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## *Letter to the Editor*

# Significance of CD20 Expression by Lymphoproliferative Lesions Developing after Liver Transplantation: Post-transplant Lymphoproliferative Disorders International Survey

*To the Editor,*

Post-transplant lymphoproliferative disorders (PTLD) encompass a wide range of abnormal lymphatic proliferations and have become more and more clinically relevant in the recent two decades due to the use of new highly potent immunosuppressive drugs. Besides the immunosuppression employed, Epstein Barr virus (EBV) has also been demonstrated to play a major causative role in the pathogenesis of PTLD as it has been detected in up to 90% of PTLD lesion cells.[1,2] Other factors that have been found to be associated with lymphoproliferation in solid organ transplant recipients are younger age of the recipient, viral infections other than EBV (e.g., hepatophil viruses) and the recipients' personal vulnerability to developing lymphomas.[1,2]

The reported incidence of PTLD in different transplant populations is extremely varied, with a relatively lower rate of occurrence in renal transplant patients and highest incidences in multi-visceral graft recipients. The incidence of PTLD in liver transplantation is considered to be low to intermediate and about 1.5–3%, with EBV-negative transplant recipients being at a considerably higher risk of developing a PTLD.[3,4]

Human cells express several proteins on and in their cell membranes that can affect their resistance and weakness to several diseases, including PTLD. Several proteins have been identified in human cells that have been reported 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 involved in the regulation of transmembrane calcium conductance and cell-cycle progression during human B-cell activation.[5]

The data available regarding the relevance of CD20 expression in the tumoral cells in PTLD recipients and its potential prognostic effect is very limited. However, due to the small number of cases and the inconsistencies, the findings of the only study we found in the literature are not totally acceptable.[6] For example, it is known that prognosis of a kidney or liver recipient after developing PTLD is better than that for heart recipients.[7] Therefore, the data from the analysis of a limited number of patients who received different types of organ transplantation is not entirely reliable.

We conducted a study by performing a very comprehensive review of the literature, aiming to find and garner data on liver recipients who have developed a PTLD in their post-transplant period, and had a documented report on CD20 antigen testing results. This large data was analyzed to reveal any potential specific features, behavior and prognosis of CD20-positive PTLD lesions compared with those of CD20-negative ones.

A comprehensive search of the literature was conducted for the available data using the Pubmed and Google scholar search engines on reports indicating test results for CD20 antigen among liver transplant recipients who developed lymphoproliferative disorders. Keywords used for this purpose were "lymphoproliferative disorders + liver transplantation + CD20," "lymphoproliferative disorders + liver graft + CD20," "PTLD + CD20 + Liver transplant," "PTLD + CD20 + liver graft." In cases for which we were not able to retrieve the full text of the articles, we sent e-mails to the correspondent authors requesting for the article. To minimize selection bias, we only included studies reporting their series of patients from single or multicenter populations and studies with any specific selection criterion were excluded from the analysis. A standard questionnaire was developed to collect data from different published studies. Finally, data from 32 previously published studies from various countries[8-39] were obtained and was taken up for analysis. The time between transplantation and PTLD onset was defined as the period between the graft transplant surgery and the first signs or diagnosis of PTLD.

Overall, 121 recipients of hepatic allograft were included into analysis. One hundred six (87.6%) patients of the study population were patients with a positive result for CD20 antigen of their PTLD lesions, while the remaining 15 (12.4%) patients were CD20.

Because of the inconsistencies existing in the approaches of different studies, we were not able to get all the data we needed from all the included patients, and in some cases we had to introduce new standardized measures to be able to gather data from different studies into a unique database. Disseminated lymphoma, diagnosed when it was declared by the authors or at least three different organs (excluding different lymph node areas) were involved by PTLD, were reported in 20 (16.5%; 34 unreported) patients. Multiorgan involvement, defined as involvement of more than a unique organ as well as more than one lymphatic region, was found in 46 (46.5%; 22 unreported) patients.

At lymphoma diagnosis, all patients were receiving and had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil and antithymocyte/lymphocyte globulin (ATG/ALG) and OKT3. More or less, a rather uniform approach was used to manage all PTLD patients in the included reports. After the diagnosis of PTLDs, 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 of the patients.

Response to treatment was defined as any favorable change in the cancer measures as well as patients' clinical condition; data of PTLD response to treatment was reported by the authors for 65 (53.7%) patients, of whom 54 (83.1%; 56 unreported) patients responded to anti-malignancy treatment. However, we developed new criteria for defining remission rates for the study population; while a remission episode was defined when patients were alive after their 24$^{th}$ month of PTLD diagnosis (because all reported cases having this criterion had at least one confirmed remission episode) and no remission was defined when a patient died within the first month post-PTLD diagnosis. According to the abovementioned criteria, eight patients were added to the list and remission episodes reached to 62 cases (84.9% of the study population). The overall mortality was 35 (39.8% of the reported cases; 33 unreported) patients; death due to PTLD was defined when (1) if authors state it, (2) when patient dies within six months post-diagnosis or (3) when patients die due to PTLD treatment complications. Nineteen (54.3% of the overall mortality rate) patients died due to the disease based on the abovementioned criteria.

Software used for data analyses was SPSS v.13.0. Statistical differences between patients' subgroups were performed by using $\chi^2$ and Fishers' exact tests for proportions and the Student's t test for continuous data. Survival analysis was performed with life tables and Kaplan–Meier methods and log-rank test. All

Table 1. Characteristics of PTLD patients with CD20-positive and -negative results

| Variables | CD20 positive | CD20 negative | Significance | Available data |
|---|---|---|---|---|
| Age (years) | 43.6 ± 19.1 | 25.5 ± 24.2 | 0.014 | 101 |
| Pediatric (%) | 13 (14) | 4 (50) | 0.026 | 101 |
| Gender male (%) | 50 (56.8) | 6 (85.7) | 0.234 | 95 |
| Time to PTLD development (months) | 39 ± 48.2 | 94.5 ± 63.6 | 0.003 | 89 |
| Multiorgan involvement (%)* | 39 (46.4) | 7 (46.7) | 1.0 | 99 |
| Disseminated PTLD (%)* | 15 (20.5) | 5 (35.7) | 0.296 | 87 |
| Remission episode (%) | 56 (85) | 6 (85.7) | 1.0 | 73 |
| Use of induction therapy | 16 (37.2) | 5 (62.5) | 0.249 | 51 |
| Early onset (within the first 12 months post Tx) | 39 (44.3) | 0 | 0.02 | 96 |
| EBV positive (%) | 50 (72.5) | 9 (60) | 0.362 | 84 |
| Histopathological evaluation | | | | |
| All together | | | 0.002 | 92 |
| Polymorphic ly. | | 21 (26.6) | 3 (23.1) | |
| Monomorphic ly. | | 57 (72.2) | 7 (53.8) | |
| Hodgkin's ly. | | 1 (1.3) | 3 (23.1) | |

*according to the criteria defined in the methods section, **IS; immunosuppression

statistical tests were performed at the 0.05 significance level.

Data of overall 121 liver transplant recipients developing lymphoproliferative disorders were entered into analysis. There were 56 (58.9%) males and 39 (41.1%) females (26 unreported). Mean age at diagnosis of PTLD was 42.2 ± 20 years. The mean interval between transplantation and the diagnosis of PTLD was 44 ± 51.9 months, whereas the follow-up time after the diagnosis of PTLD was 34.3 ± 42 months.

Characteristics of the patients regarding their malignancy site are summarized in Table 1. Chi square test showed that CD20-positive PTLD patients were significantly older at the time of transplantation ($P$ = 0.014), but they had a significant shorter time from transplantation to PTLD development ($P$ = 0.003). None of the patients who had an early-onset PTLD were CD20 negative. Moreover, patients with a positive CD20 test result were more likely to have lesions with monomorphic histopathological features, but less frequently had Hodgkin's disease ($P$ = 0.002).

CD20-positive PTLD patients were comparable with their CD20-negative counterparts regarding their immunosuppression types ($P$ = 0.249), multiorgan involvement ($P$ = 1.0) and

Table 2. PTLD organ involvement with respect to their CD20 test result.

| Organ involved by PTLD | CD20 positive | CD20 negative | Significance |
|---|---|---|---|
| Skeleton (%) | 4 (4.7) | 0 | 1.0 |
| Spleen (%) | 7 (8.9) | 4 (26.7) | 0.071 |
| Colon (%) | 15 (18.8) | 2 (13.3) | 1.0 |
| Small intestine (%) | 10 (13.2) | 4 (28.6) | 0.22 |
| Kidney (%) | 5 (7.4) | 1 (7.1) | 1.0 |
| Liver (%) | 26 (28.6) | 6 (40) | 0.377 |
| Respiratory system (%) | 11 (13.9) | 3 (21.4) | 0.437 |
| Bone marrow (%) | 7 (9.5) | 3 (21.4) | 0.194 |
| Orbit (%) | 1 (1.2) | 1 (7.1) | 0.262 |
| Skin (%) | 1 (1.3) | 0 | 1.0 |
| Stomach (%) | 5 (6.7) | 3 (21.4) | 0.108 |
| Genitalia (%) | 2 (2.5) | 1 (7.1) | 0.384 |
| Central nervous system (%) | 3 (3.2) | 1 (6.7) | 0.455 |

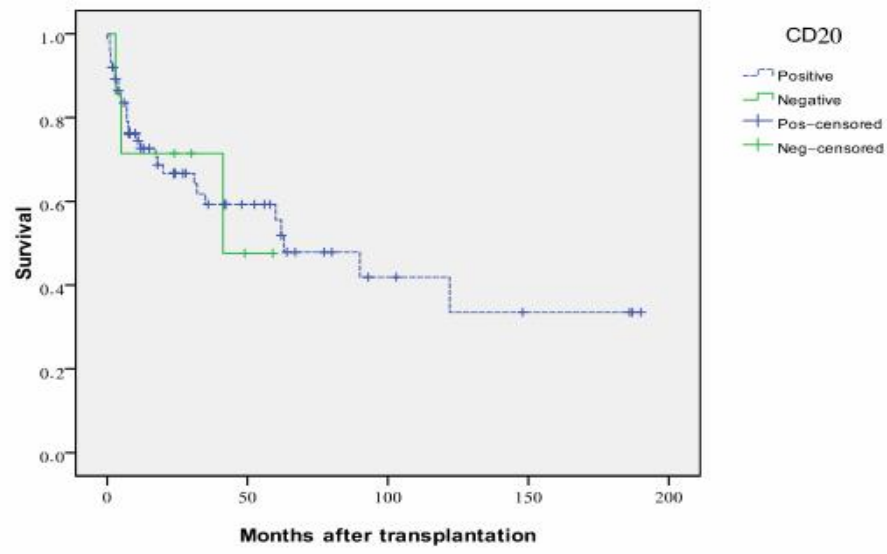


Figure 1. Survival curves of liver transplant recipients developing PTLD regarding their CD20 test result.

disseminated PTLD ($P$ = 0.296) rates. The EBV positivity rate were also comparable between the two patient groups.

Table 2 summarizes the frequencies of organ involvement in the two patient groups. As evident in Table 2, no difference was found in the involvement of the organs related to CD20 positivity. At the last follow-up, 35 (28.9%) patients were dead (33 unreported). When death, irrespective of the reason, was used as the final outcome, the log-rank test did not show any difference between the two groups in their survival ($P$ = 0.841; Figure 1); the same finding was also seen when death specifically due to PTLD was used as the final outcome and deaths with non-related reasons were censored ($P$ = 0.647). The one and five years survival rates for PTLD patients with CD20-positive results were 73% and 59%, respectively, compared with 71% and 48%, respectively, for CD20-negative PTLD patients.

It is known that PTLDs are one of the most prevalent neoplasms among solid organ recipients, lowering both graft and patient survival.[40-42] Previous studies have proposed several factors that are supposed to play major roles in the presentation and outcome of PTLD.[43-46] CD20 protein expression is very heterogeneous between different lymphoma subtypes and possibly can act as a predictor to drug therapy.[47-51] Most of the earlier studies have been performed in a non-transplant context. Our data represents virtually a primary data on the relevance of CD20 positivity in PTLD complicating liver graft recipients, and we focused our study on CD20 antigen expression in PTLD lesions developing in these patients.

In this study, we found that liver recipients developing CD20-positive PTLD lesions are significantly older at the time of transplantation, and they also had a shorter time from transplantation to PTLD diagnosis than those in their CD20-negative counterparts. The higher percentage of older liver recipients in the CD20+ group looks ominous because PTLD in older transplant patients is usually associated with inferior outcome.[52,53] On the other hand, CD20+ PTLD lesions developed early during the post-transplantation period. In fact, there was no case of early-onset PTLD (presenting within the first post-transplant year) in CD20-negative patients. This can promise a survival advantage for CD20+ PTLD patients, because late-onset PTLD is generally considered as having a non-favorable outcome. Based on this finding, one may assume that we might be able to start anti-CD20 therapy for all liver recipients developing early-onset PTLD. But, future studies are needed

to further evaluate this conclusion.

The prognostic significance of CD20 expression in PTLD patients has been investigated before. In the non-transplant era, Tzankov et al[54] have shown a superior survival for Hodgkin's lymphoma patients with CD20+ positive lesions. In transplantation practice, in a very recent study, Orjuela et al[6] has also suggested a better survival for CD20+ PTLD patients compared with their CD20-negative counterparts. However, in the current study, we did not detect any survival advantage for liver recipients developing CD20+ PTLD lesions. Similar to our study, Rassidakis et al,[55] 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 et al,[56] who reported no effect of CD20 expression on clinical outcome. However, we should note that they were in non-transplant patients, and results in transplant patients might be different.

In this study, we also found that histological features of PTLD lesions are different regarding their CD20 gene expression, with a higher rate of monomorphic phenomenon but a lower rate of Hodgkin's disease in the CD20+ group. This also predicts a non-favorable outcome for the CD20+ PTLD group. However, analyzing all possible aspects of CD20+ PTLD patients, their overall disease characteristics do not support a superior or inferior outcome for liver recipients regarding their CD20 antigen expression.

This study has several limitations. First of all, the data for this study was gathered from different reports having inconsistent approaches. For overcoming this issue and have a straight database, we standardized our data and made them in a unique way.

This study, using a very large patient population, showed that liver transplant patients who develop CD20-positive PTLD lesions are significantly older at the time of transplantation and the lesions are more likely to develop in the early post-transplantation period and represent monomorphic feature. We suggest that, although the overall picture does not support a superior or inferior outcome for liver recipients regarding their CD20 antigen expression, all liver transplant recipients who develop PTLD within their first post-transplantation year should be given anti-CD20 therapy; moreover, PTLD in liver recipients with older age can also be another target for this therapy. Future prospective studies with larger numbers are needed to further evaluate these findings.

## Conflict of Interest

There is no conflict of interest among authors of this study. This study has not been published or is not under consideration anywhere else, in full or in part.

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