

CD20 Antigen Expression by Lymphoproliferative Disorders after Kidney Transplant is Independently Associated with a Poor Outcome: PTLD.Int Survey

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Abstract

Objectives: Antigen expression by neoplastic cells is important because of its effects on the behavior and survival of patients. We sought to gather data on renal transplant recipients who had developed posttransplant lymphoproliferative disorders in their posttransplant era, and had a documented report on CD20 antigen testing.

Materials and Methods: A comprehensive search of the literature was done for reports that indicate test results for the CD20 antigen in kidney recipients having lymphoproliferative disorders after transplant. Their demographics, disease characteristics, and prognoses were analyzed.

Results: CD20-positive posttransplant lymphoproliferative disorder patients had a significantly shorter time from transplant to developing posttransplant lymphoproliferative disorder ($P < .001$). None of patients who had early onset posttransplant lymphoproliferative disorder was CD20 negative. Bone marrow involvement was significantly more prevalent among CD20-negative patients ($P < .05$) with no CD20-positive patient developing a bone marrow metastasis. Log-rank test showed a relatively worse survival for renal recipients expressing the CD20 antigen ($P = .07$).

Conclusions: CD20-positive posttransplant lymphoproliferative disorder lesions in kidney transplant patients are significantly more likely to develop early after transplant and represent an inferior outcome.

We suggest that all renal transplant recipients who develop posttransplant lymphoproliferative disorder within their early time after surgery should be given anti-CD20 therapy. Future prospective studies are required to confirm our conclusions.

Key words: Cell surface antigens, Renal transplantation, PTLD, Survival, Predictors

Introduction

Posttransplant lymphoproliferative disorder (PTLD) represents a wide spectrum of neoplastic lymphatic proliferations that have come into view in the last 20 years, mostly after the development of highly potent immunosuppressive drugs used to prevent or treat rejection episodes. The first report on this entity was published by Penn and associates¹ in a patient who had undergone living-related renal transplant in 1969. Since then, several reports have been published indicating a high incidence of PTLD among recipients of all types of organs including the kidney. Besides the immunosuppression used, other factors including the Epstein-Barr virus (EBV) also have been shown to play causative roles in the pathogenesis of PTLD.²⁻⁴

The reported the incidence of PTLD in different transplant populations as variable, with a lower rate of occurrence in kidney graft recipients, and highest incidences in multivisceral transplant patients. The incidence of PTLD in renal transplant is considered intermediate and is usually about 1% to 1.5%. Not surprisingly, transplant recipients with a negative serology for EBV are at considerably higher risk of developing PTLD.^{5, 6} Other factors that promote lymphoproliferation in solid organ recipients are the type of transplanted organ, the age of the recipient,

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viral infections other than EBV (eg, hepatotropic viruses), and the recipients' personal vulnerability to develop lymphomas.⁷⁻¹¹

Human cells express several proteins on, in, and within their cell membranes that have a high range of biological functions and can affect their resistance and weakness to several diseases, including PTLD. Several proteins have been identified in human cells, having been proposed relevant in the behavior and prognosis of PTLD. The CD20 antigen is a transmembrane protein located on the surface of mature B cells, but not on hematopoietic stem cells or plasma cells. The CD20 antigen is suggested to be involved in regulating transmembrane calcium conductance and cell-cycle progression during human B-cell activation.¹² Data are scarce regarding the relevance of CD20 expression in tumoral cells in PTLD recipients, and its prognostic value. In the current study, we conducted a comprehensive review of the literature seeking to gather data on renal transplant recipients who developed a PTLD in their posttransplant era, and had documented positive CD20 antigen result, to reveal any specific features, behaviors, or prognoses of CD20-positive PTLD lesions compared to CD20-negative ones.

Materials and Methods

Approach to the study

We performed a comprehensive search of the literature for data by PubMed and Google regarding reports with test results for the CD20 antigen in kidney recipients (representing lymphoproliferative disorders after transplant). Key words used were "lymphoproliferative disorders + renal transplantation + CD20," "lymphoproliferative disorders + renal graft + CD20," "PTLD + CD20 + kidney transplant," and "PTLD + CD20 + renal graft." When we were unable to obtain the full text of the articles, we sent e-mails to the corresponding authors requesting the article. Then, only studies in which data of each patient were presented separately were included. To minimize selection bias, we included only series reporting patients from single or multicenter populations. Reports with any particular selection criterion were excluded. A standard questionnaire was developed to collect data from different reports. Finally, data from 26 previously published studies¹³⁻³⁸ were included in the analysis (Table 1). The time between

transplant and onset of PTLD was defined as *the period between the graft and the first signs of PTLD or diagnosis*, based on the studies' approaches. In all cases, the first PTLD diagnosis was used as the reference. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Table 1. Frequency of Patients Enrolled From Each Study

Studies	Frequency	Percentage
Mamzer-Bruneel, et al.	16	15.5
Jain, et al.	3	2.9
Castellano-Sanchez, et al.	5	4.9
McDonald, et al.	19	18.4
Vakiani, et al.	7	6.8
ISSA, et al.	6	5.8
Phan, et al.	3	2.9
Davis, et al.	2	1.9
Frias, et al.	1	1.0
Rohr, et al.	2	1.9
Oertel, et al.	4	3.9
Ganne, et al.	6	5.8
Gheorghe, et al.	2	1.9
Pitman, et al.	1	1.0
Ziarkiewicz-Wróblewska, et al.	3	2.9
Abe, et al.	1	1.0
Bianchi, et al.	2	1.9
Theate, et al.	1	1.0
Hsi, et al.	1	1.0
Schlieper, et al.	1	1.0
Muzaffar, et al.	1	1.0
Ng, et al.	1	1.0
Orjuela, et al.	2	1.9
Nozu, et al.	2	1.9
Johnson, et al.	3	2.9
Ifthikharuddin, et al.	8	7.8
Total	103	100.0

Study population

Overall, 103 kidney allograft recipients were included in the analysis. A total of 93 patients (90.3%) had a positive result for the CD20 antigen of their PTLD lesions, while the remaining 10 patients (9.7%) had negative CD20 test results.

Owing to inconsistencies of the different studies approaches, we could not acquire all the data from the included patients, and sometimes we had to introduce new standardized measures to accumulate data from different studies into a unique database. Disseminated lymphoma was diagnosed when it was declared by the authors, or when at least 3 different organs (excluding different lymph node areas) were involved with the PTLD (reported in 7 patients [13.7%] and unreported in 52 patients [86.3%]). Multiorgan involvement, defined as *involvement of more than a unique organ as well as more than 1 lymphatic region*, was available in 21 patients ([38.2%]; 48 unreported [61.8%]).

At lymphoma diagnosis, all patients were receiving or had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, antithymocyte/lymphocyte globulin, and muromonab-CD3 (OKT3). A uniform approach was used to manage all PTLD patients in the included reports. On diagnosing PTLDs, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; different regimens of chemotherapy, with or without surgical interventions, also were used for some of the patients.

Response to treatment

"Response to treatment" was defined as *any favorable change in the cancer measures as well as the patient's clinical condition*; data of PTLD response to treatment were reported by authors for 44 patients (42.7%) of whom 37 patients (84.1%; 59 unreported) responded to antimalignancy treatment. However, we developed new criteria for defining remission rates for the study population. A "remission episode" was defined *when patients were alive after 24 months since the diagnosis of PTLD* (since, all cases with this criterion had at least 1 confirmed remission episode), and "no remission" was defined *when a patient died within the first month after being diagnosed with PTLD* (because among reported cases, no patients died after the first posttransplant month had any remission episodes). According to the abovementioned criteria, 20 patients were added to the list, and remission episodes reached 49 cases (76.6%). Overall mortality occurred in 30 patients (38.5% of the reported cases; 25 unreported [24.3%]).

Statistical analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 13.0, IBM Corporation, Armonk, New York, USA). Statistical differences between the patients' subgroups were performed using the chi-square and Fisher exact tests for proportions, and the *t* test for continuous data. Survival analysis was done with life tables, Kaplan-Meier methods, and log-rank tests. All statistical tests were performed at the .05 level of significance. *P* values below 0.1 were considered relevant.

Results

Data of 103 renal transplant recipients developing lymphoproliferative disorders were entered in the

analysis. There were 53 male (65.4%) and 28 female patients (27.2%) (22 unreported). Mean age at PTLD diagnosis was 40.6 ± 16.4 years. The mean interval between transplant and PTLD diagnosis was 51.4 ± 60.4 months, whereas follow-up after PTLD diagnosis was 30.2 ± 41.7 months.

The characteristics of the patients regarding their malignancy site are shown in Table 2. The chi-square test showed that CD20-positive PTLD patients had a significantly shorter time from transplant to PTLD development ($P < .001$). None of patients with early onset PTLD were CD20 negative.

Table 2. Characteristics of PTLD Renal Recipients Regarding CD20 Positive and Negative Results

Variables	CD20 Positive	CD20 Negative	P	Available Data
Age (y)	40.9 $\pm$ 16.4	37.7 $\pm$ 17.4	.579	83
Pediatric (%)	25 (26.9)	1 (11.1)	.442	102
Sex male (%)	45 (62.5)	8 (88.9)	.151	81
Time to PTLD development (mo)	44.4 $\pm$ 54.8	119.1 $\pm$ 73.9	< .001	96
Multiorgan involvement (%)*	18 (38.3)	3 (37.5)	1.0	55
Disseminated PTLD (%)*	6 (13.3)	1 (16.7)	1.0	51
Remission episode (%)	43 (78.2)	6 (66.7)	.427	64
Use of induction therapy	32 (78)	3 (50)	.164	47
Early onset (within first 12 months after TX)	40 (46)	0	.009	96
EBV positive (%)	44 (67.7)	6 (60)	.794	75
Histopathologic evaluation				
All together			.2	48
Polymorphic lymphoma	13 (31)	0		
Monomorphic lymphoma	19 (45.2)	3 (50)		
Hodgkin lymphoma	10 (23.8)	3 (50)		

*According to the criteria defined in the Materials and Methods section

Abbreviations: EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorder; TX, treatment

We entered patients in a linear regression for time from transplant to development of PTLD based on their CD20 test result. CD20 was significantly associated with time to PTLD ($P < .001$; $B=74.7$; 95% CI: 35.3-114). Further analyses showed that only EBV positivity—besides CD20 positivity—was significantly associated with earlier onset PTLD. A multivariable linear regression showed both of them are significantly associated with a shorter time to PTLD (Table 3). CD20-positive PTLD patients were comparable with their CD20-negative counterparts regarding age, sex, immunosuppression type, histopathologic phenomena of PTLD lesions, remission rates, multiorgan involvement, and disseminated PTLD rates. Epstein-Barr virus

Table 3. Linear Regression Analysis for Factors Significantly Associated with Time to PTLD Development

Model	Unstandardized Coefficients		Standardized Coefficients	P	95% Confidence Interval for B	
	B	Standard error			Lower boundary	Upper boundary
EBV	44.663	13.966	0.350	.002	16.771	72.555
CD20	55.675	20.535	0.296	.009	14.664	96.686

Abbreviations: EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorder

positivity rates also were comparable between the patient groups.

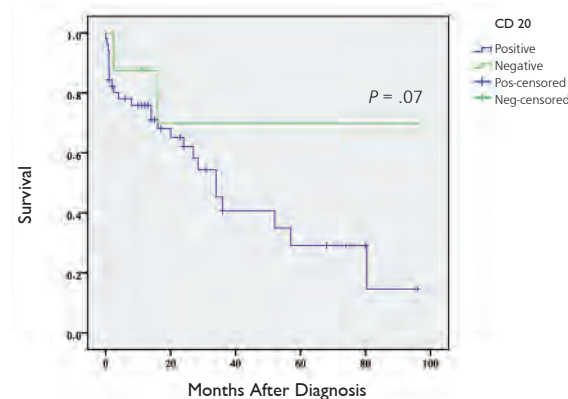
Table 4 summarizes organ involvement frequencies in the patient groups. Table 4 shows no priority in organ complications regarding CD20 positivity, unless there was bone marrow involvement significantly more prevalent among CD20-negative patients. At last follow-up, 30 patients (38.5%) were dead (25 unreported [24.3%]). When death (irrespective of the reason) was used as the final outcome, a log-rank test showed a relatively worse survival for renal recipients representing CD20 antigen expression—although not significant, it was borderline ($P = .07$; Figure 1). One- and 5-year survival rates for PTLD patients with CD20-positive results were 76% and 34%, compared with 87% and 71% for CD20-negative PTLD patients.

Table 4. PTLD Organ Involvement with Respect to Their CD20 Test Result

Organ Involved by PTLD	CD20 Positive (%)	CD20 Negative (%)	P
Skeleton	1 (1.9)	1 (11.1)	.275
Spleen	0	1 (11.1)	.155
Colon	4 (7.7)	2 (22.2)	.212
Small intestine	7 (13.5)	3 (33.3)	.157
Kidney	5 (9.6)	0	1.0
Liver	7 (13.5)	0	.58
Respiratory system	5 (9.6)	0	1.0
Bone marrow	0	2 (22.2)	.023
Skin	1 (2)	1 (11.1)	.28
Stomach	5 (10)	0	1.0
Central nervous system	13 (21.3)	1 (10)	.674

Discussion

Transplant patients are at a substantially increased risk of developing lymphomas, and it is postulated that the type and degree of immunosuppression, viral infections, and the type of allograft play major roles in this enhanced risk.^{39, 40} It also has been demonstrated that PTLD features and behaviors are associated with personal vulnerability of patients. However, the specific characteristics of each patient that can predict different disease patterns have not been widely investigated. The main reason for this paucity of data is the limited number of patients who have similar disease characteristics as well as personal specifications that let us enter them into a data analysis.

Figure 1. Survival Curves of Renal Recipients Developing PTLD Regarding Their CD20 Antigen Expression

Abbreviations: PTLD, posttransplant lymphoproliferative disorder

Previous studies have proposed several factors that play major roles in the presentation and outcome of PTLD. We focused on CD20 antigen expression in renal allograft recipients developing PTLD in the posttransplant era. Data exist in the literature regarding this study have been rarely investigated, and the existing data that was gathered through the literature review represents the largest population ever studied. The PTLD.Int survey is an attempt to accumulate international data from published reports on the largest PTLD patient population to discover new perspectives on the disease, most especially on the rare aspects.

B-cell lymphoma represents a majority of the non-Hodgkin lymphoma cell types and expresses the classic B-cell markers including the CD20 antigen, which normally can be found on B lymphocytes.⁴¹ The CD20 antigen is a membrane protein of B cells that is known to play a role in B-cell activation, differentiation, and cell-cycle progression.^{42, 43} CD20 protein expression, as determined by flow cytometry, is heterogeneous between different lymphoma subtypes and may be considered a predictor for responsiveness to specific drug therapy.^{44, 45} However, all these studies have been conducted in a nontransplant context, and as we stated before, data on the transplant population of the same organ are extremely limited. Our study is the first study to provide data on the relevance of

CD20 antigen expression in renal graft recipients developing PTLT.

We found that renal recipients developing CD20-positive PTLT lesions represent a significantly shorter time from transplant to PTLT diagnosis than those of their CD20-negative counterparts. In fact, none of the CD20-negative PTLT cases were of early onset (representing the first posttransplant year). An interesting issue on this is that in a prior review of the literature for CD20 antigen expression in liver graft recipients, we found the same finding, and all the early onset PTLT cases were from the CD20-positive group. Taken together, the evidence is powerful regarding the association between CD20 positivity and the time of PTLT presentation. A multivariate analysis showed that for a simultaneous CD20 test, EBV positivity is also associated with an earlier onset of PTLT in renal recipients. Considering this finding, one may presume that one could start anti-CD20 therapy for all renal recipients developing early onset PTLT. However, future studies are required to confirm this conclusion.

The prognostic significance of CD20 expression in PTLT patients has been investigated before. In the nontransplant era, Tzankov and associates⁴⁶ have shown superior survival for Hodgkin lymphoma patients with CD20+ PTLT lesions. In transplant practice, Orjuela and associates⁴⁷ also have suggested better survival for CD20+ PTLT patients compared with their CD20-negative counterparts. However, in the current study, we found an opposite finding for renal recipients, with a relatively lower outcome for patients developing CD20+ PTLT lesions. Rassidakis and associates,⁴⁸ analyzing 598 previously untreated lymphoma patients for the prognostic significance of CD20 expression, found no association between antigen expression and survival in patients treated with equivalent regimens. The same finding was reported by Molot and associates,⁴⁹ who reported no effect for CD20 expression on clinical outcome. In the current study, 2 of our findings might be considered predictors for a better outcome for CD20-positive PTLT patients: the higher share of early onset PTLT and the lower rate of bone marrow involvement. However, a previous study of ours showed no survival advantage for early onset PTLT in renal recipients,⁵⁰ but bone marrow involvement was a predictor for lower outcome (unpublished data). Our finding about the inferior outcome of PTLT in renal recipients expressing the CD20 antigen on their

tumor cells cannot be explained by simultaneous characteristics and seems to be independent. Further studies are required to confirm our findings.

This study has several limitations. First, data for this study were gathered from different reports that had inconsistent approaches. To overcome this and have a straight database, we standardized our data and made them in a unique way. For example, different studies used various methods to report remission episodes, while some of them used terms like "complete or partial remissions," others talk only about "a remission episode," and others reported what happened to their patients (ie, changes in tumor size and general conditions). In this case, we categorized the term into 2 subcategories: "remission" and "no remission." When authors reported any positive reaction to therapy, we used the term *remission*, and when the disease progressed, we used the term *no remission*. Other standardized policies we used are described in the Materials and Methods section.

In this study on the relevance of CD20 antigen expression in renal transplant recipients developing PTLT, using a relatively large patient population, we showed that CD20-positive PTLT lesions in kidney transplant patients are significantly more likely to develop in the early time after transplant and represent inferior outcome. We suggest that all renal transplant recipients who develop PTLT within their first posttransplant time should be given anti-CD20 therapy. Future prospective studies are required to confirm our conclusions.

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