the patients. So we tried to standardize the data. We recorded disseminated PTLD when it was reported by the study authors or if at least three different organs were involved by the PTLD (different lymph node areas were excluded from analysis due to lack of knowledge on how to categorize; unless they were concomitant with other organs involvements; or other authors specifically presented them as having disseminated disease). According to the above mentioned, data on disseminated PTLD was available for 90 patients (53.6%; 78 unreported data) of which 29 (32.2%) were disseminated PTLD. Multi-organ involvement, defined as involvement of more than one organ (the second organ could be a lymphatic region), was available in 117 patients (69.6%%; 51 unavailable data) of which 64 (54.7%) were multi-organ PTLD.

At PTLD onset, all patients were under immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolatemofetil, ATG/ALG and OKT3. A rather uniform approach was used to manage most of the included PTLD renal recipients. On diagnosis of PTLD, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; various regimens of chemotherapy with or without surgical interventions were also used for some patients.

Response to treatment

We defined response to treatment as any favorable change both in PTLD measures and the patient's clinical condition. Data on response to treatment was reported for 96 patients (57.1%), of whom 69 (71.9%) responded to treatment and had a remission episode. To create a common standard across the studies, we defined a remission episode as when a patient was alive 24 months after PTLD onset (because all reported cases meeting this criterion had at least one confirmed remission episode) and no remission as when a patient died within the first month after PTLD onset (because there were no patients dying at the first post-transplant month that was reported to have any remission episodes). According to these criteria, data on remission was available for 123 patients (73.2%), of whom 76 (61.8%) had at least one response to treatment, irrespective of their future disease course. Data on mortality was available for 154 patients (91.7%), of whom 85 (55.2%) died. We defined death due to PTLD when the authors stated it, death was within six months after onset, or death was reported to be due to PTLD treatment complications. Based on these criteria, 50 patients (58.8% of reported deaths) died due to PTLD.

Statistical analysis

SPSS v.13.0 software was used for data analyses. Statistical comparisons between patient subgroups were performed using Chi-square and Fisher's exact tests for proportions, and the Student's t-test for continuous data. Survival analysis was done with life tables, Kaplan–Meier method and log-rank test. A *P*-value of 0.05 was taken as the threshold for significance and of 0.1 was defined as relevance level.

RESULTS

Overall 168 patients with lymphoproliferative disorders after renal transplantation were entered into analysis. There were 95 (62.5%) males and 57 (37.5%) female patients (16 unreported). Mean age at diagnosis of PTLD was 42.6±16 years. The mean interval between transplantation and the diagnosis of PTLD was 57.1±52.6 months whereas follow up time after diagnosis of PTLD was 22.9±32.3 months.

Characteristics of the patients regarding their malignancy site are summarized in Table 1. Chi-square test showed that renal recipients with BM PTLD were significantly more likely to represent multi-organ disease ($P<0.001$), and disseminated PTLD ($P<0.001$). BM PTLD was also more frequently seen among pediatric renal recipients who had developed PTLD ($P=0.016$). Renal transplant recipients with BM PTLD localization were comparable to their counterparts with other PTLD localization in their gender, lymphoma cell types, immunosuppression type, presentation time, and EBV positive rate. Overall mortality rate was relevantly more frequent in the BM PTLD group than in controls ($P=0.06$); however, death due to the PTLD was not statistically different between the two groups.

Table 2 summarizes different organ involvements by PTLD when they concomitantly do or do not complicate the BM. PTLD, in BM PTLD renal recipients more significantly complicated liver ($P=0.008$), but less commonly affected skin ($P=0.045$), simultaneous to the BM. Other organs were equally involved by the neoplasm between the two groups.

Patients with BM PTLD were significantly younger at the time of transplantation ($P=0.04$); but had comparable time from transplantation to PTLD development ($P=0.728$). Histopathological evaluations were also comparable for PTLD occurring within BM PTLD patients versus other renal recipients developing PTLD [Table 1]. However, BM PTLD lesions were relevantly more likely to be of monomorph phenomenon ($P=0.06$).

When death irrespective of the reason was used as the outcome, log-rank test showed a significant inferior outcome for BM PTLD renal recipients ($P=0.001$; Figure 1); as well, when death only due to PTLD was used as the outcome (based on the defined criteria in the methods section), the BM PTLD group again represented lower survival than patients with other localizations ($P=0.02$; Figure 2). One and two years survival rates for BM PTLD patients were 46 and 17%, respectively, compared to 63 and 50%, respectively, for the control group.

DISCUSSION

PTLD are one of the most prevalent malignancies complicating recipients of various organs reducing graft and patient survival and inducing a high financial and medical burden to patients and the society. PTLD. Int. survey is an attempt at reviewing and gathering international data from PTLD patients to conduct analyses on the largest possible patient population to discover new perspectives on the disease. In this study, we analyzed one of the ever largest series of PTLD patients to discover various characteristics of PTLD presenting within BM in renal transplant recipients, and their histopathological features, disease behavior and prognostic factors.

In general practice, BM biopsy is recommended routinely for the staging of patients developing PTLD in their disease course.[31] According to the Ann Arbor staging system for non-Hodgkin's lymphoma, BM involvement at diagnosis defines stage IV disease,[32] and is associated with a more ominous clinical course.[33,34] Our data shows that BM involvement by neoplastic lymphomatoid cells in PTLD, as mentioned for that in non-transplant era, is associated with an inferior outcome. Moreover, we found that BM PTLD lesions were more likely to be monomorphic than benign features with

Table 1: Characteristics of renal transplant recipients with or without bone marrow involvement by post-transplant lymphoproliferative disorder

Variables	BM PTLD	Controls	Sig.	Available data
Age (years)	37.1±18.7	43.8±15.2	0.041	156
Pediatric; <18 year/o (%)	7 (25.9)	10 (8.2)	0.016	149
Gender male (%)	19 (70.4)	76 (60.8)	0.389	152
Time to PTLD development (mo)	60.2±58.9	56.3±51.2	0.728	145
Early onset (vs. late)	7 (26.9)	27 (24.1)	0.801	138
Multi organ involvement (%)*	24 (88.9)	40 (44.4)	<0.001	117
Disseminated PTLD (%) *	14 (70)	15 (21.4)	<0.001	90
Morphology			0.295	140
Early lesion (plasmacytic hyperplasia)	0	7 (6)		
Polymorphic B cell lymphoma	4 (17.4)	36 (30.8)		
Monomorphic PTLD	16 (69.6)	61 (52.1)		
Hodgkin lymphoma	3 (13)	13 (11.1)		
EBV status (%)	11 (52.4)	64 (73.6)	0.124	108
Mortality (%)	20 (71.4)	65 (51.6)	0.06	154
Remission episode (%)	13 (52)	34 (34.7)	0.166	123
Lymphoma cell type B cell (%)	17 (70.8)	67 (72.8)	0.804	116
Use of induction therapy (%)	6 (75)	31 (63.3)	0.699	57

*According to the criteria defined in the methods section.

Table 2: Frequency of involved organs in 120 kidney transplant recipients with or without bone marrow complication by post-transplant lymphoproliferative disorder

Involved organs	BM PTLD	Controls	Sig.
Heart	2 (12.5)	2 (3.8)	0.332
Skin	1(3.6)	22 (20.2)	0.045
Stomach	1 (4.2)	6 (6.4)	1.0
Genitalia	0	2 (2.1)	1.0
CNS	4 (14.3)	18 (16.2)	1.0
Spleen	4 (15.4)	6 (6.4)	0.221
Colon	2 (7.7)	5 (5.3)	0.644
Small intestine	1 (4.2)	11 (11.7)	0.455
Renal involvement	5 (20)	24 (25)	0.792
Liver involvement	12 (44.4)	16 (17)	0.008
Respiratory system	8 (30.8)	22 (23.2)	0.448

no case in the early lesion category, although the difference did not reach significance level. These findings are consistent with our previous knowledge in transplant ear, where PTLD involving BM was a predictor for a worse outcome.[34] These findings confirm our previous assumptions on considering BM complication as a high-grade disease for lymphoma.

There is a high inconsistency in the current literature respecting the incidence of BM involvement in different patient groups and in various PTLD subtypes. The incidence of BM PTLD in different series have been reported from 15%[33] to 40%[35] in different series. Methodology employed in the current study does not empower us to present a precise frequency of BM involvement by the PTLD in renal transplant population; however, nothing wrong exists if we want to compare these frequencies among different subpopulations of our study data. Our study showed that BM PTLD is significantly more likely to occur in pediatric renal recipients. There is a shortage of data on this in the literature, but comparing different studies, our finding is novel. While Maecker*et al*.,[33] have reported a 15% incidence rate for BM involvement in children developing PTLD, Knight *et al*.[36] have reported 19.6% BM PTLD in their series of adult patients and Houriganet *al*.,[35] also reported a 40% incidence of BM PTLD in renal transplant context. Putting together, one may assume that BM PTLD incidence in pediatric setting is comparable to that in adults. Nevertheless, this conclusion is not in concordance with what we may expect from outcome analysis. Overwhelming data has confirmed that PTLD has a substantially higher mortality among children than in adults. So, we should expect that children also represent more aggressive types of the disease like that in BM PTLD. Our study finding is consistent with this assumption, but we should take attention that this finding is in renal recipients developing PTLD and may not be globalized to other solid organ recipients, as the study populations of Knight *et al*.[36] and Hougarian*et al*.[35] enrolled other types of organ recipients.

PTLDs are believed to have a tendency for extranodal organ involvements.[37-43] However, factors playing major roles in spread of the disease are not well defined. The current

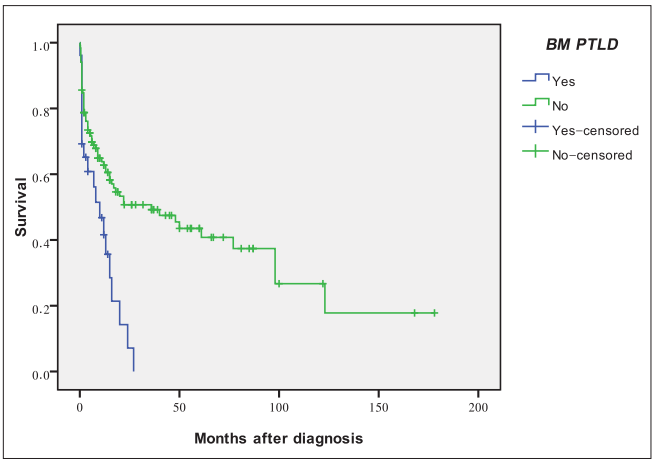

Figure 1: Survival curves of renal transplant recipients regarding bone marrow involvement by the PTLD (outcome: death irrespective of reason)

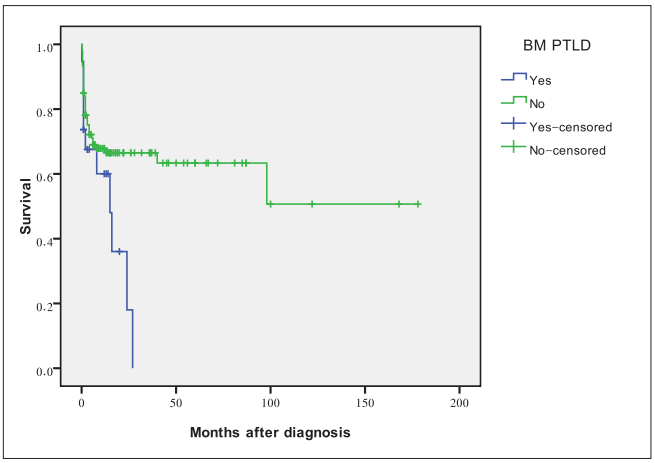

Figure 2: Survival curves of renal transplant recipients regarding bone marrow involvement by the PTLD (outcome: death due to PTLD)

study showed that almost 90% of renal recipients who have developed within their BM have had a multi-organ involvement whose proportion is almost twice as the controls. Moreover, we found some predilection to some specific organs involvement for patients with BM PTLD. As summarized in Table 2, over 44% of BM PTLD renal recipients had a concomitant liver involvement which was significantly higher than controls while skin complication was significantly lower in the case group. In a previous study on hepatic graft involvement by the PTLD in liver recipients, we found a similar finding indicating a higher prevalence of BM involvement by the PTLD in patients whose hepatic graft was complicated by the disease.[43] These findings are of outmost relevance, because discovering concomitant involvement organs by the disease will alert us to more directly search for the PTLD sites in different patient populations which results in an earlier diagnosis and survival advantages.

In summary, our study population of renal recipients with

BM PTLD can be considered as a good representative for the mentioned patient population, because it was gathered from different series with no special selection bias. Through this study, we found that renal recipients with BM PTLD represent worse outcome and more unfavorable histopathological phenomenon than in other organ involvements. Moreover, a concomitant PTLD involvement site in liver was found which necessitates full hepatic evaluation for a potential complication by the disease in renal recipients whose BM is involved.

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