Bone Marrow Involvement by Lymphoproliferative Disorders Post Liver Transplantation: PTLD Int Survey

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ABSTRAK

Tujuan: *untuk menganalisis kasus BM PTLD pada penerima transplantasi hati untuk menemukan prediktor tertentu atau faktor prognostik yang berhubungan dengan lokalisasi penyakit.* ***Metode:*** *pencarian menyeluruh dari kepustakaan yang ada dilakukan dalam penelitian ini dan ternyata 173 penerima transplantasi hati yang mengalami PTLD pasca pelaksanaan transplantasi ditemukan dari 19 penelitian dan dimasukkan ke dalam analisis. Sebanyak 36 pasien merupakan penderita BM PTLD dan sisanya merupakan kelompok kontrol.* ***Hasil:*** *resipien atau penerima transplantasi hati yang mengalami BM PTLD secara bermakna lebih banyak ditemukan pada pasien laki-laki (p=0,042) dan pasien berusia lanjut (p=0,08). BM PTLD tampaknya secara bermakna lebih sering menjadi komplikasi pada allograft hati (p=0,027) dan limpa (p=0,013). Pemeriksaan histopatologik menunjukkan bahwa lesi BM PTLD lebih sering berupa tipe monomorfik (p=0,025). PTLD multi organ dan PTLD diseminata secara bermakna lebih sering didapatkan pada pasien dengan BM PTLD (p<0,001, untuk keduanya). Kelompok BM PTLD menunjukkan tingkat ketahanan hidup atau survival yang lebih rendah daripada letak lainnya, meskipun demikian hal ini secara statistik tidak bermakna (p=0,1).* ***Kesimpulan:*** *hasil penelitian ini membuat kita menyadari pentingnya penggunaan metode yang lebih sensitif untuk mencari lesi metastasis yang potensial ditemukan bersamaan untuk organ-organ yang telah disebutkan sebelumnya, pada penerima transplantasi hati yang mengalami BM PTLD. Penelitian lebih lanjut dengan pendekatan prospektif diperlukan untuk memastikan hasil penelitian kami.*

Kata kunci: *sumsum tulang, transplantasi hati, kelainan limfoproliferatif pasca transplantasi, ketahanan hidup, prediktor.*

ABSTRACT

Aim: *to analyze cases of BM PTLD in liver transplant recipients to find any specific predictor or prognostic factor associated with this disease localization.* ***Methods:*** *a comprehensive search of the existing literature was performed, and 173 liver recipients who had developed PTLD in their post transplant course from 19 studies were found and enrolled into analysis. 36 of the patients were BM PTLD cases and the remaining was used as controls.* ***Results:*** *liver transplant recipients with BM PTLD were significantly more likely to represent in male patients (p=0.042) and the elderly (p=0.08). BM PTLD was significantly more likely to complicate liver allograft (p=0.027) and spleen (p=0.013). Histopathological evaluations showed that BM PTLD lesions were more likely of monomorphic type (p=0.025). Multi-organ and disseminated PTLD were significantly more prevalent among BM PTLD patients (p<0.001, both) The BM PTLD group represented relatively lower survival than patients with other localizations, although it did not reach significant level (p=0.1).* ***Conclusion:*** *our findings alert us to use more sensitive methods to find potential simultaneous metastatic lesions in the mentioned organs for liver recipients developing BM PTLD. Future studies with prospective approaches are needed to confirm our findings.*

Key words: *bone marrow, liver transplantation, post transplantation lymphoproliferative disorders, survival, predictors.*

INTRODUCTION

Posttransplant lymphoproliferative disorders (PTLD) represent a heterogeneous spectrum of abnormal lymphoid tissue proliferations occurring in solid organ recipients in the setting of cytotoxic T cells deficiency induced by anti-rejection immunosuppression therapy. The first evidence on PTLD was published in 1969 by Penn et al.[1] and since then, several scientists around the world have reported several similar cases indicating a high incidence of PTLD among organ recipients. The incidence of PTLD varies from 1% to as high as 30% in different organ transplant recipients with a wide range of 0.9% to 9% in liver transplant populations.[2-5] The reason behind the augmented incidence of the lymphomas after transplantation as well as the wide range of the incidence rates even within the same type of transplant population is related to several factors including seropositivity to viral infections or seroconversion, and most especially the potency of pharmacologic immunomodulation.[3-9]

PTLD emerges in a wide spectrum from a limited disease to quite a disseminated neoplasm. Bone marrow (BM) examination is a relevant part of evaluating patients with non-Hodgkin lymphomas because BM involvement is often associated with an independent adverse prognostic outlook, indicating stage IV disease.[10] Differences in the incidence of BM complication by PTLD regarding different factors including histopathological phenotype of the lesions or association with Epstein–Barr virus (EBV) infection are currently not known. In transplant and non-transplant era, general belief is that BM involvement by monomorphic lymphoma is uncommon; however, new evidence suggests several individual reports on the occurrence of monomorphic BM infiltrations by lymphomatoid cells. 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 of PTLD in liver transplant recipients. Knowing these factors will empower us to design and conduct preventive and screening strategies, which can lead to a decrease in the incidence of the disease or promote its prognosis due to an earlier diagnosis of the disease, resulting in better outcome. In the current study, we aimed to search the existing literature to find reports of liver recipients developing PTLD within their bone marrow, and to compare their demographic data, histological phenomena and survival with liver recipients representing PTLD in other organs to find potential predictive and prognostic factors which play major roles in this patient population.

METHODS

Approach to The Study

A comprehensive search was performed to find available data on PTLD localization in bone marrow among liver allograft recipients, though PubMed and Google Scholar. Search terms used were "lymphoproliferative disorders + liver transplantation + bone marrow" "lymphoproliferative disorders + liver transplantation + bone marrow localization" "PTLD + liver 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. From the full texts obtained, we only included subjects from studies representing data for each individual patient, separately. Control patients were liver recipients whose PTLD localization was not bone marrow. For minimizing interfering factors including center-selection bias, control patients were also enrolled only from the same studies reporting BM PTLD localization. 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

Nineteen international published studies[11-29] were found that met our criteria. A total of 171 liver recipients with a documented PTLD site, of whom 36 (21.1%) had BM PTLD were included in the analysis. The remaining 135 (78.9%) patients had developed non-BM PTLD. EBV status was documented in 125 (73.1%) patients, of whom 88 (70.4%) were reportedly positive.

Because of different methodologies employed in the enrolled studies, some of our measures were not available for all the patients, or their presentation was not consistent. 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 stated a disseminated disease for them). According to the abovementioned, data on disseminated PTLD was available for 134 patients (78.4%; 37 unreported data) from which 46 (34.3%) 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 152 patients (88.9%; 19 unavailable data) of which 81 (53.3%) were multi-organ PTLD.

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 or without surgical interventions were also used for some patients.

Response 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 was available for 71 patients (41.5%), of whom 60 (84.5%) responded to treatment and had a remission episode, irrespective of their future disease course. Data on mortality was available for 98 patients (57.3%), of whom 44 (44.9%) 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, 34 patients (77.3% 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. p value level of 0.1 was considered relevant.

RESULTS

Overall 171 patients with lymphoproliferative disorders after liver transplantation were entered into analysis. There were 58 (54.2%) males and 49 (45.8%) female patients (64 unreported). Mean age at diagnosis of PTLD was 31.4±24.3 years. The mean interval between transplantation and the diagnosis of PTLD was 37.3±43.3 months whereas follow up time after diagnosis of PTLD was 31.3±35.6 months.

Characteristics of the patients regarding their malignancy site are summarized in **Table 1**. Chi square test showed that liver transplant recipients with BM PTLD were significantly more likely to represent in male patients (p=0.042). Moreover, BM PTLD was relevantly more frequently seen among younger liver recipients, although it did not reach significant level (p=0.08). Liver transplant recipients with BM PTLD localization were comparable to their counterparts with other PTLD localization in their immunosuppression type, presentation time, EBV positive rate, overall mortality rate, and death due to PTLD.

Table 2 summarizes different organ involvements by PTLD when they concomitantly do or do not complicate the bone marrow. PTLD, in BM PTLD liver recipients more significantly complicated liver (p=0.027) and spleen (p=0.013) but less commonly affected pharynx (p=0.028), simultaneous to the BM. Other organs were equally involved by the neoplasm regarding the two study groups.

Patients with BM PTLD had comparable time from transplantation to PTLD development to the control patients (p=0.494). Histopathological evaluations showed that BM PTLD lesions were more likely monomorphic and less benign phenomena (p=0.025), and T cell type of lymphoma cells were significantly more prevalent among BM PTLD (p=0.014).

Multi-organ PTLD involvement and disseminated disease were both significantly more prevalent among BM PTLD liver recipients

Table 1. Characteristics of liver transplant recipients with or without BM involvement by PTLD

Variables	BM PTLD	Controls	Sig.	Available data
Age (yr)	37.9±22.9	29.6±24.5	0.08	146
Pediatric; <18 yr/o (%)	8 (25.8)	49 (42.6)	0.10	146
Gender male (%)	9 (36)	49 (59.8)	0.042	107
Time to PTLD development (mo)	32.6±29.9	38.7±46.6	0.494	132
Early onset (vs. late)	9 (30)	44 (43.1)	0.213	132
Multi organ involvement (%)*	27 (81.8)	54 (45.4)	<0.001	152
Disseminated PTLD (%)*	21 (72.4)	25 (23.8)	<0.001	134
Morphology			0.025	126
Early lesion (Plasmacytic hyperplasia)	0	5 (4.9)		
Polymorphic B cell lymphoma	4 (16.7)	38 (37.3)		
Monomorphic PTLD	19 (79.2)	59 (57.8)		
Hodgkin lymphoma	1 (4.2)	0		
Clonality (%)	6 (60)	26 (72.2)	0.465	46
EBV status (%)	19 (65.5)	69 (71.9)	0.498	125
Mortality (%)	11 (52.4)	33 (42.9)	0.467	98
Remission episode (%)	16 (80)	44 (86.3)	0.491	71
Lymphoma cell type B cell (%)	11 (78.6)	41 (100)	0.014	55

*according to the criteria defined in the methods section

(p<0.001, both; **Table 1**). When death irrespective of the reason was used as the outcome, log-rank test showed no difference regarding outcome of PTLD liver recipients with or without BM PTLD (p=0.45; **Figure 1**); nevertheless, when death only due to PTLD was used as the outcome (based on the defined criteria in the methods section), the BM PTLD group represented relatively lower survival than patients with other localizations, although it did not reach significant level (p=0.1; **Figure 2**). One and five years survival rates for BM PTLD patients were 68% and 37%, respectively; compared to 69% and 49%, respectively, for the control group.

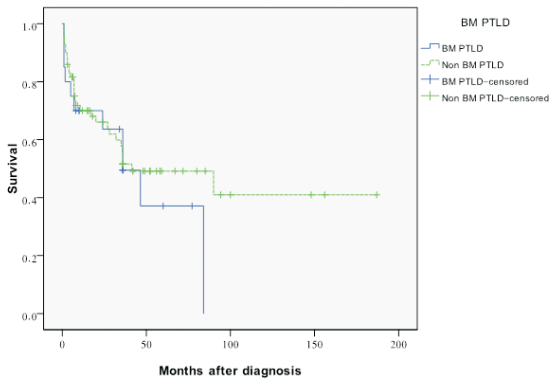

Figure 1. Survival curves of liver recipients with or without BM complicated PTLD (Outcome: death irrespective of the reason)

Table 2. Frequency of involved organs in liver transplant recipients with or without bone marrow PTLD complication

Involved organs	BM PTLD	Controls	Sig.
Orbit	1 (2.9)	2 (1.6)	0.516
Heart	0	1(2.6)	0.807
Skeleton	1 (2.9)	3 (2.3)	1.0
Skin	1 (2.9)	1 (0.8)	0.381
Stomach	3 (9.1)	7 (5.7)	0.442
Genitalia	1 (2.9)	1 (0.8)	0.377
CNS	2 (5.6)	5 (3.8)	0.643
Spleen	10 (31.3)	15 (11.8)	0.013
Colon	0	11 (8.6)	0.122
Small intestine	3 (9.4)	29 (23)	0.137
Renal involvement	1 (2.9)	6 (4.7)	1.0
Liver involvement	17 (47.2)	36 (27.3)	0.027
Respiratory system	8 (25)	16 (13.3)	0.169
Pharynx	1 (2.9)	22 (18)	0.028

DISCUSSION

In the era of new immunosuppressive agents' introduction, transplantation practice has witnessed substantial improvements both in patient and graft survival. However, these advantages were associated with some disadvantages endangering transplant patients at a remarkable increase in the risk for infections as well as developing malignancies.[30-32] PTLD

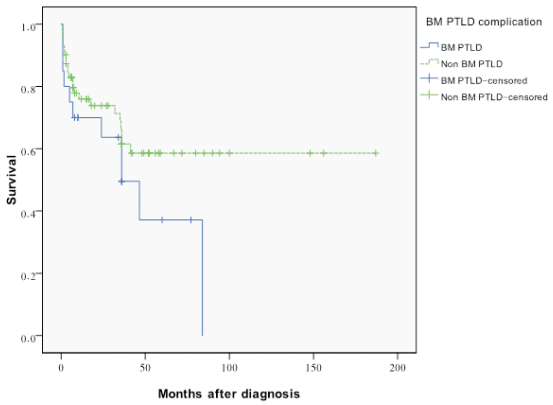

Figure 2. Survival curves of liver recipients regarding BM involvement by PTLD (outcome: death due to PTLD)

are one of the most prevalent malignancies complicating solid organ recipients and reducing both graft and patient outcome. Several factors have been shown to play major roles in the presentation and outcome of PTLD, from which we have focused on bone marrow localization of the disease in liver transplant patients. Previous studies have demonstrated that localization of PTLD is extremely relevant due to the conflicting clinical and histopathological features and prognosis.[33,34] PTLD.Int Survey is an attempt to gather international data on the largest possible PTLD patient population to discover new perspectives on the disease.[8,31,34] The current study deals with the largest-ever investigated population of patients with BM localization of PTLD in liver transplant recipients; looking for particular characteristics of BM PTLD, including morphology and clonality, EBV infection status, and prognostic factors.

In the current study, we found that BM involvement is more frequently seen among male recipients of liver graft and elderly patients. Moreover, we found that liver recipients with BM PTLD were more likely to develop a simultaneous graft involvement by the disease. This finding is consistent with a previous study in which we have shown a higher rate of BM metastasis in liver recipients who develop allograft PTLD.[35] Furthermore, in another study on renal recipients developing BM PTLD [not published data], we found the same finding, and a higher rate of simultaneous liver involvement which confirms our previous findings and suggests a correlation between BM and liver PTLD metastasis in different transplant recipients. Spleen which is another found metastasis site is more frequently complicated by PTLD, when it involves BM. These findings are of high relevance, because finding those organs are significantly more likely to be complicated by PTLD when it has already involved BM alerts us to pay more attention to find potential metastases in the mentioned organs, when we recognize a liver recipient with BM PTLD.

One of the major findings of the current study is that patients who develop BM PTLD are highly more frequently to have disseminated disease. This finding is consistent with our knowledge on the prognosis of BM PTLD which is generally considered very poor. However, there are controversial reports as well. A previous study has suggested that BM PTLD patients are significantly less likely to develop extranodal metastasis.[36] Nevertheless, we believe that our finding is more confidential, because in a previous study on renal recipients, we similarly found the same finding with higher metastasis rate for BM PTLD patients. Moreover, this finding is more in agreement with the known inferior prognosis of BM involving PTLD patients.

Morphology of PTLD lesions is of outmost importance, as well. In the current study, PTLD lesions of patients with BM PTLD were significantly more frequently of monomorphic type. This can provide another explanation for what is considered a non-favorable disease site for BM. To our knowledge, this finding is first reported by the current study, although previous studies have also found a high rate of monomorphic cells in BM PTLD lesions[36], ours presented a statistically significant difference.

Inconsistent to our expectations, no significant difference was found regarding the outcome of patients regarding BM localization of PTLD. However, when data were reanalyzed with death due to PTLD as the final outcome, a relatively lower survival for BM PTLD patients was found in our series, although statistical significance was not achieved. Another finding of the current study is a statistically significant higher rate of T cell type for BM PTLD lesions. This finding can also confirm our expectations, because of a worse outcome for BM PTLD patients.

This study has some limitation. Maybe the most important criticism that may rise over our article is that the enrolled population of the current report is from different reports which

may have used different approaches toward their surveys. This was exactly our biggest problem to cumulate data of different reports for conducting analysis. To be able for this purpose, we tried to standardize data of different reports into one unique type, so we would be able to compare them. For example, we defined new terminologies like multi-organ and disseminated disease to show the extent of disease spread. Moreover, we recategorized different PTLD morphologies into four main categories defined by the World Health Organization.[37] Despite all these modifications and standardizations, we believe that our findings, as the premier data on BM PTLD in liver recipients should be highly respected and can be used for clinical practice. We also suggest more prospective studies to confirm or reject our findings.

CONCLUSION

We found that male and elderly patients are more likely to develop BM PTLD. Patients with BM PTLD have a relatively lower survival and are at a high risk for developing multi-organ and disseminated disease. They are also more likely to have metastatic lesions in liver and spleen. These findings alert us to use more sensitive methods to find potential simultaneous metastatic lesions in the mentioned organs for liver recipients developing BM PTLD. Future studies with prospective approaches are needed to confirm our findings.

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