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REVIEW ARTICLE

Hepatic involvement by lymphoproliferative disorders post liver transplantation: PTLD.Int. Survey

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Abstract
Background It is speculated that different localizations of lymphoproliferative disorder after solid organ transplantation (PTLD) have different features and represent specific behavior as well as prognostic individualities.
Objectives To compare characteristics of hepatic PTLD (H-PTLD) with non-hepatic PTLD (NH-PTLD) in liver transplant recipients.
Materials and methods We searched PubMed and Google Scholar for all published reports of PTLD in liver recipients within their liver. Reported characteristics of H-PTLD and NH-PTLD were compared.
Results A total of 21 studies from various countries were found. Overall, 169 liver recipients with PTLD were included in the analysis, of whom 83 (49%) had H-PTLD. Patients with H-PTLD were more likely to test positive for Epstein–Barr virus (EBV) ($p < 0.0001$), be older at the time of transplantation ($p = 0.009$), have a shorter time to PTLD development (80 vs. 41% early-onset PTLD; $p < 0.001$), and have bone marrow involvement ($p = 0.03$). Multivariate linear regression showed that H-PTLD and EBV positivity, but not age at transplant, were independently associated with time to PTLD development ($p = 0.003$, $p < 0.0001$, and $p = 1.0$, respectively).
Conclusions Liver transplant patients exhibiting early deterioration of graft function or other hepatic symptoms should, in addition to assessment for rejection, be evaluated for H-PTLD. In addition, all H-PTLD patients should be evaluated for bone marrow involvement, especially if they are EBV positive. Prospective studies with large patient populations are needed to confirm our results.

Keywords PTLD · Liver transplantation · Hepatic · Allograft involvement · Review

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Background

Development of the lymphoproliferative disorder after solid organ transplantation (PTLD) remains a challenging diagnostic and therapeutic problem. It is characterized by lymphoid proliferation of B- or T-cell origin. The first report on this entity was published in 1969 by Penn et al. [1], in a patient who had undergone living-related kidney transplantation. Since then, several reports from all over the world have been published indicating a high incidence of PTLD among recipients of all types of organs, including liver. The incidence of lymphoma after transplantation is quite higher than that in the general population [2–7]. Reported reasons for this high incidence include Epstein–Barr virus (EBV) infection, greater levels of immunosuppression, and use of OKT3, antilymphoblast globulin (ALG), and antithymocyte globulin (ATG) [5–7]. Investigators have suggested that the incidence, time interval, presentation, and prognosis of PTLD vary depending on the organ transplanted, recipient age, and immunosuppression intensity [8–16]. The reported incidence of PTLD in liver recipients ranges from 1.7 to 9%, with most cases occurring within the first 1.5 years after transplantation [2–7, 17–19].

There are several reports on the development of hepatic PTLD (H-PTLD) in liver recipients. In a previous study of international data, we reviewed data of patients who developed PTLD within their renal allograft [11]. Allograft PTLD complicated about 37% of recipients; although due to the inclusion criteria, we were not able to calculate the incidence rate. The number of reported cases of H-PTLD in liver recipients is quite limited and only a small number of histologically proven cases have been reported. Due to the limited number of reports, data scarcity exists on various aspects of PTLD in liver recipients.

Pooling data of PTLD in liver recipients from the existing literature, we sought to analyze and compare characteristics, predictors, and prognosis of H-PLTLD to non-hepatic PTLD (NH-PTLD) in liver graft recipients.

Materials and methods

Approach to the study

We conducted a comprehensive search for the available data through PubMed and Google Scholar for reports of HPTLD and surrounding lymph nodes in liver recipients. Search terms used were "lymphoproliferative disorders + transplantation + liver", "lymphoproliferative disorders + transplantation + liver allograft", "lymphoproliferative disorder + transplantation + liver localization", "lymphoproliferative disorders + transplantation + liver graft", "PTLD + liver allograft", and "PTLD + liver localization". In cases where we were not able to obtain the full text of the article, emails were sent to corresponding authors requesting the article. Of the full texts obtained, we only included studies in which data on each patient were presented separately. To minimize selection bias, we only included studies reporting the series of patients from single- or multi-center populations, and studies with any specific selection criterion were excluded from the analysis. 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

A total of 21 international published studies [13, 20–39] were found that met our criteria. Table 1 summarizes data of the enrolled studies. Table 2 shows comparative epidemiology of organ failure reasons. A total of 169 cases of PTLD of liver recipients were included in the analysis; of whom 83 (48%) were H-PTLD and the remaining 86 (52%) patients had developed NH-PTLD. 11 (17.2%) of H-PTLD patients were reported to go under surgical therapy while this rate was 7 (14%) in NH-PTLD patients (53 missing data). EBV status was documented in 97 (58%) patients, of whom 73 (75%) were reported positive.

Because methodologies differed among the published studies, not all our measures were available for all patients. 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). Such information was reported for 102 patients (61%; 65 missing data). Multi-organ involvement, defined as involvement of more than one organ (the second organ could be a lymphatic region), was available in 117 patients (70%; 50 missing 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 liver recipients. On diagnosis of PTLD, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; various regimens of chemotherapy with

Table 1 Enrolled studies and frequencies of case and control patients

	Study	Frequency (%)	H-PTLD (%)	NH-PTLD (%)
1	Baron et al. [20]	2 (1.2)	2 (2.4)	0
2	Nuckols et al. [13]	23 (13.6)	23 (27.7)	0
3	Niedobitek et al. [21]	1 (0.6)	1 (1.2)	0
4	Pitman et al. [22]	1 (0.6)	1 (1.2)	0
5	Morovic et al. [23]	1 (0.6)	1 (1.2)	0
6	S. Sevmis et al. [24]	5 (3.0)	1 (1.2)	4 (4.7)
7	Cacciarelli et al. [25]	17 (10.1)	2 (2.4)	15 (17.4)
8	Kerkar et al. [26]	21 (12.4)	12 (14.5)	9 (10.5)
9	Allen et al. [27]	13 (7.7)	1 (1.2)	12 (14)
10	Dusenbery et al. [28]	3 (1.8)	1 (1.2)	2 (2.3)
11	Rohr et al. [29]	1 (0.6)	1 (1.2)	0
12	Gerstenkorn et al. [30]	5 (3.0)	2 (2.4)	3 (3.5)
13	Norin et al. [31]	12 (7.1)	5 (6)	7 (8.1)
14	Capello et al. [32]	15 (8.9)	10 (12)	5 (5.8)
15	Muti et al. [33]	5 (3.0)	3 (3.6)	2 (2.3)
16	Jain et al. [34]	13 (7.7)	1 (1.2)	12 (14)
17	Paraskevas et al. [35]	1 (0.6)	1 (1.2)	0
18	Duvoux et al. [36]	16 (9.5)	7 (8.4)	9 (10.5)
19	Smets et al. [37]	6 (3.6)	4 (4.8)	2 (2.3)
20	Carpentier et al. [38]	3 (1.8)	2 (2.4)	1 (1.2)
21	Avolio et al. [39]	5 (3.0)	2 (2.4)	3 (3.5)
	Total	169 (100)	83 (!00)	86 (100)

Table 2 Cause of liver failure in the study population

Organ failure reason	Liver graft PTLD ($n = 62$)	Controls ($n = 33$)	Organ failure reason	Liver graft PTLD ($n = 62$)	Controls ($n = 33$)	Organ failure reason	Liver graft PTLD ($n = 62$)	Controls ($n = 33$)
Alfa 1 antitrypsin deficiency	1 (1.6)	0	Extra hepatic biliary atresia	7 (11.3)	11 (33.3)	Primary biliary cirrhosis	5 (8.1)	2 (6.1)
Alcoholic cirrhosis	10 (16.1)	0	Fulminant hepatic failure	3 (4.8)	1 (3.0)	Sclerosing cholangitis	1 (1.6)	1 (3.0)
Hemachromatosis	1 (1.6)	0	HCC	4 (6.5)	0	Toxins	1 (1.6)	0
Cirrhosis	5 (8.1)	4 (12.1)	Other cancers	4 (6.4)	0	Wilson's disease	3 (4.8)	0
Congenital disorders	1 (1.6)	0	Hepatitis B virus infection	2 (3.2)	2 (6.1)			
Cryptogenic cirrhosis	4 (6.5)	1 (3.0)	Hepatitis C virus infection	9 (14.5)	5 (15.2)			
Cyst	1 (1.6)	0	Concomitant B and C hepatitis	1 (1.6)	0			

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 were reported for 61 patients (36%), of whom 52 (85%) responded to treatment. 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 were available for 99 patients (59%), of whom 80 (81%) had at least one response to treatment, irrespective of their future disease course. Data on mortality were available for 127 patients (76%), of whom 51 (40%) 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, 32 patients (63% of reported deaths, 25% of patients for whom mortality data were reported) 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.

Results

Overall, 169 cases of PTLD were found. There were 71 (70%) male and 31 (30%) female patients (65 missing data). Mean age at onset was 30.9 ± 24.0 years. The mean interval between transplantation and the onset of PTLD was 26.6 ± 40.9 months and the mean follow up time after onset of PTLD was 27.2 ± 31.0 months.

Characteristics of PTLD patients with and without liver involvement are summarized in Table 3. Chi-square test showed that patients with H-PTLD were significantly more likely to have EBV positive test results (92 vs. 56%, respectively; $p < 0.001$). H-PTLD patients were comparable to NH-PTLD liver recipients in gender (70% male for both groups; $p = 1.0$), lymphoma cell type (97 vs. 85% B-cell, respectively; $p = 0.2$), remission (29 vs. 14%, respectively; $p = 0.1$), mortality rate (39 vs. 42%, respectively; $p = 0.9$), and multi-organ involvement (based on our definition; 57 vs. 42%, respectively; $p = 0.1$). Disseminated PTLD, based on our definition, was significantly more prevalent in H-PTLD than in NH-PTLD (43 vs. 16%, respectively; $p = 0.004$); however, when only considering "diffuse disease" as defined by authors, no difference was found (20 vs. 27%, respectively; $p = 0.7$). Table 4 shows comparison of liver to NH-PTLD with respect to other organs involved.

H-PTLD patients were significantly older at the time of transplantation than NH-PTLD liver recipients (median: 45.0 vs. 17.2 years; $p = 0.009$) and had a shorter time from transplantation to PTLD development (median: 6.8 vs. 25.1 months; $p < 0.001$). Multivariate linear analysis showed that H-PTLD and EBV positivity were independently associated with time to PTLD development, while age at the time of transplantation was not ($p = 0.003$, $p < 0.0001$, and $p = 1.0$, respectively; Table 5). Histopathological evaluations were not significantly different between the H-PTLD and NH-PLTLD patients (65 vs. 57% monomorphic, $p = 0.6$; 87 vs. 92% monoclonal, $p = 1.0$). The two groups were also similar in the frequency of Hodgkin and non-Hodgkin PTLD lesions ($p = 1.0$).

At the last follow up, 51 patients (40% of reported; 40 missing data) were dead. Using death by any cause as the final outcome, log-rank test neither showed any difference between the two groups in survival ($p = 0.6$; Fig. 1) nor was any difference seen between the two groups when only death due to PTLD (based on our definition) was used as the final outcome ($p = 0.4$, Fig. 2). However, Fig. 2 suggests a sudden drop in survival for H-PTLD patients at 40 months after onset. Therefore, we reanalyzed our data, starting with PTLD patients who survived at least for 30 months after disease onset and incrementally adding 1 month. For patients who survived at least 33 months after onset, we found that H-PTLD patients had lower survival than NH-PTLD ($p = 0.028$). One- and five-year survival rates for H-PTLD patients were 71 and 55%, respectively, compared to 77 and 70%, respectively, for NH-PLTLD patients.

Table 4 Frequency of involved organs in 144 liver transplant recipients with allograft complicated PTLD

Involved organs	H-PTLD (%)	NH-PTLD (%)	Sig.
Orbital	0	1 (1.2)	1
Skin	1 (1.7)	3 (3.5)	0.6
Stomach	4 (6.9)	6 (7)	1.0
Genitalia	1 (1.7)	1 (1.2)	1.0
Central nervous system	0	0	
Skeleton	0	2 (2.3)	0.5
Spleen	8 (14)	4 (4.7)	0.07
Colon	0	4 (4.7)	0.2
Small intestine	9 (16)	11 (13)	0.6
Renal involvement	2 (3.4)	3 (3.5)	1.0
Respiratory system	4 (6.9)	11 (13)	0.4
Bone marrow	8 (14)	3 (3.5)	0.03

Discussion

Newly introduced immunosuppressive agents besides their favorable impact on preventing rejection episodes, have endangered transplant patients at a remarkable increase in the risk for infections as well as developing malignancies [40–42]. It is postulated that the type and degree of immunosuppression, as well as the type of allograft, have major roles in this risk enhancement. PTLDs are one of the most prevalent malignancies complicating various organ grafts, reducing both graft and patient survival. Several factors have been shown to play major roles in the incidence and outcome of PTLD. Organ localization of PTLD

Table 3 Characteristics of PTLD with and without liver involvement

Variables	H-PTLD[a]	NH-PTLD[b]	Sig.	Available data
Age (years)	35.9 ± 21.9	26.1 ± 25.1	0.009	162
<18 years old (%)	22 (27)	41 (50)	0.004	162
Gender male (%)	41 (70)	30 (70)	1.0	102
Time to PTLD development (months)	14.1 ± 25.6	44.1 ± 51.1	<0.001	130
Multi-organ involvement (%)[c]	30 (58)	28 (42)	0.1	118
Disseminated PTLD (%)[c]	19 (43)	10 (16)	0.004	105
Hodgkin disease (%)	3 (6.8)	1 (2.0)	0.4	93
EBV status (%)	49 (92)	26 (56)	<0.001	99
Remission episode (%)	36 (45)	44 (55)	0.1	99
Azathioprine-based immunosuppression (vs. MMF/FK-506)	17 (71)	9 (90)	0.1	34
Use of induction therapy	17 (49)	8 (50)	1.0	51
Early onset (within first 12 months after transplant)	61 (80)	22 (41)	<0.001	130
Monoclonal lesions (%)	21 (88)	11 (92)	1.0	36
Monomorphic lesions (%)	14 (35)	15 (43)	0.6	75
Lymphoma cell type B-cell (%)	36 (97)	23 (85)	0.2	67

[a] Hepatic-PTLD

[b] Non-hepatic PTLD

[c] According to the criteria defined in the "Materials and methods" section

Table 5 Linear regression evaluating impact of different factors with time interval between transplantation and PTLD development

Model	Unstandardized coefficients		Standardized coefficients	Sig.
	B	Std. error	Beta	
Constant	−61.597	14.144		0.000
H-PTLD	24.080	7.884	0.280	0.003
Age (years)	0.006	0.168	0.003	1.0
EBV positivity	44.965	9.225	0.448	<0.001

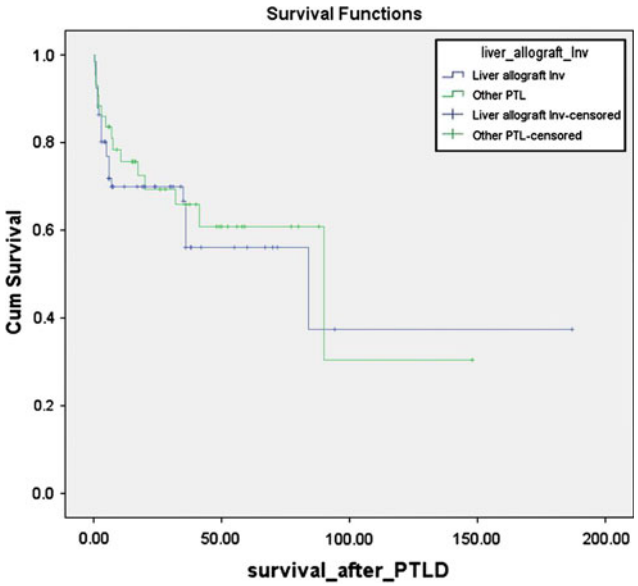

Fig. 1 Survival curves of PTLD patients with and without hepatic involvement when death irrespective of its reason was defined as the final outcome

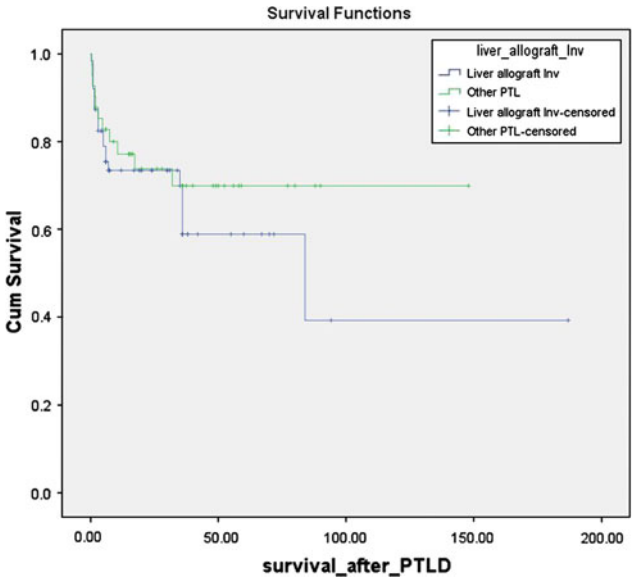

Fig. 2 Survival curves of PTLD patients with and without hepatic involvement when only death due to PTLD was defined as the final outcome

is extremely relevant due to the differing clinical and histopathological features and prognosis [9, 11]. PTLD.Int. survey is an attempt to gather international data on the largest possible PTLD patient population to discover new perspectives on the disease [11, 41, 42]. The current study is one of the largest-ever analyses of data of PTLD patients, looking for various characteristics of H-PTLD, including morphology and clonality, EBV infection status, and prognostic factors.

In a previous survey, we found that PTLD in renal transplant recipients has a more benign course and better survival rate when it presents within the allograft than in other localizations [11]. Renal allograft involvement is one of the most prevalent localizations for PTLD in renal transplant recipients. However, in liver transplant recipients, allograft PTLD is a rare condition, and most data of the current study were gathered from small case series. This paucity of data inevitably limits our ability to study the disease, including its natural course, precursors, preventive methods, and treatments. For example, in renal graft PTLD, the typical presenting sign is worsening graft function [43]. In our previous study [11], we showed that PTLD presenting in renal grafts is significantly more likely to develop within the first year after transplantation. Putting these together, we concluded that all renal transplant patients presenting with graft dysfunction in the early stage after transplantation should, in addition to assessment for rejection, be evaluated for graft PTLD.

Nuckols et al. [13] reviewed characteristics of 25 cases of H-PTLD drawn from 21 case reports and their own series. Due to lack of a control group, they were not able to compare data of their patients with NH-PTLD patients. Consistent with our results, they found that nearly all cases of H-PTLD presented during the first 12 months following transplantation. In our study, 80% of H-PTLD cases developed PTLD within the first year after transplantation, compared to 41% of NH-PTLD cases ($p < 0.001$). However, in Nuckols et al.'s review, most H-PTLD cases occurred in males, with a male:female ratio of over 3:1. But our data involving all subjects of the mentioned review

article did not show any gender difference between the two groups, with 69% male subjects in the H-PTLD group compared to 70% for the NH-PTLD group. Moreover, Nuckols et al.'s [13] review did not include any pediatric patients with H-PTLD. Pediatric patients constituted 27% of our H-PTLD group (vs. 50% of the non-liver PLTLD group), indicating that children are significantly less likely to develop PTLD within their liver.

The pathophysiology of PTLD is not well understood. In the general population, viral hepatitis has been proposed as a predictor of the development of lymphoma [44]. Among transplant patients, however, EBV infection is reported to be one of the leading risk factors associated with PTLD [45–47]. EBV is suggested to induce a prolonged state of activation in B-lymphocytes, which may provide conditions for eventual acquisition of an irreversible transforming genetic event [48]. In our study, EBV was detected in 92% of H-PTLD patients, compared to 56% of NH-PTLD patients ($p < 0.001$). This finding is in concordance with Nuckols et al. [13], in which their three reported cases and nearly all of the tumors they reviewed were positive for EBV, as examined by a variety of techniques, including immunohistochemistry, in situ hybridization for DNA or RNA, and PCR.

It has been speculated that PTLD arising within grafted organs, including bone marrow, kidney, and liver, are more likely to be of donor origin [13, 49, 50], although a small number of primarily pulmonary PTLDs in lung transplant patients were reported to be of host origin [51]. The prognosis of PTLD of donor origin has been reported to be better than PTLD of host origin [52]. Proposed explanations for this include: a heightened immune response against tumor cells that express antigens of both the donor and EBV; presentation of most host-origin PTLD at higher stages than donor-origin PTLD; earlier detection of donor-origin allograft PTLD because of higher clinical surveillance of the graft; and restriction of donor-origin PTLD to the graft. In the present study, PTLD origin was not included in the analysis due to lack of data for most of the patients. However, we did not find any difference in the outcome of our liver transplant subjects with respect to whether or not PTLD involved the liver, though we found that by 33 months after PTLD onset, H-PTLD had a worse outcome; nevertheless, due to the limited number of included subjects into the latter analysis, the relevance of this finding should be considered with caution. Future prospective studies with large study populations are needed to better elucidate these questions.

We also found that H-PTLD in liver recipients is independently associated with a shorter time from transplantation to PTLD development. We previously reported a similar finding for patients with PTLD in their renal allograft [11]; while we have found PTLD arising within pancreas graft to be associated with a longer time to PTLD [53]. On the other hand, we have seen no difference in time to PTLD development in central nervous system and adenotonsillar PTLD in different types of graft recipients; while we have found PTLD arising within pancreas graft to be associated with a longer time to PTLD [53–55]. In the present study, H-PTLD was more likely than NH-PTLD to concomitantly involve the bone marrow ($p = 0.03$) and marginally more likely to involve the spleen, although the latter did not achieve statistical significance ($p = 0.07$). Based on this finding, it might be advisable to evaluate patients with H-PTLD for bone marrow involvement as well.

We conclude that liver transplant patients exhibiting early deterioration of graft function or other hepatic symptoms should, in addition to assessment for rejection, be evaluated for H-PTLD. In addition, all H-PTLD patients should be evaluated for bone marrow involvement, especially if they are EBV positive. Prospective studies with large patient population are needed to confirm our results.

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