Hepatic Lymphomas Post Renal Transplantation May Signify Worse Disease Behavior: Analysis of Data from 26 International Studies

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Abstract

Introduction: Hepatic involvement by posttransplant lymphoproliferative disorders (PTLD) is an important but rarely investigated issue. In the current study, we aimed to pool data of cases of PTLD localization in liver (L-PTLD) among renal allograft recipients from different series to find new perspectives on the disease.

Methods: We conducted a comprehensive search for the available data through PubMed and Google Scholar for reports of PTLD localization in the liver and surrounding lymph nodes in renal allograft recipients. Data of 232 cases from 26 international studies have been pooled and reanalyzed.

Results: Patients with L-PTLD were significantly more likely to be of male gender (P=0.02). Death due to PTLD was higher in L-PTLD patients (P=0.06). Disseminated PTLD, based on our definition, was significantly more prevalent in L-PTLD than in none-liver-PTLD (NL-PTLD) (P=0.001); the same finding was noted with multi-organ involvement which was significantly higher in L-PTLD (P<0.001). L-PTLD was significantly more likely to complicate heart (P=0.03), bone marrow (P=0.002), spleen (P=0.01), and kidney allograft involvement (P=0.04).

Conclusion: We conclude that renal transplant patients exhibiting liver localization for PTLD should be carefully followed for multi-organ involvement. Most notably, bone marrow biopsy should be considered, and evaluations for renal allograft, heart and spleen localization for PTLD should be executed. Due to the unfavorable characters of liver localization by PTLD in renal recipients, we propose higher levels of evaluations and follow up for these patients. Prospective studies with larger patient populations are needed to confirm our results.

Keywords: Kidney Transplantation; Liver Localization; Lymphoproliferative Disorders

The authors declared no conflict of interest

Introduction

Malignancies occurring post renal transplantation are important complications which seriously threat patient and graft survival [1-3]. Cancers complicating renal allograft recipients are considered as the third reason of death in this patient population, after cardiovascular diseases and infections [4]. Post transplant lymphoproliferative disease (PTLD) is a well-known and one of the most prevalent malignancies in transplant recipients and an important cause of morbidity and mortality in these patients. PTLD represents a wide spectrum of abnormal lymphoid proliferations taking place in the setting of ineffective T-cell function due to immunosuppression after organ transplantation. Viral infection most notable for Epstein-Barr virus (EBV), type of organ transplantation, type and potency of immunosuppressive agents employed, and some demographic features of the organ recipients have all been associated with a higher incidence or outcome of PTLD in transplant era [5-9]. As mentioned above, the type of organ transplanted is a key factor in determining the incidence and features of PTLD. The incidence of PTLD is reportedly lowest in renal transplant recipients (0.8-2%) [10,11]. Moreover, it is generally considered that PTLD has a better outcome in renal allograft recipients compared to some other types of organ transplant patients such as heart graft recipients [12].

Complications of specific organs in various types of organ transplantation are of outmost relevance. Knowing susceptible organs for getting involved by PTLD in renal allograft recipients, we would be able to target our preventive endeavors more accurately, and to minimize morbidity and mortality in renal transplant population who develop PTLD in their disease course. On the other hand, revealing factors which play major roles in
inducing or preventing more aggressive forms of the disease or non-favorable histopathological features of PTLD lesion will also help us enhance our treatment strategies and improve outcomes. The overall number of liver involvement by PTLD in renal graft recipients is very limited and its cases are hidden in series related to single- or multi-center reports. In fact, until now, no study has focused on liver localization of PTLD in renal recipients; and to the extent of our knowledge, this is the first attempt on the issue. In the current study, we aimed to pool data of cases of PTLD localization in liver of renal recipients from different series to find new perspectives on the disease.

Methods

Approach to the study: We conducted a comprehensive search for the available data through PubMed and Google Scholar for reports of PTLD localization in liver and surrounding lymph nodes in renal allograft recipients. Search terms used were “lymphoproliferative disorders + renal transplantation + liver”, “lymphoproliferative disorders + kidney transplantation + hepatic localization”, “lymphoproliferative disorder + renal transplantation + liver localization”, “lymphoproliferative disorders + kidney transplantation + liver”. In cases where we were not able to obtain the full text of the article, e-mails were sent to the correspondent authors requesting the article. Of the full texts obtained, we only included studies in which data on 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 in whom PTLD localization organ was not the liver. 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 sign(s) of PTLD or diagnosis, depending on the study’s approach.

Study population: Twenty-six internationally-published studies [13-38] were found that met our criteria. A total of 232 renal recipients with a documented PTLD site were included in the analysis; of whom 44 (19%) had liver PTLD (L-PTLD) and the remaining 188 (81%) patients had developed non-liver PTLD (NL-PTLD). EBV status was documented in 157 (67.7%) patients, of whom 113 (72%) were reportedly positive. Because of different methodologies employed in the published studies enrolled into this study, 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 involvement; or other authors specifically presented them as having disseminated disease). According to the above mentioned, data on disseminated PTLD was available for 167 patients (72%; 65 unreported data). Multi-organ involvement, defined as involvement of more than one organ (the second organ could be a lymphatic region), was reported in 216 patients (93.1%; 16 unavailable data).

At PTLD onset, all patients were under immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, 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 as well as the patient’s clinical condition. Data on response to treatment was reported for 114 patients (49.1%), of whom 71 (62.3%) 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). "No remission" was defined 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 were reported to have any remission episode). According to these criteria, data on remission was available for 171 patients (73.7%), of whom 98 (57.3%) had at least one response to treatment, irrespective of their future disease course. Data on mortality was available for 219 patients (94.4%), of whom 133 (60.7%) died. We defined death due to PTLD when the authors stated it, death was within 6 months after onset, or death was reported to be due to PTLD treatment complications. Based on these criteria, 82 patients (61.7% 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. Multivariate linear regression was used to detect independent association of various factors with the time interval between transplantation and PTLD onset. A
P-value of 0.05 was taken as the threshold for significance and of 0.1 was defined as relevance level.

Results

Overall, 232 cases of PTLD in renal allograft recipients were included. There were 133 (61.6%) male and 83 (38.4%) female patients (16 unreported data). Mean age at onset was 39.9 ± 17.3 years. The mean interval between transplantation and the onset of PTLD was 58.3 ± 56.1 months and the mean follow up time after onset of PTLD was 23.9 ± 32.4 months.

Characteristics of PTLD patients with and without liver involvement are summarized in Table-1. Chi-square test showed that patients with L-PTLD were significantly more likely to be of male gender (P=0.02). L-PTLD patients were comparable to NL-PTLD kidney recipients in their age (P=0.3), immunosuppressive drug basis (P=0.5), history of induction therapy (P=1.0), lymphoma cell type (P=0.3), histopathological features of PTLD lesions (P=0.8), time from transplantation to PTLD diagnosis (P=0.6), remission rates (P=0.1), and mortality rate (P=0.3). However, death due to PTLD was higher in L-PTLD patients (P=0.06). Disseminated PTLD, based on our definition, was significantly more prevalent in L-PTLD than in NL-PTLD (P<0.001); the same finding was achieved reporting multi-organ involvement which was significantly higher in L-PTLD (P<0.001).

Table-2 compares liver to NL-PTLD with respect to other organs involved. L-PTLD was significantly more likely to complicate heart (P=0.03), bone marrow (P=0.002), spleen (P=0.01), and kidney allograft involvement (P=0.04).

At the last follow up, 133 patients were dead. Using death by any cause as the outcome, log-rank test did not show any difference between the two groups in survival (P=0.4; Figure-1). Renal recipients with L-PTLD had a relevantly poorer PTLD-related outcome when only death due to PTLD (based on our definition) was used.
One- and five-year survival rates for L-PTLD patients were 47% and 29%, respectively, compared to 57% and 31%, respectively, for NL-PTLD controls.

**Discussion**

PTLD is a life-threatening and not such a rare complication of transplantation with a very wide spectrum of clinical findings ranging from a focal and limited disease to a disseminated and rapidly progressive disorder. The frequency has been reported to range very widely depending on the organ transplanted and the type, dosage and duration of immunosuppressive agents employed for preventing rejection episodes, with a reported incidence range of less than 1% to 30% in different transplant populations [10, 39, 40]. In renal allograft recipients, the incidence of PTLD is reported to range from 0.7% to 2.6% in different series [18,41,42]. The outcome of PTLD in renal recipients has also been implicated to be better than other types of organ recipients, although the reported survival of renal recipients with PTLD in different series was quite variable. Several factors can play major roles in these disparities among which the histopathological features of the PTLD lesions, the type and number of organs involved by the cancer, therapeutic approaches employed for managing the disease, and physical status of the patients can be relevant. To clarify factors most likely to influence PTLD behavior, we need to study a large number of patients to analyze the potential contributing factors. Nevertheless, due to the very limited number of patients who provide information on each of the aforementioned, our knowledge on these would be essentially limited. So, in our PTLD questionnaire we tried to gather data from individual patients reported in different published series to make the largest possible population to investigate the impact of these factors. In a previous study, we analyzed hepatic graft involvement by PTLD in liver recipients [9] and in the present study; we explore the same organ complication by PTLD in renal allograft recipients.

In the current study, we found that renal allograft recipients with liver PTLD localization are more likely to represent a disseminated disease, with a relatively poorer outcome, although the difference did not reach the significance level in the latter case. However, adding this to the higher rate of multi-organ PTLD in L-PTLD, this study shows a relatively more ominous disease in renal graft recipients whose liver has been complicated by PTLD compared to other disease localizations. In our previous study on liver transplant patients [9], consistent with the current study, we found that disseminated disease is significantly higher in patients representing hepatic localization for the PTLD; however, in that study, no outcome difference has been implicated. Moreover, liver recipients with hepatic PTLD were significantly older at the time of transplantation and had a shorter time to PTLD development, observations which have not been repeated in the current study on kidney recipients. Nuckols et al [43] have also found that

<table>
<thead>
<tr>
<th>Involved organs</th>
<th>L-PTLD</th>
<th>NL-PTLD</th>
<th>P value</th>
<th>Available data</th>
</tr>
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<tbody>
<tr>
<td>Orbital</td>
<td>0</td>
<td>1 (0.7)</td>
<td>1.0</td>
<td>193</td>
</tr>
<tr>
<td>Skeleton</td>
<td>0</td>
<td>5 (3.3)</td>
<td>0.4</td>
<td>192</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 (2.7)</td>
<td>9 (5.9)</td>
<td>0.7</td>
<td>189</td>
</tr>
<tr>
<td>Genitalia</td>
<td>2 (5)</td>
<td>3 (2)</td>
<td>0.3</td>
<td>191</td>
</tr>
<tr>
<td>CNS</td>
<td>3 (6.8)</td>
<td>24 (15.3)</td>
<td>0.2</td>
<td>201</td>
</tr>
<tr>
<td>Spleen</td>
<td>8 (20)</td>
<td>9 (6.1)</td>
<td>0.01</td>
<td>188</td>
</tr>
<tr>
<td>Colon</td>
<td>4 (10)</td>
<td>5 (3.3)</td>
<td>0.09</td>
<td>193</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3 (8.3)</td>
<td>27 (17.5)</td>
<td>0.2</td>
<td>190</td>
</tr>
<tr>
<td>Kidney</td>
<td>13 (33.3)</td>
<td>26 (17.1)</td>
<td>0.04</td>
<td>191</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>7 (18.9)</td>
<td>15 (10.4)</td>
<td>0.2</td>
<td>181</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>8 (20)</td>
<td>6 (4)</td>
<td>0.002</td>
<td>190</td>
</tr>
<tr>
<td>Skin</td>
<td>2 (4.9)</td>
<td>20 (13.2)</td>
<td>0.2</td>
<td>192</td>
</tr>
<tr>
<td>Heart</td>
<td>3 (10.7)</td>
<td>1 (1%)</td>
<td>0.03</td>
<td>133</td>
</tr>
</tbody>
</table>

Data presented as number (%); PTLD: posttransplant lymphoproliferative disorders; L-PTLD: PTLD localization in the liver; NL-PTLD: non-liver PTLD
* statistically significant
Figure 1: Survival curves of renal graft recipients with and without hepatic PTLD (outcome: death irrespective of the reason)

almost all of their hepatic PTLD liver transplant cases were of early onset. Put together, these findings may indicate that this is a special character of liver PTLD in liver recipients. Moreover, Nuckols et al [43] reported a three times larger share of males in hepatic PTLD in liver recipients. In the current study, we also found that male renal recipients were significantly more likely to develop hepatic PTLD, although in our previous report on liver recipients, we did not find any gender disparity regarding liver involvement by the PTLD [9]. An interesting similar finding of the current study to our previous report on liver transplantation is heart and bone marrow involvement. In both, renal and liver recipients whose livers have been involved by PTLD, there were significantly higher tendencies for heart and bone marrow involvement by the PTLD, simultaneous to the liver disease. This finding is of utmost relevance; suggesting that liver involvement by lymphomas can be associated with the same complication in bone marrow and/or heart. These findings more intensively alert us to assess the heart and bone marrow of patients who have already developed lymphomas within their liver. Kidney allograft and spleen were also more likely to be complicated by the PTLD simultaneously with a liver involvement in our series of renal allograft recipients, a finding that seems to be special for kidney recipients, since it was not reported in liver transplant patients.

This study has several limitations. Firstly, this is a retrospective review of studies that used different methodologies to report on PTLD. Secondly, the enrolled data gathered from those studies were not originally presented in the same way, and it was not possible to pool them without some manipulations. So, we had to standardize data to be able to compare them with each other. Standardization of data was not easy, and some people may not fully agree with us on the standardization methods employed in the current study.

Conclusion

We conclude that renal transplant patients exhibiting liver localization for PTLD should be carefully evaluated for multi-organ involvement. Most notably, bone marrow biopsy should be considered, and evaluations for renal allograft, heart and spleen localization for PTLD should be executed. Due to the unfavorable characters of liver localization by PTLD in renal recipients, we propose higher levels of evaluations and follow up for these patients. Prospective studies with large patient populations are needed to confirm our results.

References


34. Gallagher H, Kwan JT, Andrews PA. Post-transplant lymphoproliferative disorder: an unusual


