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Clinical Considerations In Pediatric Patients Undergoing Liver Transplantation With A Diagnosis Of Post-Transplant Lymphoproliferative Disease In A Latin American Fourth-Level Hospital: A Descriptive Observational Historical Cohort Study (2007-2020)

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Abstract

Purpose: Post-transplant lymphoproliferative disease (PTLD) encompasses a spectrum of lymphoproliferative syndromes that develop as complications following solid organ or hematopoietic cell transplantation, leading to liver involvement from 9.7% to 20% of pediatric cases. Its distribution exhibits a bimodal pattern, with a peak occurrence during the first-year post-transplant associated with primary Epstein-Barr virus (EBV) infection, followed by a second peak after 5 years attributed to other causes in 50% during this period.

Methods: A descriptive observational historical study was conducted on a cohort of patients under 18 years of age who underwent liver transplantation at Fundación Cardioinfantil – La Cardio (Bogotá, Colombia) between 2007 and 2020. Anthropometric variables, primary liver disease, donor type, serological status, immunosuppression regimen, clinical manifestations, PTLD subclassification, and other relevant factors were considered in the study.

Results: Out of the 216 cases examined, 18 (8.3%) were confirmed to have PTLD. Women accounted for 61.1% and the median age at the time of PTLD diagnosis was 2.68 years (IQR: 2.58 – 3.08). The primary cause of liver transplantation was biliary atresia in 83.3%, and living donors contributed 88.8% of transplanted organs. Active EBV infection was documented in only two recipients at the time of transplantation. During PTLD diagnosis, 88.8% of patients presented an alteration in EBV viral load. According to the 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, 12 cases were identified as Florid Follicular Hyperplasia and 6 cases as Monomorphic PTLD.

Conclusion: Data regarding the incidence and prevalence of PTLD following liver transplantation in Latin American children is limited; however, this study revealed prevalence rates comparable to those reported in the literature for other contexts. There is a pressing need for multicenter randomized clinical trials on a national and international scale. These trials would enable controlled exposure, offering more precise insights into the causal relationship and identification of triggering risk factors.

Keywords: Liver transplant, Lymphoma, Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection

Introduction

The term Post-Transplant Lymphoproliferative Disease (PTLD) was introduced by Starzl et. al. (1984) (1) and is currently defined as a group of lymphoproliferative syndromes, predominantly involving B cells, linked to immunosuppression. It emerges as a complication following a solid organ or hematopoietic cell transplant due to loss of control in immune regulation in cases of viral infection (2). Its worldwide prevalence ranges from 1% to 20% in solid organ transplants and from 1% to 3% in hematopoietic cell transplants, primarily affecting the intestine in 32% of cases (3). Specifically, in cases of PTLD in pediatric patients with liver transplants, the incidence is reported to be between 9.7% and 20%, with a higher occurrence during the first year after transplantation (4) (5).

PTLD distribution shows a bimodal pattern, with a peak during the first year post-transplant related to primary Epstein-Barr virus (EBV) infection (6) and subsequently at 7-10 years post-transplant (7). This distribution is associated with multiple factors such as the type of transplanted organ, EBV infection reactivation, type and duration of immunosuppression, lymphoid graft load, genetic variations, among others (6) (8).

Historically, the pathogenesis of this disease has been linked to EBV infection. Although, in the second peak of PTLD distribution (>5 years), EBV infection has been documented in less than 50% of PTLD cases. Consequently, other factors have been suggested in relation to PTLD development, including prolonged immunosuppression, advanced age, and exposure to specific agents (7) (9).

However, primary infection or reactivation of EBV holds considerable importance, being described in up to 90% of instances. In the absence of prior exposure, a seronegative recipient becomes susceptible to EBV infection through reactivation from a seropositive donated organ (6). During the acute phase of EBV infection, there is an infection of naive B lymphocytes in the lymphoid tissue of the oropharynx. These B lymphocytes ultimately differentiate into memory cells that persist latent in the body (10). In states of immunosuppression, such as those required after liver transplantation, the absence of a cytotoxic T lymphocyte response and uncontrolled proliferation of infected B cells contribute to the pathogenesis of PTLD (11).

The clinical presentation of PTLD is highly diverse, depending on the affected organ. It can range from asymptomatic or mononucleosis-like conditions to abnormal lymphoid invasion, acute graft rejection, sepsis, multiple organ dysfunction, or even death reported within 100 days post-transplantation in up to 23% of cases (6). Its histopathological classification is established according to the 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (12).

As previously mentioned, there is extensive information on the etiology, risk factors and epidemiology of PTLD worldwide. However, data regarding the epidemiology of this disease in Latin America is limited and, in the specific case of Colombia, completely absent. For this reason, the significance of conducting a descriptive observational study in a Latin American context is justified to identify the factors present in pediatric patients undergoing liver transplantation at the onset of PTLD. The research was conducted at Fundación Cardioinfantil - La Cardio in Bogotá, Colombia, a national and regional reference center for liver transplantation, where more than 250 procedures have been performed in children under 18 years of age during the recent years (13).

PATIENTS AND METHODS

Study design and settings

This descriptive observational historical study was conducted at Fundación Cardioinfantil – La Cardio (Bogotá, Colombia). This study aimed to identify the factors present in pediatric liver transplant patients at the onset of PTLD in this Latin American fourth-level hospital with extensive expertise in pediatric liver transplantation. The study period spanned from 2007 to 2020.

Study population and data collection

We included all post-liver transplant patients under 18 years of age diagnosed with PTLD at Fundación Cardioinfantil – La Cardio from January 1, 2007, to December 31, 2020. We excluded all other patients diagnosed with PTLD in a healthcare institution other than Fundación Cardioinfantil – La Cardio, and whose immunohistochemistry report could not be verified by the institutional pathology group. Additionally, liver transplant patients who underwent loss of follow-up post-transplantation were also excluded.

Data collection

The database of patients undergoing liver transplantation at the medical institution was reviewed from 2007 to 2020. Electronic medical records were reviewed to evaluate the inclusion and exclusion criteria. The dependent variable was Diagnosis of PTLD post-liver transplant. The collected variables encompassed age, sex, weight, health regimen, primary liver disease, type of donor, serological status of the patient, immunosuppression regimen, clinical manifestations, type of diagnosis, lesion status, classification according to the WHO (2017), PTLD subclassification, bone marrow infiltration, central nervous system infiltration, treatment used, viral load for EBV, and dose of immunosuppressant received per kg of weight. Variables with more than 20% missing data were excluded. SPSS statistical software version 21 was used to analyze the information collected.

Histopathological classification

For the analysis of the variable Diagnosis of PTLD post-liver transplant, the 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues was employed (12). This classification is based on histopathological, morphological, immunophenotypic, and molecular characteristics, categorizing it into four distinct groups: a) Non-destructive post-transplant lymphoproliferative disorders type: plasmocytic hyperplasia, infectious mononucleosis-like PTLD and florid follicular hyperplasia, b) polymorphic PTLD (monoclonal or polyclonal), c) monomorphic PTLD and d) classic Hodgkin’s lymphoma-like PTLD (14).

For histopathological findings predating 2017, the diagnoses in the patients' medical records were categorized based on the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (15). Nevertheless, the 2017 classification facilitated the clarification of confusions that arose with the prior classification (12). Adapting the diagnoses identified in this research to the new categorization did not pose any issues leading to losses or changes in the collected information.

Statistical analysis

Statistical analysis included descriptive summary measures to characterize patient attributes. A univariate analysis was conducted, determining both absolute and relative frequencies for qualitative variables. For quantitative variables, Shapiro–Wilk or Kolmogorov-Smirnov tests were conducted to assess the normality of the data. If the data exhibited a normal distribution, the mean with the respective standard deviation was used as a summary measure of central tendency and dispersion. In contrast, if the data did not follow a normal distribution, the median with interquartile range was used.

Bias assessment

An attempt was made to control selection bias by including patients diagnosed with PTLD within the same medical institution where the study was conducted.

Likewise, observer-related information bias was managed through the use of standardized and comprehensible data collection forms. Verification ensured that the recorded information was complete, orderly, and sequential. The study adhered to the quality department's guidelines of the institution, in line with the good clinical practice standards required by the Joint Commission International. During data processing, the information gathered in the collection instrument was transcribed into an Excel database using standard numerical measures for encoding.

Regarding confounding bias, data standardization was performed to manage confounding variables. Stratification of data was deemed unnecessary to preserve the impact, internal validity, and external validity of the study considering sample size.

Ethical considerations

This research adhered to international guidelines concerning recommendations for human research outlined in the Declaration of Helsinki and the Belmont Report. The risk associated with the investigation and the processing of personal data was determined according to Colombian legislation (Resolution 8430 of 1993 of the Ministry of Health and Statutory Law 1581 of 2012). Privacy and anonymity of personal data were ensured by assigning a unique code to each patient during the selective extraction of relevant data.

RESULTS

Patient characteristics

During the study period, 216 liver transplants were conducted at Fundación Cardioinfantil - La Cardio, of which 49 (22.9%) patients with suspected PTLD were identified. Among these, 18 patients (8.3%) received a definitive diagnosis of PTLD, with 15 (83.3%) being under 5 years of age and 3 (16.7%) over 5 years of age.

Regarding sociodemographic characteristics, it was observed that the median age at the time of PTLD diagnosis was 2.68 years (IQR: 2.58 – 3.08), and 61.1% were female. These variables, along with nutritional diagnosis and health affiliation regime, are presented in Table 1.

TABLE 1. Sociodemographic characteristics of patients diagnosed with PTLD following liver transplantation (n = 18).

Variable	Frequency	%
Gender		
Male	7	38.8%
Female	11	61.1%
Nutritional diagnosis in patients under 5 years of age (n = 15)		
Eutrophic	6	40%
Moderate acute malnutrition	4	26.6%
Risk of malnutrition	2	13.3%
Risk of overweight	1	6.6%
Obesity	1	6.6%
Unknown	1	6.6%
Nutritional diagnosis in patients over 5 years of age (n = 3)		
Eutrophic	2	66.7%
Underweight	1	33.3%

Health affiliation regime		
Contributory	9	50%
Subsidized	7	38.8%
Special	1	5.6%
Unknown	1	5.6%

The main cause for liver transplantation in patients was biliary atresia in 83.3%, followed by primary biliary cholangitis in 11.1% and another type of primary liver disease in only one case. The prevailing type of donor was a living donor in 88.8% of transplanted organs, and 88.8% of donors had a history of prior exposure to EBV, as evidenced by reactive IgG antibodies. Active EBV infection was documented in 10.5% of recipients at the time of transplantation. The EBV serological status of both patients and donors is summarized in Table 2.

TABLE 2. EBV serological status of patients and donors before transplantation.

Variable	Frequency	%
EBV IgG status of the donor		
Negative	2	11.1%
Positive	16	88.8%
EBV IgG status of the transplant recipient		
Negative	15	83.3%
Positive	3	16.6%
EBV IgM status of the transplant recipient		
Negative	15	83.3%
Positive	2	10.5%
Unknown	1	5.5%

PTLD diagnosis, histopathological classification, and treatment

The median time to PTLD diagnosis since transplantation was 9 months (IQR: 6 - 14), with early onset of the disease, i.e., within the first year, in 61.6%. According to the 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (12) (14), 33.3% presented monomorphic PTLD and 66,7% Non-destructive post-transplant lymphoproliferative disorders type florid follicular hyperplasia. In those patients who presented monomorphic PTLD, 83.3% were subclassified as Diffuse large B cell lymphoma and a single case as Burkitt lymphoma. Among the 18 included patients, only one exhibited infiltration of the bone marrow and central nervous system. Table 3 summarizes the onset of the disease and its histopathological classification.

TABLE 3. PTLD onset and its histopathological classification.

Variable	Frequency	%
PTLD onset after transplantation		
Early onset (within the first year)	11	61.1%
Late onset	7	38.9%
Diagnosis according to the 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues		
Florid follicular hyperplasia	12	66.7%

Monomorphic PTLD	6	33.3%
Subclassification of patients diagnosed with Monomorphic PTLD		
Diffuse large B cell lymphoma	5	83.3%
Burkitt lymphoma	1	16.7%
Bone marrow infiltration		
Yes	1	5.6%
No	17	94.4%
Central nervous system infiltration		
Yes	1	5.6%
No	17	94.4%

The clinical manifestations at the time of diagnosis were diverse, emphasizing that no patient was asymptomatic. The most common symptom was the presence of lymphadenopathy in 66.7% of patients. The most frequent laboratory abnormality was the alteration in EBV viral load in 88.8%, followed by changes in the blood count in 44.4%. The clinical considerations, paraclinical and radiological abnormalities identified in the patients are described in Table 4.

TABLE 4. Clinical considerations, paraclinical and radiological abnormalities.

Variable	Yes	%	No	%	Unknown	%
Clinical considerations						
Lymphadenopathy	12	66,7%	3	16,7%	3	16.7%
Fever	5	27,8%	7	38,9%	6	33.3%
Jaundice	-	-	12	66,7%	6	33.3%
Abdominal pain	1	5,6%	11	61,1%	6	33.3%
Adenoid hypertrophy	8	44,4%	4	22,2%	6	33.3%
Abscessed adenitis	1	5,6%	11	61,1%	6	33.3%
Digestive bleeding	1	5,6%	11	61,1%	6	33.3%
Constitutional syndrome	2	11,1%	9	50,0%	7	38.9%
Paraclinical and radiological abnormalities						
Alteration in EBV viral load	16	88,8%	1	5,6%	1	5.6%
Changes in the blood count	8	44,4%	10	55,6%	-	-
Abnormal liver function	4	22,2%	6	33,3%	8	44.4%
Retroperitoneal conglomerates	3	16,7%	9	50,0%	5	27.8%

Regarding the EBV viral load values obtained from plasma in relation to the diagnosed histological lesion type, 66.6% of patients with Monomorphic PTLD exhibited values greater than 100,000 IU/mL, while 83.3% of patients with Florid follicular hyperplasia had values lower than 10,000 IU/mL.

Immunosuppressive regimen at the time of PTLD diagnosis is presented in **Table 5**. 50% of PTLD patients experienced a modification in the immunosuppression regimen 6 months before diagnosis. Similarly, 61.5% maintained immunosuppression within the optimal range based on the time elapsed from the transplantation to the diagnosis of PTLD. All patients with Monomorphic PTLD received chemotherapy management with R-CHOP protocol.

TABLE 5. Immunosuppressive regimen at the time of PTLD diagnosis.

Variable	Frequency	%
Tacrolimus and Corticosteroid	10	55.4%
Tacrolimus	4	22.2%
Everolimus and Corticosteroid	1	5.6%
Tacrolimus, Mycophenolate, and Corticosteroid	1	5.6%
Mycophenolate, cyclosporine, and Corticosteroid	1	5.6%
Corticosteroid	1	5.6%

Out of the 18 patients only 1 died, 30.9 months after diagnosis. The duration from PTLD diagnosis to the last medical consultation date in this study varied between 11 and 68 months. Survival after diagnosis was calculated at 100% in the first year and 91.6% in the second and third years of follow-up. Twelve of the patients studied have surpassed a survival period of more than 3 years since the diagnosis of PTLD.

DISCUSSION

The frequency of PTLD after liver transplant in the studied cohort was 8.3%, a finding consistent with that reported in the literature in other geographical contexts (4) (16). 83.3% of patients had biliary atresia as the reason for liver transplantation, and the same percentage were younger than 5 years at the time of PTLD diagnosis, with a median age of 2.68 years (IQR: 2.58 – 3.08).

Similar to findings in the literature, a higher occurrence of PTLD was observed during the first year after transplantation (61.6%) (4) (5). As described, in the pediatric population, this may correspond to the increased risk of primary EBV infection in immunosuppressed states, taking into account the seropositivity of the donors (7) (14) (17). In this study, seropositivity for EBV was found in 88.8% of the donors, while in patients, it was only 16.6%. Although a clear association between nutritional status and the disease was not found in the reviewed literature, factors such as deficient IgA secretion or alterations in mucosal integrity (9), were identified as potential contributors to an increased incidence of PTLD.

Concerning clinical characteristics, PTLD can manifest with variable and non-specific symptoms, although the literature has reported a tendency towards fever (50%), lymphadenopathy (30%) and weight loss (18). In the studied cohort, the most prevalent symptom at the time of diagnosis was lymphadenopathy in 66.7%, followed by fever in 27.8%. A notable consideration is that an alteration in EBV viral load occurred in 88.8% of the cases concurrently with PTLD diagnosis.

Regarding the histopathological classification of PTLD, the study observed an incidence of 66.7% for Non-destructive post-transplant lymphoproliferative disorders. EBV seropositivity at the time of PTLD diagnosis has been described as 100% for Non-destructive post-transplant lymphoproliferative disorders, 90% for polymorphic PTLD and Hodgkin's lymphoma-like PTLD, and 50% for monomorphic PTLD (14). In patients diagnosed with PTLD, it was found that EBV seropositivity was predominant in all histopathological subtypes. However, 66.6% of patients with Monomorphic PTLD exhibited values greater than 100,000 IU/mL, while 83.3% of patients with Florid follicular hyperplasia had values lower than 10,000 IU/mL

According to the American Society of Transplantation, monitoring the viral load for EBV is recommended, particularly in seronegative recipients and those under 1 year of age as a sensitive and specific monitoring method (19). This recommendation is based on the suggestion that EBV viral load values correlate with viral replication and the risk of developing PTLD (14) (20), enabling the implementation of preventive strategies towards the disease's progression. Nevertheless, there is no clear correlation in the literature between an elevated viral load and the histopathological subtype of PTLD presented.

50% of PTLD cases experienced a modification in the immunosuppression regimen 6 months before diagnosis and more than half were receiving treatment with a calcineurin inhibitor at the time of diagnosis. Retrospective studies suggest that calcineurin inhibitors increase the risk by 2 to 5 times, especially with the use of tacrolimus compared to cyclosporine (21) (22). Inconsistent data suggest that the risk of PTLD is associated with the transplant process and secondary immunosuppression, but not with a specific immunosuppression regimen (23).

For the treatment of PTLD, in Non-destructive post-transplant lymphoproliferative disorders (the most common subtype in this cohort), it has been studied that a reduction between 15 and 25% of immunosuppression has described remission rates of up to 92% (3) (6) (8). As per institutional guidelines, all patients with Monomorphic PTLD received chemotherapeutic management with the R-CHOP protocol. This therapy has been employed as the first line of treatment in aggressive types of PTLD such as Monomorphic and Burkitt lymphoma, as well as in extensive cases refractory to initial therapy (3).

In the 13-year follow-up conducted, only one death occurred out of the 18 cases identified. The 5.6% mortality found in this study is lower than that reported in the literature, where mortality rises up to 40% during the first year after diagnosis (23). The study by Hsu, et al. (16), published in 2019, followed a cohort with similar size (n= 16) and characteristics between 2001 and 2013 at a tertiary referral center in Taiwan. The results of this research evidenced a higher mortality (18.8%) and a lower survival at the first (87.5%) and fifth year (79.5%) of follow-up to those in our investigation, which is probably related to advances in early diagnosis and multidisciplinary management protocols.

It is crucial to acknowledge that biases, such as sampling and collection biases, were present in our study. Sampling bias arises from the sample size, which may not be representative of the study population. Similarly, data collection bias, particularly in the quantification of EBV viral load, since several laboratories with differing techniques were utilized, leading to non-comparable results. Despite this, our study reveals noteworthy characteristics in Latin American pediatric patients with PTLD following liver transplant.

As a result of this research and the literature review, it is recommended that more studies with similar characteristics be conducted in Latin America. Furthermore, questions arise, such as the correlation between EBV viral load values and the histopathological subtype of PTLD, as well as the association of immunosuppressive agents or regimens with the development of PTLD. Therefore, conducting multicentric international studies is necessary to assess the role of more specific conditions related to established risk factors (e.g., viral load value, doses of immunosuppressants, etc.) and their relationship with PTLD development or its subtypes.

CONCLUSION

PTLD is a disease with highly diverse characteristics, and it may manifest involvement in multiple systems, constitutional symptoms, or nonspecific features. Therefore, maintaining a high level of suspicion in patients with risk factors is essential for accurate diagnosis. Data regarding the incidence and prevalence of PTLD following liver transplantation in Latin American children is limited; however, this study revealed prevalence rates comparable to those reported in the literature for other contexts. There is a pressing need for multicenter randomized clinical trials on a national and international scale. These trials would enable controlled exposure, offering more precise insights into the causal relationship and identification of triggering risk factors.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

All authors – none to declare.

DATA SHARING STATEMENT

The data supporting the findings of this study are available from the corresponding author, upon reasonable request.

AUTHOR CONTRIBUTIONS

LB, PG and IA designed the study. LB, PG and IA collected data. CD curated and analyzed the dataset. LB, PG and IA wrote the first version of the manuscript. CD supervised the project. All authors read, reviewed and approved the final version of the manuscript.

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