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Burkitt's Lymphoma Post Renal Transplantation: PTLD.Int Survey

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Abstract

Introduction: Burkitt's lymphoma is a well known type of malignant lymphoma in the general population; but in transplant era, it has not been defined as a distinct category of post transplant lymphoproliferative disorders (PTLD), possibly due to the very rare nature of this disease type in this population. In this first study, however, we aimed to find individual cases of Burkitt's lymphomas reported by different series in the literature, and to compare their disease characters, behavior and prognosis with other PTLD patients reported by the same studies.

Methods: A comprehensive search of the current literature was performed through Pubmed and Google Scholar for reports or series including individual cases of Burkitt's lymphomas developing post renal transplantation. Overall 23 cases of Burkitt's PTLD were found whose data were compared to 103 renal transplant patients with other PTLD types. Immunosuppression types were comparable between the two groups (p=0.922).

Results: Burkitt's PTLD were significantly more likely to occur in the paediatric age (vs. adults; 41% vs. 13%, respectively; p=0.005); and as late onset disease (>1 year posttransplant; 100% vs. 81%; p=0.035). Multi-organ PTLD (53% vs. 15%, respectively; p=0.004), Bone marrow complication (26% vs. 2%, respectively; p=0.003) and liver metastasis (12.5% vs. 0; p=0.043) were more frequently seen in the Burkitt's PTLD group. Time interval from transplantation to PTLD development and survival of the patients were comparable between the two groups.

Conclusions: Burkitt's lymphoma in renal transplant recipients is more likely to complicate children and to develop metastatic disease, especially within the bone marrow and the liver. So it is recommended to evaluate renal recipients whose PTLD lesions were histopathologically defined as Burkitt's lymphoma, for potential metastatic lesions especially within the liver and/or bone marrow. Prospective studies are suggested for confirming these results.

Keywords: Burkitt, Lymphoma, Renal, Transplantation, PTLD, Survey

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Introduction

Posttransplant lymphoproliferative disorder (PTLD) is a well known complication of solid organ transplantation, which overwhelming evidence suggests accuses potent immunosuppression used for preventing rejection episodes as the main responsible [1-3]. The incidence of PTLD in renal transplant recipients has reportedly been including a very wide range from 0.4% upto 10% according to the demographics of the patients and therapeutic approaches of their transplant centers [4]. The histopathological and behavioral characteristics of PTLD are also very diverse between patients reported in different series, based on their demographics and disease and treatment specifications [5,6]. Lymphoproliferative disorders developing after transplantation are not usually subjected to be classified according to formal categorizations of lymphomas in non-transplant era; and instead they are generally referred as PTLD with four general subcategories: (1)early lesions; (2) polymorphic lesions; (3) monomorphic lesions; and (4) Hodgkin's disease. However, different types of lymphomas have unequal behavior and prognosis, so it is important to define lymphoma types of PTLD lesions, like those in patients of non-transplant context.

Burkitt's lymphoma has rarely been reported as a PTLD [7]. The hallmark of Burkitt lymphoma is the t(8;14) translocation, and it is defined as an undifferentiated malignant growth of lymphoreticular cells with mild to moderate nuclear and cytoplasmic variations. Burkitt's lymphoma is categorized as a type of mature B-cell neoplasm which encompasses an immunodeficiency-related subtype [8,9]. The typical presentation of Burkitt's lymphoma includes multifocal, rapid growing of extranodal masses with a priority in the retroperitoneum and abdominal viscera. In histological evaluations, the tumor is highly active mitotically and cell nuclei appear round or slightly uniform with a prominent nuclear membrane and slight nuclear indentation [9].

In the current study, we aimed to performed a very comprehensive and thorough review of the literature to find individual cases of Burkitt's lymphoma occurring after renal transplantation to review their clinical, pathological, and prognostic data to evaluate factors which can affect disease course and prognosis in this patient population.

Methods & material

Approach to the study: A very comprehensive and thorough search of the literature was performed for the

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available data by Pubmed and Google scholar search engines on reports of Burkitt's lymphoma developing in kidney graft recipients after transplantation. Keywords used for this purpose were "lymphoproliferative disorders + Burkitt + renal transplantation" " Burkitt's lymphoma + renal transplant" "PTLD + Burkitt + kidney transplant" "PTLD + Burkitt + renal graft". In cases we were not able to obtain the full text of the articles; we sent emails to the corresponding authors, and when thei email addresses were not available, to any of other authors, requesting the article. Then only studies in which data of each individual patient was presented separately were included. To enhance the power of our search, we researched all articles searched in our previous review endeavors on the PTLD.Int surveyes for any individual cases of Burkitt's lymphoma. Then, a standard questionnaire was developed to collect data from different published reports, and finally, a database was developed to gather data of these patients. Finally, data from 14 published case reports or series from single- or multi-center reports [9-22] have been included into analysis. The time from transplantation to PTLD onset was defined as the period between the grafting and the first signs of PTLD or diagnosis, based on the studies approaches.

Study population: Overall 126 recipients of kidney allograft were included into analysis. 23 (18.3%) of the study population were patients with PTLD lesions of Burkitt's histopathology, while the remaining 103 (81.7%) patients were kidney recipients developing other histopathological features of PTLD.

Because different included studies had inconsistent approaches, it was not possible to attain all data needed from all the included patients in a unique format, and in some cases we had to introduce new standardized measures to become able to cumulate data from different studies into a unique database. Disseminated lymphoma was diagnosed when it was declared by the authors or at least three different organs (excluding different lymph node areas) were involved by PTLD, reported in 5 (9.3%; 72 unreported) patients. Multi organ involvement defined as involvement of more than a unique organ as well as more than one lymphatic region was available in 15 (23.8%; 63 unreported) patients.

Response to treatment: Any favorable change in the cancer measures as well as patients' clinical condition was considered a response to treatment termed as "remission"; data of PTLD response to treatment was reported by authors for 46 (36.5%) patients of whom 39 (84.8%) patients responded to anti malignancy treatment. However, we developed new criteria to define remission rates for the study population; while 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 dies within the first month post PTLD diagnosis (because among reported cases there were no patients dying at the first post transplant month and reported to have any remission episodes). According to the abovementioned criteria, remission rate reached to 72 cases (80.9%; 37 unreported). Overall mortality was 40 (33.1% of the reported cases; 5 unreported) patients, of which 18 (45%) of deaths were due to PTLD.

Statistical analysis: Software used for data analyses was SPSS v.17.0. Statistical differences between patients' subgroups were performed by using $\chi 2$ and Fishers' exact tests for proportions and the Students t test for continuous data. Survival analysis was done with life tables and Kaplan-Meier methods and log-rank test. Univariate and multivariate logistic regression models were used for evaluating relationships to bone marrow PTLD involvement. All statistical tests were performed at the 0.05 significance level. p values below 0.1 were considered relevant.

Results

Overall 126 patients developing Burkitt's lymphomas after renal transplantation were entered into analysis. There were 49 (68.1%) males and 23 (31.9%) female patients (54 unreported). Mean age at diagnosis of PTLD was 38±18.1 years. The mean interval between transplantation and the diagnosis of PTLD was 87.4±75.4 months (for 96 patients) whereas follow up time after diagnosis of PTLD was 35.9±39.2 months (for 74 patients).

Characteristics of the patients regarding their malignancy site are summarized in table 1. Chi square test showed that patients with Burkitt's lymphoma were significantly more likely to happen in pediatric age group (vs. adults; 41% vs. 13%, respectively; p=0.005; 11 unreported data). But it was equally prevalent among males and females (p=0.39). On the other hand, compared to other types of lymphomas, renal recipients with Burkitt's lymphoma were significantly more likely to develop the neoplasm within the late period (>1 year) post transplantation; in fact, all cases of Burkitt's lymphoma were late onset while this rate was 81% in the controls (p=0.035). EBV infection rates were also comparable between the two groups (p=0.8).

Table 1. Characteristics of the study patient groups based on their PTLD pathology

Variables	***Burkitt's PTLD***	***Control patients***	***Sig.***	***Available data***
Age (yr)	28.2±15.3	40.3±18	0.004	115
Gender male (%)	14 (78)	35 (65)	0.39	72
Time to PTLD development (mo)	70.2±33.1	92.2±83.1	0.07	96
Early onset (%)	0	14 (18.7)	0.035	96
Multi organ involvement (%)*	8 (53.3)	7 (14.6)	0.004	63
Disseminated PTLD (%) *	3 (23.1)	2 (4.9)	0.084	54
Remission episode (%)	14 (93.3)	58 (78.4)	0.285	89
Monoclonal lesions vs. polyclonal (%)	6 (85.7)	17 (73.9)	0.468	30
CD10 positive lesions (%)	9 (100)	1 (16.7)	0.002	15
CD20 positive lesions (%)	9 (100)	6 (100)	-	15
EBER positive lesions (%)	7 (53.8)	11 (78.6)	0.236	27

Bcl-6 positive lesions (%)	7 (100)	2 (33.3)	0.021	13

Then organ involvement rates were compared between the two groups (table 2). Burkitt's lymphoma lesions were significantly more likely to complicate more than one organ (multi-organ PTLD; p=0.004), while the difference for disseminated lymphoma did not reach significance level (p=0.08). Moreover, hepatic involvement was also more frequently observed in patients with Burkitt's lymphoma (p=0.043). Bone marrow was also a predominated metastasis site for Burkitt's lymphoma. While only 2% of the controls developed bone marrow lymphoma complication, this rate reached to over 26% in renal recipients developing Burkitt's lymphoma (p=0.003). To evaluate whether this association is independent from patients age group, a multivariable logistic regression was conducted which confirmed the independence of the relation (p=0.012; table 3).

At the last follow, 40 (33.1%) patients were dead (5 unreported data). To have more comparable groups to conduct a survival analysis, we compared outcome of renal recipients with Burkitt's PTLD with those with non-Burkitt's monomorphic PTLD. Figure 1 shows the survival curves. Although survival curve of patients with Burkitt's PTLD appear to be higher than that of monomorphic PTLD patients in the control group, the difference did not reach significance (p=0.09). Changing the outcome parameter to the "death due to PTLD" did not change the result, either.

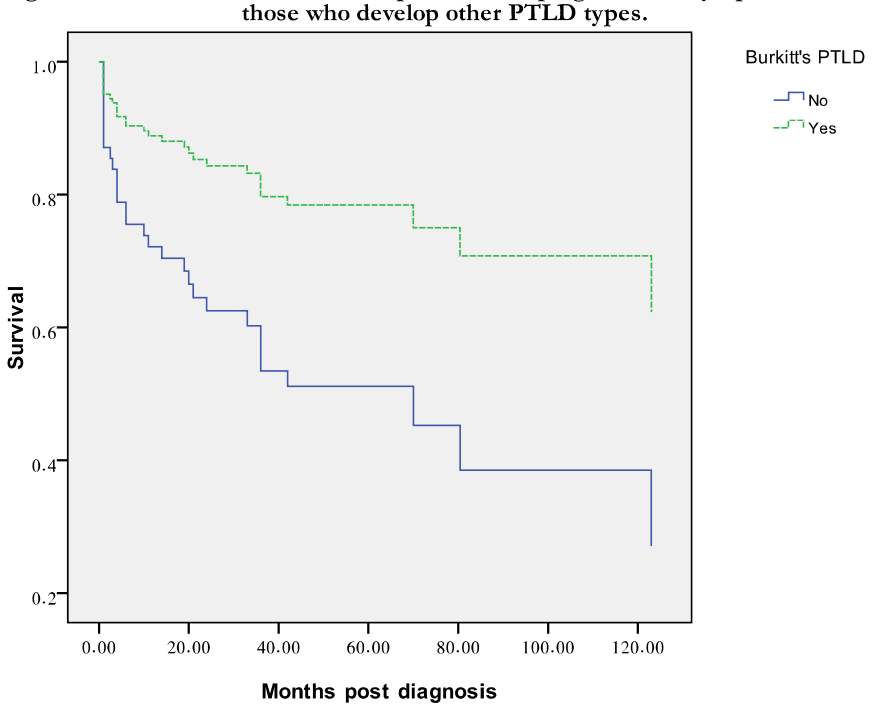
Table 2. Frequency of metastases to different organs regarding patients' PTLD type

Organ involved by PTLD	***Burkitt's PTLD***	***Controls***	***Sig.***	***Available data***
Skeleton (%)	1 (5.9)	0	0.218	78
Spleen (%)	1(6.3)	3 (5)	0.62	76
Colon (%)	1 (6.7)	0	0.2	75
Small intestine (%)	2 (15.4)	2 (3.3)	0.143	73
Kidney (%)	2 (12.5)	5 (8.3)	0.634	76
Liver (%)	2 (12.5)	0	0.043	75
Respiratory system (%)	1 (5.9)	4 (6.9)	0.683	75
Bone marrow (%)	5 (26.3)	1 (1.7)	0.003	77
Orbit (%)	0	0	-	75
Skin (%)	0	5 (8.5)	0.581	84
Stomach (%)	3 (18.8)	2 (3.3)	0.06	76
Central nervous system (%)	1 (5)	3 (4.7)	0.671	84

Table 3. multivariable logistic regression model to evaluate independent association between Burkitt's lymphoma amd bone marrow complication.

Variables	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
							Lower	**Upper**
Pediatric age	.133	1.009	.017	1	.895	1.142	.158	8.244
Burkitt's lymphoma	2.922	1.158	6.362	1	.012	18.572	1.918	179.799

Figure 1. Survival curves of renal recipients developing Burkitt's lymphoma versus those who develop other PTLD types.



Discussion

Transplant patients are at a considerable increased risk for developing lymphomas and it is suggested that the type and degree of immunosuppression, viral infections, and the type of allograft play the major roles in this risk enhancement [23,24]. On the other hand, it has been demonstrated that behavior and prognosis of the PTLD is highly dependent to the histopathological characteristics of the disease lesions. For the same reason, physicians pay much attention to evaluate and categorize PTLD lesions of their patients, and they conduct their therapeutic strategies based on it.

In transplant context, formal categorizations for lymphomas scarcely applied. Instead, according to a protocol suggested by the world health organization (WHO) [25], they usually categorize PTLD into four histopathological subgroups namely: early lesions, polymorphic PTLD, monomorphic PTLD, and Hodgkin's lymphomas, and each of the subcategories constitutes several formal types of lymphomas. Burkitt's lymphoma arising in the transplant patients has not been well characterized, and they have generally been categorized as monomorphic PTLD. Only a few cases have been described in single case reports and series. As in its previous reports, PTLD.Int Survey aims to cumulate international data from the published reports of individual case reports or series on rare disease characteristics trying to provide an analysis on the largest possible PTLD patient population to discover new perspectives on the most crucial but rare aspects of the disease.

In the current study, several new and interesting data have been emerged which can substantially add to our knowledge on Burkitt's lymphomas arising in renal transplant patients. We found that Burkitt's lymphoma is significantly more likely to develop in the pediatric setting than adults. This finding is of utmost importance while Burkitt's lymphoma in children has different characteristics in children to the extent that some authors have suggested classifying pediatric Burkitt's lymphoma as a new entity [26]. Some of these differences include a prominent male predominance in the incidence, as well as different disease behavior and organ involvements in children than adults [26].

In the population-based studies [27] as well as international surveys [28], a male predominance has been observed in the incidence of Burkitt's lymphoma. In the current study, although there was a large gap between incidence of Burkitt's lymphoma regarding transplant patients gender groups (78% vs. 22%), this disparity was not significantly different to that of other subcategories of PTLD patients in this series, suggesting that, in the transplant era, this gap exists not only in Burkitt's lymphoma, but also it emerges in other types of lymphomas developing in the transplant setting. On the other hand, at least in some proportions, this disparity might mirror the overall larger number of males who are more vulnerable to developing ESRD and undergo renal transplantation [29,30], and a male predominance in the access to renal grafts even in the developed countries [31].

Analyzing metastatic activities of the neoplasms, we also found that patients representing Burkitt's lymphomas are significantly more likely to complicate liver and bone marrow. It has previously been suggested that Burkitt's lymphoma in pediatric setting is more likely to complicate extranodal organs [26]. However, analyzing age subgroups only within patients with Burkitt's lymphoma showed no significant difference. So, we conclude that it is Burkitt's lymphoma itself and not age of the renal transplant recipients with PTLD that exposes them to develop metastatic lesions in their bone marrow and/or liver.

Then we tried to correlate patients survival to their PTLD type. However, no significant survival disparity was found

between the two patient groups. Taking a look at figure 1 may makes one surprise, since survival curve of patients with Burkitt's lymphoma seems to be quite higher than that of other PTLD groups. It is speculated that Burkitt's lymphoma is an aggressive type of lymphoma that has an ominous behavior [32]. We have some explanations for this observation: (1) In some studies Burkitt's lymphoma has shown quite better remission rates as well as survival rates than other lymphoma types [33]. (2) Burkitt's lymphoma might have different behavior in the transplant setting; this is a new finding of our study which should be more investigated in future, preferably in prospective multicenter experiments; (3) it has been shown that younger age of patients with lymphomas is associated with better survival [34,35] that can modify the inauspicious behavior of Burkitt's lymphoma. (4) Patients with Burkitt's PTLD might have gone under better surveillance and treatments. On the other hand, there is evidence also against our conclusion; extranodal involvement has been suggested as a prognostic factor for Non-Hodgkin's lymphomas; although the same study found no prognostic value for bone marrow involvement [36].

This study is associated with some limitations. Firstly, patients whose data were used for analysis in this study was gathered from different case reports or series which one may assume that they had more or less inconsistent approaches. For overcoming this issue, we used to strategies. First we tried to gather control patients from the same studies from which cases have been entered. Second, we tried to standardize our data in the most modest manner possible. For example, report style of remission episodes in different studies were not comparable; while some of them had used terms like "complete or partial remissions", some others only talked about experiencing remission episodes, and some others have just reported some favorable change in their patients' disease measures (changes in tumor size, general conditions and so on). In this case, we used only two terms to categorize all of them: "remission" and "no remission." When authors had reported any positive reaction to therapy, we used term "remission" and when disease progressed, we used the second term. Some other standardization policies have been employed which have been described in the methods section.

In conclusion, in this study, we found that renal transplant recipients developing Burkitt's lymphoma in their post transplant era are of younger age and have comparable survival rate to their counterparts developing other lymphoma types. On the other hand, Burkitt's lymphoma was associated with higher rate of metastatic disease especially liver and bone marrow metastasis. Future prospective studies seemed to be needed to confirm our conclusion.

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