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Indication for tonsillectomy in pediatric patients with suspected post-transplant lymphoproliferative disorder

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ABSTRACT

A common site of lymphoid hyperplasia in post-transplant lymphoproliferative disorders (PTLD) is the palatine tonsils. However, tonsillar hypertrophy is extremely common in children, which hinders the suspicion of PTLD. A case series of transplanted patients undergoing tonsillectomy for suspected PTLD was conducted at a tertiary care children's hospital in Argentina between January 2014 and December 2021. The objective of this study is to expose the clinical characteristics of transplanted patients who underwent a tonsillectomy to diagnose PTLD.

Key words: *lymphoproliferative disorders; organ transplantation; tonsillectomy.*

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INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLD) are clinical entities characterized by lymphoid tissue hyperplasia due to solid organ transplantation or hematopoietic progenitor cell transplantation.[1] B-cell lymphoproliferation has been associated with Epstein-Barr virus (EBV) infection, either by primary infection through the donated organ or environmental exposure, or by post-transplant viral reactivation.[2–4] The suppression of T-cell surveillance that occurs with the use of immunosuppressive drugs to prevent graft rejection predisposes to uncontrolled proliferation of EBV-infected B cells.[2–6] PTLD encompasses a whole array of diseases ranging from benign proliferation of lymphoid tissues to frank malignant neoplasm with aggressive behavior.[1–3,6,7]

A common site of lymphoid hypertrophy is the tissues of Waldeyer's ring, especially in the palatine tonsils.[4] However, tonsillar hypertrophy is extremely common in children, hindering the differentiation between benign lymphoid hyperplasia and PTLD, which underscores the fact that diagnostic suspicion is a challenge.[4–6]

PTLD is one of the most devastating complications of organ transplantation.[1] The incidence of PTLD is increasing in the pediatric solid organ transplant population and is the most common secondary malignancy in children after transplantation, with a mortality rate of 20%.[4,6] It has been described that mortality at 100 days after the development of PTLD in children remains high.[6]

A timely diagnosis allows to establish an early intervention schedule so that, in some non-destructive PTLD types, a reduction of immunosuppression is enough.[4,8] Diagnosis is histopathological.[1,2]

The incidence of PTLD varies among different centers and depends mostly on patients' age, the solid organ transplanted, and the immunosuppressive treatment administered.[6]

The objective of this study is to expose the clinical characteristics of transplanted patients in whom a diagnostic tonsillectomy was indicated due to suspected PTLD.

METHODOLOGY

Here we describe a case series of transplanted patients who underwent tonsillectomy for suspected lymphoproliferative disorders at the Department of Ear, Nose and Throat of Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan between January 2014 and December 2021.

The hospital's IT system was used for the search. Only patients younger than 18 years with a history of solid organ or hematopoietic stem cell transplantation were included in the study. PTLD was diagnosed based on the histopathological study of tonsillar biopsy specimens, by means of positive immunolabeling for CD3 or CD20. Patients with other forms of immunosuppression were excluded.

The study variables were age at the time of transplantation and at the time of diagnosis, type of transplantation, immunosuppressive regimen established, clinical suspicion, and time between transplantation and PTLD diagnosis. In addition, the histopathological line and RNA *in situ* hybridization targeting EBV-encoded small RNAs (EBERs) were also recorded.

The study was assessed and approved by the hospital's Ethics Committee.

CASE PRESENTATION

The sample was made up of 14 transplanted patients seen at the Department of Ear, Nose and Throat for indication of tonsillectomy due to suspected lymphoproliferative disorder between January 2014 and December 2021. Ten of them were diagnosed with lymphoproliferative disorder through tonsillar tissue biopsy.

The mean age at which patients with lymphoproliferative disorders were transplanted was 3.5 years (standard deviation: ± 2.9). The mean age at diagnosis of lymphoproliferative disorder was 6.5 years (standard deviation: ± 3.8).

Of the 10 cases of PTLD diagnosed by tonsillectomy, 5 were liver transplant recipients (all receiving tacrolimus monotherapy); 2, heart transplant recipients (combination therapy); 2, bone marrow transplant recipients (1 tacrolimus monotherapy and 1 combination therapy); and 1 was a kidney transplant recipient (combination therapy). Of the 4 patients with suspected PTLD who did not show lymphoproliferation, 3 were kidney transplant recipients (1 tacrolimus monotherapy and 2 combination therapy) and 1 was a liver transplant recipient (combination therapy).

According to the clinical presentation, 5 patients diagnosed with PTLD were suspected of having obstructive symptoms (all with recent onset of chronic snoring); 3 had tonsillar hypertrophy without symptoms (on follow-up physical exam), and 2 had general symptoms

(1 with abdominal pain and nausea; 1 with anemia and splenomegaly).

Based on the histopathological changes of tonsillar biopsies showing lymphoproliferative tissue alterations, 8 cases showed plasmacytic hyperplasia; of these, 6 were positive for *in situ* hybridization for EBV. The other 2 biopsies showed 1 follicular lymphoid hyperplasia and 1 polymorphous findings, both negative for EBER.

Lastly, the mean time elapsed between transplantation and PTLD diagnosis was 3.3 years (standard deviation: ± 1.5).

DISCUSSION

Several studies agree that the varied clinical presentation of PTLD has not allowed distinguishing the symptomatological characteristics suggestive of the development of this disease at the tonsillar level.[1,4–7]

It is worth mentioning that, although all patients had records of EBV copies in their medical records, none were referred due to high EBV copies leading to suspected PTLD.

According to some studies, the optimal way to perform, interpret, and use quantitative EBV viral load assays for the surveillance, diagnosis, and monitoring of PTLD remains uncertain.[1,2,4,6] The authors agree that the preferred approach and the correct way to establish a relation between PTLD and the presence of EBV infection is through RNA *in situ* hybridization targeting EBERs.[1,2]

The sample of this study was not large enough to look for associations between the variables collected and the development of lymphoproliferation at the tonsillar level. These results are expected to contribute to the creation of multivariate studies that seek to determine which type of transplanted organ and immunomodulatory therapy are more related to the development of PTLD in the palatine tonsils and the role played by local EBV infection in the tonsils in the development of these lymphoproliferative processes.

In the meantime, given the risk associated with PTLD, tonsillectomy is still necessary on clinical suspicion of palatine tonsil enlargement or symptoms of upper airway obstruction. ■

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