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Brief Communication

Colorectal Involvement by Post-Transplant Lymphoproliferative Disorders: A Review of 81 Cases

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ABSTRACT. The reported number of patients representing post-transplant lymphoproliferative disorders (PTLD) within the colorectal region is quite limited. In this study, we sought to analyze and compare the characteristics, predictors and prognosis of colorectal localization of PTLDs arising in transplant recipients. A comprehensive search was performed through Pubmed and Google scholar to find case reports and series of colorectal localization of PTLD. Data of each individual patient from different studies were entered into a database and analyzed. Colorectal PTLD was significantly more prevalent in male patients (19.3% vs. 8.5%, respectively; $P = 0.002$) and represented a significantly shorter time to diagnosis than other localizations ($P = 0.044$). Multi-organ involvement (75% vs. 46%, respectively; $P < 0.001$) and disseminated disease (43% vs. 26%, respectively; $P = 0.014$) were more frequently observed in the colorectal PTLD. There was no survival difference between the two groups. Organ recipients representing colorectal involvement by PTLD are significantly at higher risk for metastasis, especially in their small intestine. Moreover, patients who underwent surgical intervention had low mortality, and, accordingly, we suggest using surgery to manage colorectal PTLD when it is applicable. Prospective studies with larger patient populations are needed to confirm these results.

Introduction

Post-transplant lymphoproliferative disorders (PTLD) represent a major challenging diagnostic and therapeutic dilemma in organ transplant patients. Several authors from all over the world have reported their experience with the PTLD, indicating a high incidence of the disease among recipients of all types of organs.[1] The use of highly potent immunosuppression and viral infections, most notably Epstein–Barr virus (EBV), are the major predisposing factors in the development of the PTLD.[2-4]

Investigators have suggested that the incidence, time interval, prognosis and presentation of PTLD vary and depend on age of patients, viral infections, immunosuppression intensity, antigen expression and the transplanted organ.[5-8] The incidence of PTLD has been reported to range from 1–20% in the different

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populations.[9-12]

PTLD encompasses a spectrum of clinical manifestations in addition to a wide range of histopathologic findings from B-cell hyperplasia to lymphoma. Lesions primarily occur in the gastrointestinal tract, central nervous system, transplanted organ and, less commonly, lymph nodes.[11,12] However, the reported number of patients representing PTLD within the colorectal region is quite limited and only a small number of cases with histologically proven PTLD arising in the colon and rectum have been previously reported. Because of the limited number of reports on the issue, data scarcity exists on various aspects of colorectal PTLD occurring in transplant recipients.

We aim in this study to analyze the studies and reports from the medical literature and compare the characteristics, predictors and prognosis of colorectal localization of PTLDs arising in allograft recipients.

Patients and Methods

We conducted a comprehensive search for the available data by Pubmed and Google scholar for reports of lymphoproliferative disorders occurring in organ transplant patients within their colorectal region. We searched inside the full text of the articles available in the English medical literature and used keywords including "lymphoproliferative disorders + transplantation + colon," "lymphoproliferative disorders + transplantation + rectum," "lymphoproliferative disorder + transplantation + colorectal," "lymphoproliferative disorder + transplantation + sigmoid," "lymphoproliferative disorder + trans-plantation + caecum," "PTLD + colon," "PTLD + rectum" and "PTLD + caecum." In cases where we were not able to achieve the full text of the articles, e-mails were sent to the correspondent authors requesting the articles. Then, we only included studies in which data of each patient was presented separately and excluded the others.

Lymphoproliferative disorders occurring after transplantation within the colon and rectum were considered as our case group and other transplant patients developing PTLD in other sites were used as controls. A standard questionnaire was developed to collect data from the different published studies. Finally, data from 55 published reports[12-66] were included in the analysis. The time between transplantation and PTLD onset was defined as the period between the graft and the first signs of PTLD or diagnosis. If the PTLD lesion developed before the end of the first year post-transplantation, then the PTLD was considered "early onset," otherwise it was considered as "late onset" PTLD.

Overall, there were 563 recipients of allografts who developed PTLD through their treatment course; of them, 81 (14.4%) patients had colorectal localization of PTLD.

The PTLD patients' status regarding EBV infection was defined according to the results of the serological or polymerase chain reaction (PCR) assays, and it was documented in 429 (76.2%) PTLD patients, of whom 328 (76.5%) were reported positive.

At diagnosis of lymphoma, all patients were receiving immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil and antithymocyte/lymphocyte globulin (ATG/ALG), OKT3, tacrolimus, mTOR inhibitors and alemtuzumab. Very close approach was used to manage the PTLD patients in the included reports; the first step in almost all reports was to decrease or discontinue immunosuppressive therapy, and different regimens of chemotherapy with or without surgical interventions were also used in some of patients.

Response to treatment was defined as any favorable change in the cancer measures as well as patients' clinical condition; data of PTLD on treatment were reported by authors for 186 (33%) patients, of whom 130 (69.9%) responded to therapy. A remission episode was defined as patients being alive after their 24th month of PTLD diagnosis (as all reported cases having this criterion had at least one confirmed remission episode) and no remission was defined as patients dying within the first month post-PTLD diagnosis (because among reported cases there were no patients who died at the first post-transplant month and reported to have any remission episodes). According to these criteria,

Table 1. Characteristics of organ transplant recipients with colorectal PTLD versus other PTLD localizations.

Variables	Colorectal PTLD	Controls	Sig.	Available data
Age (year)	33.9 ± 21.1	32.7 ± 21.5	0.655	438
Gender, male (%)	51 (77.3)	213 (57)	0.002	440
Time to PTLD development (months)	37.0 ± 47.1	49.7 ± 49.9	0.044	488
Multi-organ involvement (%)*	50 (74.6)	117 (46.1)	<0.001	451
Disseminated PTLD (%) *	23 (42.6)	84 (25.8)	0.014	379
Morphology			0.238	404
Early lesion (plasmacytic hyperplasia)	1 (1.8)	23 (6.6)		
Polymorphic B cell lymphoma	18 (31.6)	119 (34.3)		
Monomorphic PTLD	36 (63.2)	180 (51.9)		
Hodgkin lymphoma	2 (3.5)	25 (7.2)		
EBV status (%)	48 (76.2)	280 (76.5)	1.0	429
Author-defined remission episode (%)	22 (71)	111 (70)	1.0	189
Remission; criteria defined (%)	16 (41)	78 (31.8)	0.275	284
Monoclonal lesions vs. polyclonal (%)	10 (83.3)	55 (64)	0.328	98
Lymphoma cell type B cell (%)	34 (91.9)	205 (94.5)	0.438	253
Use of induction therapy (%)	11 (45.8)	130 (75.6)	0.006	196

281 (50%) patients had data on remission, of whom 187 (66.5%) had at least one response to treatment, irrespective of their future disease behavior. Overall mortality was 201 patients (53.7% of the reported cases; 189 patients had missing data); death due to PTLD was defined when (1) authors stated it or (2) patient died within six months post-diagnosis unless the authors stated other causes for death, (3) patients died due to PTLD treatment complications. Overall, 127 (63.2% of the whole mortality rate) patients died due to the disease based on the above-mentioned criteria.

Statistical Analysis

We used SPSS v.13.0 software for data analyses. Statistical differences between patients' subgroups were performed by using the χ^2 and Fishers' exact tests for proportions and the Student's "t" test for continuous parameters. Survival analysis was performed with life tables and Kaplan–Meier methods and log–rank test. We considered P <0.05 as the level of significance for this study.

Results

Overall, 563 patients with PTLD after organ transplantation were entered into analysis. There were 264 (60%) male and 176 (40%) female patient (123 missing data). Mean age at diagnosis of PTLD was 32.8 ± 21.5 years. The mean interval between transplantation and the diagnosis of PTLD was 48.7 ± 49.8 months, whereas the follow-up time after diagnosis of PTLD was 26.7 ± 35.2 months.

Characteristics of the patients regarding their malignancy site are summarized in Table 1. Chi square test showed that male transplant patients were significantly more likely to develop colorectal PTLD than their female counterparts (19.3% vs. 8.5%, respectively; P = 0.002). Moreover, they had a significantly shorter time from transplantation to diagnosis than other sites of the disease (P = 0.044). Transplant recipients with colorectal PTLD were comparable to their counterparts with other PTLD groups in their age at transplantation (P = 0.655), lymphoma cell types (P = 0.438), lymphoma presentation time from transplantation (P = 0.35), EBV positive rate (P = 1.0), overall mortality rate (P = 0.242), death due to the PTLD (P = 1.0) and histopathological features of the PTLD lesions (P = 0.238).

Multi-organ involvement was significantly more prevalent in patients with colorectal PTLD than the other groups (75% vs. 46%, respectively; P <0.001). Disseminated PTLD was also more frequently seen in the colorectal PTLD than in the

Table 2. Frequency of concomitantly involved organs in transplant recipients with or without colorectal PTLD.

Involved organs	Colorectal PTLD	Controls	Sig.
Orbit	2 (2.6)	4 (0.9)	0.2
Skeleton	2 (2.7)	5 (1.1)	0.492
Skin	1 (1.4)	11 (2.4)	1.0
Stomach	2 (2.9)	18 (4.1)	1.0
Genitalia	1 (1.4)	5 (1.1)	0.595
CNS	4 (5.4)	33 (7.1)	0.805
Spleen	4 (5.5)	35 (7.7)	0.634
Renal involvement	5 (6.8)	40 (8.7)	0.792
Respiratory system	15 (20.5)	80 (17.5)	0.515
Heart	2 (5.7)	7 (3.6)	0.189
Liver	10 (13.2)	77 (16.8)	0.504
Bone marrow	3 (4.2)	37 (8.0)	0.338
Small intestine	22 (29.7)	67 (14.6)	0.002

other groups (43% vs. 26%, respectively; P = 0.014). Table 2 summarizes the different organ involvements by PTLD when they concomitantly complicate the colon and rectum.

The log–rank test did not show any difference between the colorectal PTLD from the other groups in survival (P = 0.853) (Figure 1); however, when death only due to PTLD was used as the outcome, a trend toward better outcome was seen for the colorectal PTLD group compared with the other sites (P = 0.602). The 1- and 5-year survival rates for colorectal PTLD patients were 62% and 42%, respectively, while they were 58% and 37%, respectively, for the control group.

Discussion

We found in this study no specificity for PTLD lesion arising in colorectal regions compared with those developing in other organs regarding histopathological morphology, EBV infection rate and age of the patients, but it was more likely to develop in the male gender. Moreover, patients who received induction immunotherapy were significantly less likely to develop colorectal PTLD. On the other hand, behavior of the disease was very different regarding PTLD sites; the current analysis of the literature showed that colorectal site of the PTLD is associated with a significantly higher

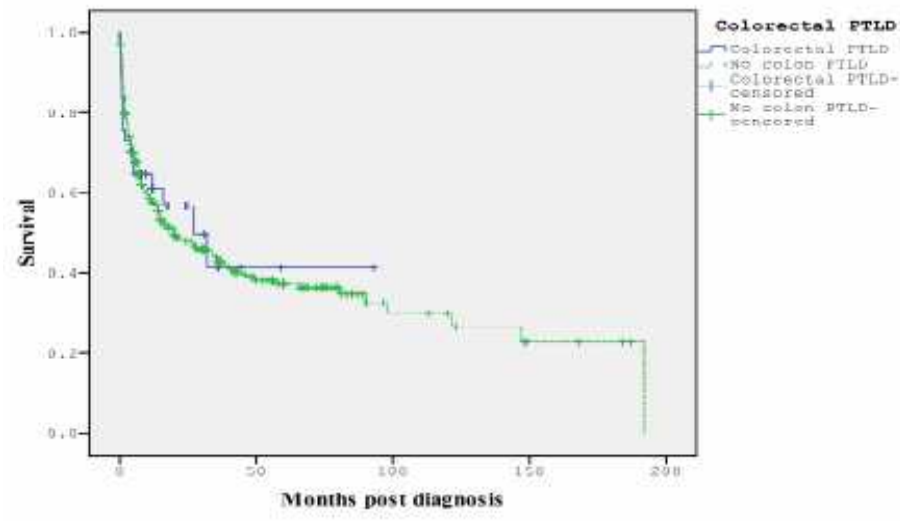

Figure 1. Survival curves of PTLD patients localizing to the colorectal region versus other sites.

rate of multi-organ and disseminated disease. Moreover, colorectal lesions were diagnosed significantly earlier than other disease sites, suggesting a more aggressive and progressive behavior for this disease location. Analysis of different organs simultaneously involved by the disease also showed that the small intestine is significantly more likely to develop in patients who already have colorectal disease. These findings are highly relevant as they necessitate a more cautious approach in any transplant patient with colorectal PTLD for a potential small bowel metastasis.

None of the treatment strategies for the colorectal PTLD resulted in any outcome advantage, although this finding should be interpreted very cautiously. Having a non-favorable outcome for patients who had undergone one therapy does not essentially show that it has minimal or no favorable effect on patients' outcome, as the investigators applied different protocols in an uncontrolled fashion. However, finding a more favorable outcome for patients who had undergone surgical intervention represented 33% mortality, rendering it the management of choice when applicable.

Several criticisms may arise over our study as it included patients from different reports and different centers. This fact may make one assume that comparing data of these patients can be associated with bias. We believe that our standardization has effectively made data of our study comparable. Moreover, in some types of data, including metastasis and demographics, center-effect is quite out of view.

In conclusion, this study found that PTLD organ recipients presenting with colorectal involvement are significantly at risk for multi-organ disease and metastasis, especially in their small intestine. Patients who underwent surgical intervention had a low mortality rate. Therefore, we suggest using surgery to manage colorectal sites of PTLD, when it is applicable. Prospective studies with larger patient populations are needed to confirm our results.

Conflict of interest: None

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