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Brief Communication

Localization of Post-Transplant Lymphoproliferative Disorders to the Stomach Might be Associated with Favorable Outcome: A Systematic Review

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ABSTRACT. Gastric localization of post-transplant lymphoproliferative disorders (PTLDs) is very rare. In this study, we aimed to accumulate existing data in the current literature to reveal the clinical, histopathological and prognostic specificities associated with gastric PTLDs and to find the best treatment strategies in this patient population. A comprehensive search was conducted for the available data in the current literature using Pubmed and Google scholar search engines for reports on gastric PTLD in renal transplant recipients. Data of different studies were standardized and entered into a database and analyzed. No statistically significant difference was found between gastric and non-gastric PTLD. Gastric PTLD was relatively more prevalent in female patients (P = 0.08) and showed a trend toward better outcome (P = 0.1) and less metastasis (P = 0.07). Surgical intervention and rituximab therapy were associated with a more favorable outcome (17% mortality). Our study showed that organ transplant recipients having gastric PTLD develop metastasis less frequently and tend to have a relatively more favorable outcome. Prospective studies with larger patient populations are needed to confirm or modify our results.

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are defined as neoplastic proliferation of lymphocytes in transplant recipients and carry varying clinical implications and can have ominous consequences if not treated. The incidence of PTLD is reported to be ten- to 100-fold higher than that in the general population,[1,2] and varies from less than one percent to over 20% in recipients of different organs.[3-6] Several factors play major roles in the development of PTLD. Epstein Barr Virus (EBV)-related lymphoproliferative disorder is a well known entity and accounts for majority of these lymphomas.[7] Immunosuppression employed after

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solid organ transplantation for preventing rejection episodes predisposes these patients to PTLD through immortalization of B lymphocytes with EBV.[8,9] The risk of lymphomas has also been correlated with ineffective T-cell function due to infections as well as the immunosuppression.[10,11] Lymphoproliferation resulting from EBV infection has a wide clinical spectrum, ranging from uncomplicated posttransplantation mononucleosis syndrome of little clinical consequence to highly aggressive neoplasms.[12,13]

Several factors play a role in the involvement of different organs by PTLD, and involvement of specific organs by the disease is associated with different disease phenomena, lesion features and survival specificities.[14-17] Moreover, involvement of some organs can predict simultaneous involvement of some other organs by the disease. Hence, identification of specific organs affected by PTLD is of enormous importance because this helps us to manage and treat the disease better. Additionally, we might even be able to design some preventive and screening measures that can potentially decrease the incidence of this disease or increase survival of the affected patients.

Individual cases of localization of PTLD in the gastrointestinal (GI) tract have been reported in the literature.[18] However, due to the limited number of cases with involvement of specific GI tract segments, there is scarcity of data on specific characteristics for disease affecting each GI tract section. Involvement of the stomach is rare in PTLD. To the best of our knowledge, until now, gastric PTLD has not been previously evaluated in any transplant population. We therefore aimed to accumulate the existing data on individual reports of gastric PTLD in the current literature and to analyze and compare this data with data on PTLD in other sites, in order to see if there are any unique clinical and histopathological features, potential predictors and prognostic factors associated with PTLD involving the stomach.

Materials and Methods

Approach to the study

A comprehensive search was conducted for available data in the current literature using the Pubmed and Google scholar search engines for reports of lymphoproliferative disorders in the gastric tissue of renal transplant patients. Keywords used for this purpose were "lymphoproliferative disorders + transplantation + stomach localization," "lymphoproliferative disorders + transplantation + gastric localization," "PTLD + stomach involvement" and "PTLD + gastric involvement." When full articles were not available, e-mails were sent to the authors requesting for the same. Only reports in which data of each patient were presented separately were included in the analysis. To minimize selection bias, we included only studies reporting their series of patients from single or multi-center populations. Studies with any specific selection criteria were excluded from the analysis; lymphoproliferative disorders occurring within the stomach after transplantation were considered as our case group, and patients developing PTLD in the other sites were used as controls. A standard questionnaire was developed to collect data from different published studies. Finally, data from 36 previously published studies[19-54] were included into the analysis (Table 1). The duration between transplantation and onset of PTLD was defined as the period between performing the transplant surgery and appearance of first signs of PTLD or its diagnosis, based on the protocol of the studies.

Study population

Overall, 472 recipients of organ grafts, who developed PTLD during their post-transplant period, were included in the analysis. Fifty-six patients (11.9%) had gastric PTLD while the remaining 415 patients (88.1%) had PTLD in other sites. The patients' status regarding EBV infection was documented in 202 patients (42.9%), of whom 146 (72.3%) were reported positive.

Because data used for this study were from different studies and they did not have any unique common approaches, we were not able

Table 1. The list of the reports included in the analysis.

Studies	Frequency	Percent
Pascual et al[54]	1	0.2
Mamzer-Bruneel et al[53]	16	3.4
Pourfarziani et al[52]	35	7.4
Hanasono et al[51]	10	2.1
Smets et al[50]	7	1.5
Hachem et al[49]	19	4.0
Paraskevas et al[48]	18	3.8
Jain et al[47]	17	3.6
Lucioni et al[46]	21	4.4
Wilde et al[45]	30	6.4
Chen et al[44]	7	1.5
Muti et al[43]	40	8.5
Herzig et al[42]	29	6.1
Bakker et al[41]	12	2.5
Davis et al[40]	4	0.8
Oertel et al[39]	15	3.2
Dusenbery et al[38]	7	1.5
Kerkar et al[37]	21	4.4
Cacciarelli et al[36]	17	3.6
Collins et al[35]	21	4.4
Ganne et al[34]	8	1.7
Sevmis et al[33]	5	1.1
Timms et al[32]	13	2.8
Craig et al[31]	8	1.7
Peraira et al[30]	6	1.3
Soler et al[29]	10	2.1
Timuragaoglu et al[28]	8	1.7
Abe et[27]	10	2.1
Koh et al[26]	10	2.1
Patel et al[25]	17	3.6
His et al[24]	5	1.1
Orjuela et al[23]	6	1.3
Medlicott et al[22]	4	0.8
Lee et al[21]	9	1.9
Jacobson et al[20]	1	0.2
Barker[19]	5	1.1
Total	472	100.0

to get all the data needed from the included patients. Disseminated lymphoma was diagnosed when it was declared by the authors or at least three different organs were involved by PTLD (different lymph node areas were excluded from analysis due to lack of knowledge on how to categorize); this was reported in 93 patients (31.4%). Multi-organ involvement, defined as involvement of more than one unique organ as well as more than one lymphatic region, was documented in 201 patients (53.5%).

At diagnosis of lymphoma, all patients were receiving or had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, anti-thymocyte/lymphocyte globulin (ATG/ALG) and OKT3. More or less, a rather uniform approach was used to manage the PTLD patients in the included reports. On diagnosis of PTLD, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; different regimens of chemotherapy, with or without surgical interventions, were also used for some patients.

Response to treatment

Response to treatment was defined when a favorable change was observed in the cancer measures as well as patients' clinical condition; data on response to treatment of the PTLD was available in 188 patients (39.8%), of whom 134 (71.3%) responded to anti-malignancy treatment. However, new criteria were laid down for defining remission rates in these patients; an episode of remission was said to occur when patients were alive after the 24th month of diagnosis of PTLD. Absence of remission was defined when a patient died within the first month after diagnosis of PTLD. According to these criteria, 297 patients (62.9%) had remission, of whom 189 (63.4%) had at least one episode of response to treatment, irrespective of their future disease course. Death was reported in 183 of the reported cases (49.3%); death due to PTLD was defined when: (a) if authors stated it or (b) when the patient died within six months post-diagnosis of PTLD unless the authors stated other causes for death and (c) when patients died due to complications related to treatment of PTLD. Based on the above-mentioned criteria, 137 patients (74.9% of the total mortality rate) died due to the disease.

Statistical Analysis

SPSS v.13.0 was the software used for data analyses. Statistical differences between patient

Table 2. Characteristics of transplant recipients with post-transplant lymphoproliferative disorders of the stomach versus other localizations.

Variables	Gastric PTLD	Controls	Sig.	Available data
Age (years)	33.1 ± 21.8	34.2 ± 21	0.736	419
Pediatric; <18 years (%)	15 (30.6)	94 (25.4)	0.488	419
Gender, male (%)	17 (51.5)	175 (65.5)	0.084	300
Time to PTLD development (months)	52.8 ± 52.3	48.5 ± 50.8	0.581	370
Early onset (vs. late)	15 (32.6)	112 (34.6)	0.869	370
Multi-organ involvement (%)*	29 (59.2)	172 (52.6)	0.444	376
Disseminated PTLD (%)*	13 (34.2)	80 (31)	0.710	296
Morphology			0.635	355
Early lesion (plasmacytic hyperplasia)	1 (2.6)	17 (5.4)		
Polymorphic B cell lymphoma	13 (33.3)	94 (29.7)		
Monomorphic PTLD	23 (59)	173 (54.7)		
Hodgkin's lymphoma	2 (5.1)	32 (10.1)		
Lymphoma cell type; B cell (%;vs. T cell)	19 (95)	171 (88.6)	0.704	213
EBV status (%)	26 (65)	196 (71.3)	0.459	315
Mortality (%)	18 (39.1)	165 (50.8)	0.09	371
Remission episode (%)				
Author defined	19 (86.4)	115 (69.3)	0.07	188
Based on the specified criteria in methods	25 (71.4)	164 (62.6)	0.204	297
Use of induction therapy (%)	9 (56.3)	97 (61.4)	0.79	174
Allograft			0.793	457
Kidney (including pancreas–kidney tx)	18 (33.3)	169 (41.9)		
Liver	19 (35.2)	103 (25.6)		
Heart	9 (16.7)	85 (21.1)		
Lung	6 (11.1)	33 (8.2)		
Cell transplant	2 (3.7)	15 (3.2)		

*According to the criteria defined in the methods section; PTLD: Post-transplant lymphoproliferative disorders, EBV: Epstein Barr Virus, **IS; Immunosuppression

sub-groups were looked for by using χ^2 and Fishers' exact tests for proportions, and the Student's t test for continuous data. Survival analysis was calculated with life tables and Kaplan–Meier methods as well as the log–rank test. All statistical tests were performed at the 0.05 significance level. *P*-value below 0.1 was considered relevant.

Results

Overall, 472 patients with lymphoproliferative disorders after organ transplantation were entered into the analysis. There were 192 male (64%) and 108 female patients (36%, 172 unreported). The mean age at diagnosis of PTLD was 34.1 ± 21.1 years. The mean interval between transplantation and the diagnosis of PTLD was 49 ± 50.9 months and the mean duration of follow-up after diagnosis of PTLD was 22.3 ± 29.8 months.

The characteristics of the patients regarding the site of malignancy are summarized in Table 2. The Chi square test showed that there was no difference between organ recipients with or without gastric PTLD regarding histopathological features, demographics, lymphoma cell types, immunosuppressive agents used, presentation time, multi-organ involvement, disseminated PTLD and EBV positive rate. Age at the time of transplantation and the interval between transplantation and development of PTLD were also comparable between the two groups. Table 3 summarizes the involvement of different organs by PTLD, with or without concomitant involvement of the intestine. Gastric PTLD was

Table 3. Frequency of concomitantly involved organs in transplant patients with post-transplant lymphoproliferative disorders enrolled in this study.

Involved organs	Gastric PTLD	Controls	Sig.
Orbit	1 (2)	2 (0.6)	0.355
Skeleton	0	6 (1.9)	0.58
Skin	0	12 (3.8)	0.38
Small bowel	13 (25.5)	53 (16.7)	0.297
Pancreas	3 (5.7)	26 (8.3)	0.742
Genitalia	0	3 (0.9)	0.729
Central nervous system	2 (3.7)	20 (5.6)	0.753
Spleen	3 (5.9)	32 (10.2)	0.446
Renal involvement	1 (2)	33 (10.3)	0.143
Respiratory system	10 (19.6)	103 (38.9)	0.01
Liver	7 (14)	63 (19.7)	0.575
Bone marrow	5 (10.2)	30 (9.6)	0.8

PTLD: Post-transplant lymphoproliferative disorders

not associated with simultaneous involvement of any other organ.

The survival rates of patients, with and without gastric PTLD, were compared. When death irrespective of the cause was used as the outcome, the log–rank test showed a trend toward a slightly superior outcome for gastric PTLD; however, a significance level was not achieved (P = 0.1; Figure 1). When death only due to PTLD was used as the outcome, no significant difference was observed. The one- and five-year survival rates for gastric PTLD patients were 71% and 54%, respectively, compared with 57% and 38%, respectively, for the control group.

We observed that none of the therapeutic strategies used was associated with a significantly better outcome. The mortality associated with each therapeutic strategy was as follows: One out of six patients (16.7%) who underwent surgical therapy died; mortality rate for rituximab therapy was similar to that for surgery. Also,

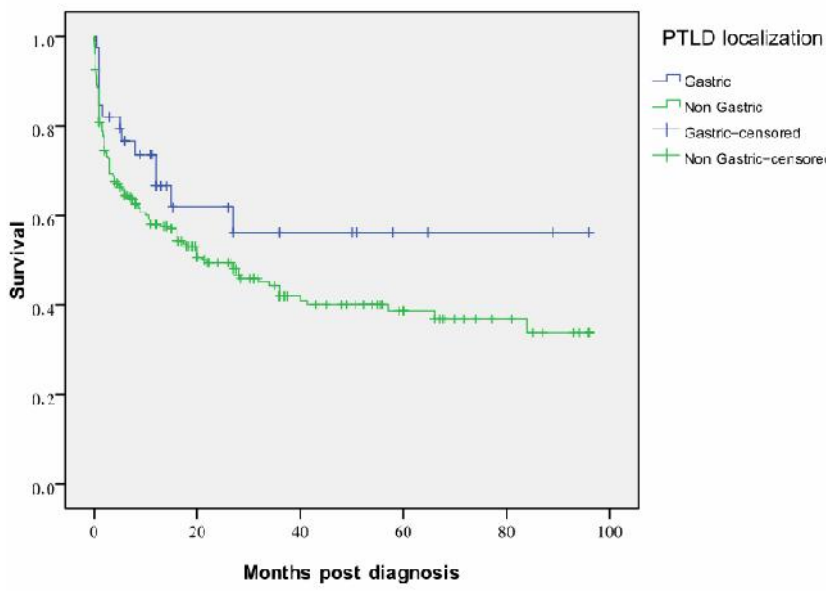

Figure 1. Survival curves of organ recipients developing post-transplant lymphoproliferative disorders within their stomach versus other localizations.

six out of 13 patients (42.6%) who received chemotherapy and 33% of patients who received alfa-interferon and radiotherapy died.

Discussion

Gastrointestinal tract (GIT) localization of PTLD usually presents with obstruction, perforation or hemorrhage and is one of the most, if not the most, frequent sites of involvement in majority of organ transplant recipients, with a reported frequency of up to 100% in children developing lymphomas in their post-transplant course.[1,55-57] Another important aspect of GIT involvement with PTLD is that the presentation often mimics non-malignant diseases.[58] In a vast majority of patients, only non-specific GI symptoms may be present; only biopsy specimen on endoscopic evaluation might reveal lymphoproliferative disorders.[59] Thus, it is suggested that endoscopy and small bowel follow-through should be considered in all transplanted patients with GI symptoms, including chronic diarrhea and abdominal pain.[58]

Most of the PTLD lesions of the GIT occur in the bowels, predominantly small bowel, and the number of reported cases of gastric involvement is extremely limited. This limited number of cases in individual as well as multi-center studies inevitably limits our knowledge on gastric PTLD. The PTLD International Survey is an attempt to gather data on the largest possible PTLD patient population to discover new perspectives on the uncommon and rarely investigated aspects of the disease.[60-62] To the best of our knowledge, the current study is the first to have specifically focused on various characteristics of PTLD, including morphology and clonality, EBV infection status, prognostic factors and efficacy of various treatment strategies employed.

In this study, no correlation was found between PTLD arising in the gastric tissue, compared with other organs, concerning most demographic characteristics, histopathological findings, EBV infection rate and presentation time. Male gender was relatively less frequent among patients who developed gastric PTLD, but the difference was not significant. Further analysis showed that gastric PTLD had a trend toward less vulnerability for developing metastasis.

When survival analysis was conducted, a trend toward better outcome was detected for gastric PTLD. This finding is in contrast to a previous study of ours that showed a low survival rate for patients who develop gastric cancer in the non-transplant population.[63] However, the current study is on patients with PTLD, which is a different issue. Several potential explanations exist for this relatively favorable outcome among gastric PTLD patients: PTLD affecting the stomach may induce signs and symptoms in early stages of the disease, resulting in earlier diagnosis and treatment, and consequently a relatively better outcome. On the other hand, the anatomical location of the stomach as well as its natural defense mechanisms can be another reason for the observation. But, are these findings specific to gastric PTLD?

Surprisingly, a previous study on small intestinal involvement of PTLD revealed findings similar to those for the current report on gastric PTLD.[15] In that study, it was found that renal recipients who develop small intestinal PTLD had comparable demographics, and they also had a relatively better outcome and lesser metastasis than PTLD in other localizations; the difference was not statistically significant. Thus, our combined data might suggest that PTLD developing in the GIT might carry better survival than other localizations; this conclusion must be considered cautiously and warrants further studies.

Additionally, different treatment strategies that were employed to manage gastric PTLD were analyzed to determine whether any specific protocol promises a significantly better outcome compared with other therapies. Judgment, based on the outcome of patients who have received different therapeutic regimens, is very controversial; it is quite logical that physicians would have decided to employ different treatment protocols for patients in different conditions. Thus, a bad outcome in patients who had received chemotherapy does not mean that chemotherapy has minimal or no favorable effect

on patients' outcome. In the current study, although survival analysis showed no signify-cant advantage for any specific therapy over others, surgery and rituximab were associated with low mortality (17%; both) while chemo-therapy was associated with poorer survival rates.

There are some limitations associated with our study. Our study included patients from differ-ent reports who were under treatment in differ-ent centers. This might imply that comparing data of these patients can be associated with bias. For example, the cause of mortality might not be uniformly represented in different stu-dies. Accepting these criticisms, we re-acknow-ledge that in this study, we standardized data of patients before enrolling them into the analysis. We believe that this standardization has effec-tively made data of our study comparable. Moreover, in data such as metastasis and demo-graphics, a center effect may not play a major role. Nevertheless, despite the limitations, we believe that our findings on gastric involvement by PTLD can be used for day-to-day practice.

In conclusion, this study revealed that organ recipients presenting with gastric PTLD have a trend toward less-frequent development of metastasis, and hence might carry a relatively more favorable outcome. Prospective studies with a larger patient population are needed to confirm or modify our results.

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