

Post-Transplantation Lymphoproliferative Disorder in a Pediatric Patient

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Immunosuppressive therapy for transplanted patients exposes them to a high risk of developing posttransplantation lymphoproliferative disorders (PTLD). We report the case of a child undergoing heart transplantation at seven months of age who developed PTLD at nine years of age, diagnosed by resection of a pulmonary nodule.

In the past few years, because of the improved preservation of donated organs and of the larger experience with immunosuppressive therapy, a significant increase in the survival of children after heart transplantation has been observed. Thus, transplantation has become a broadly accepted therapeutic option for children and adolescents with congenital heart defects or cardiomyopathies in advanced stages¹⁻³.

Immunosuppressive therapy that transplanted patients have to undergo in order to prevent organ rejection exposes them to a high risk of developing neoplasms, mainly post-transplantation lymphoproliferative disorders (PTLD)²⁻⁷. The exact incidence of PTLD is unknown, ranging from 2% to 20%; however it is known to be higher among children^{5,8}.

A higher frequency of PTLD is observed among children because the great majority of them had not been exposed to the Epstein-Barr virus (EBV) prior to heart transplantation. Therefore, post-transplantation seroconversion is a significant risk factor for the development of PTLD^{5,9,10}. Of the pediatric patients who seroconvert after heart transplantation, approximately 63% develop PTLD⁹.

The EBV is believed to play a key role in the pathogenesis of PTLD⁴. This virus is able to enter B cells and induce their proliferation, which is normally controlled by many immune mechanisms such as proliferation and activation of cytotoxic T lymphocytes. Anti-rejection immunosuppressive drugs inhibit the response of these cytotoxic T lymphocytes, which results in the proliferation of B cells induced by EBV⁷.

Treatment modalities for PTLD are varied and include reduction of the immunosuppressive therapy, control of EBV replication, conventional antineoplastic therapy (radiotherapy, chemotherapy, and surgery) and

immunotherapy⁸. However, mortality rates are quite significant, varying according to prognostic factors and the treatment chosen^{8,10}.

The purpose of this publication is to report the case of a child undergoing heart transplantation at seven months of age who developed PTLD eight years and nine months later, diagnosed by resection of a pulmonary nodule.

Case Report

Male, nine years old, male, who underwent heart transplantation at seven months of age because of dilated cardiomyopathy.

In 2000, he had a respiratory disorder characterized by persistent cough with yellowish sputum, and was diagnosed with bronchopneumonia. He was initially treated with amoxicillin for fourteen days, and cefepime for thirteen days. In 2001, a control chest computed tomography (CT) revealed perihilar lymph nodes and solid masses within the lungs with a progressive evolution, suggestive of an infectious and secondarily tumoral disorder, and the patient was hospitalized for investigation.

Systemic EBV was then diagnosed, progressing with uveitis, gastritis, and diffuse pulmonary micronodules. He was treated with two rounds of ganciclovir, and the Polymerase Chain Reaction (PCR) and serologic tests became negative.

A transbronchial lung biopsy was performed, and its result was compatible with lymphoid interstitial pneumonia. It was positive for T (CD45) and B (CD20) lymphocytes, with foci of organizing pneumonia and accumulation of histiocytes in alveolar spaces, and was negative for tumor screening, acid-fast staining, and fungi. Immunohistochemical test was negative for EBV antigens, *Toxoplasma gondii*, cytomegalovirus and adenovirus. However, the *in situ* hybridization was positive for EBV. By this time, monotherapy with cyclosporin was started after detection of EBV. The patient was discharged because he was clinically asymptomatic, although requiring clinical follow-up.

During ambulatory follow-up, a new control chest CT revealed right lower paratracheal lymph node enlargement,

Key words

Heart transplantation, lymphoproliferative disorders, immunosuppression.

Case Report

dilation of the pulmonary artery, cardiomegaly, opacities with ill-defined borders in lower lobes with air bronchograms in the right lung, and pleural thickening. A new bronchoscopy was performed, and the result was normal. A new transbronchial lung biopsy showed diffuse thickening of the alveolar septa with atypical lymphoid infiltrate, and type II pneumocyte hyperplasia. A dense lymphocytic infiltrate with BALT proliferation was observed in the bronchial wall. Alveolar fibrinous hemorrhagic exudate and accumulation of macrophages were also observed. Acid-fast staining and tests for fungi remained negative. The histopathological appearance was interpreted as the result of a post-transplantation lymphoproliferative disorder in the pre-lymphomatous stage, and the immunohistochemical findings revealed a polyclonal lymphocytic infiltrate (positive for CD45, CD20, CD3, Kappa and Lambda), and EBV was negative. During this new hospitalization the patient was treated with acyclovir. He was discharged in good clinical conditions and was followed on an outpatient basis.

In 2002, a pulmonary function test was within normal limits. Months later, a new control chest CT showed enlarged pulmonary hila with nodules with irregular borders located in the medial segment of the middle lobe. The cardiac image was enlarged with absence of adenomegaly and the pleura had a normal aspect. The patient progressed with clinical improvement and was discharged.

In 2003, although asymptomatic, the patient was hospitalized for treatment of grade III acute cellular rejection (moderate and multifocal, evidenced by endomyocardial biopsy. Months later, after treatment with pulse therapy for four days and initiation of prednisone (1 ml/kg/day), a new biopsy revealed reversion of the alterations with absence of signs of rejection. By this time, he presented with fever and deterioration on chest radiography, and was hospitalized for investigation of a pulmonary nodule. He received specific treatment for EBV with ganciclovir (for fourteen days), in addition to the treatment for pneumonia (daily fever) with vancomycin (for eighteen days), fluconazole, Bactrim™, and Tienam™ (for fourteen days).

Chest CT follow-up revealed enlargement of the nodule in left lower lobe (Fig. 1). A left pulmonary nodulectomy was indicated and performed using a video-assisted anterolateral minithoracotomy and wedge resection in September, 2004.

The gross pathological examination revealed a lymphoproliferative process infiltrating the lung fragment diffusely, in the form of septal thickening or nodules. The cell population found was polymorphic, and was mainly comprised of plasmocytes, small lymphocytes and many mononuclear cells with prominent eosinophilic nucleoli. The aspect was compatible with transplantation-related lymphoproliferative disorder. The *in situ* hybridization was positive for focal EBV (EBER 1 and 2) in nuclei of infiltrating cells. The immunohistochemical study was positive for CD3, CD20, Kappa and Lambda chains. The presence of a light Kappa chain in most of the plasmocytes suggests monoclonal proliferation of these cells. The immunohistochemical profile, in addition to

the histological aspect, is compatible with a “polymorphic posttransplantation lymphoproliferative disorder” (Figs. 2 and 3).

A control chest CT revealed a lymph node conglomerate in the retrocaval and periaortic regions, cardiomegaly, mild bilateral pleural effusion associated with adjacent passive atelectasis, thickened interlobular septa in lung base, and irregular pulmonary nodules in right upper and left upper lobes. “Frosted-glass” areas in both lung bases and pulmonary opacities with a consolidation aspect in the middle lobe, lingula and upper lobes – more intense at the left side, were also found.

The patient was enrolled in the Rituximab protocol, and received the medication for four weeks in association with immune globulins. He was discharged in November, 2004 taking cyclosporine 80mg/day, omeprazole 20mg/day, ferrous sulphate and folic acid, captopril 6.25 mg 3x/day, as well as dexamethasone, tropicamide and Alphagan™ eyedrops. After five months, the patient was clinically well.

Discussão

PTLD is a potentially fatal condition manifested by an abnormal expansion of lymphocytic cells⁴⁻¹⁰. It may have a variable distribution, affecting several organs and tissues. The most frequent sites affected are the tonsils, cervical nodes, the gastrointestinal tract, and the thorax^{2,5}.

The induction of clonal expansion is closely related to EBV infection and is facilitated by immunosuppressive therapies broadly used in the control of transplant organ rejection^{2,4,5,7,10}.

In our patient, EBV infection ultimately led to PTLD eight years and nine months after heart transplantation. In the case of post-heart transplant patients, the development of PTLD may occur one year following transplantation⁵.

By means of a transbronchial lung biopsy, a lymphocytic infiltrate positive for B (CD20) and T (CD45) lymphocytes was observed. Among the PTLD cases, those with B cell

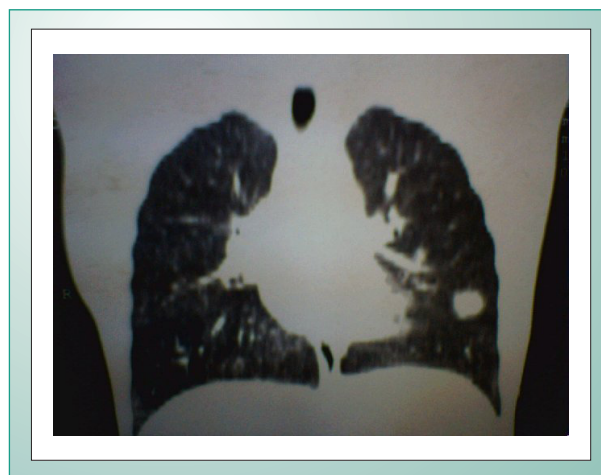


Fig. 1 - Chest computed tomography showing pulmonary nodule in the left lower lobe.

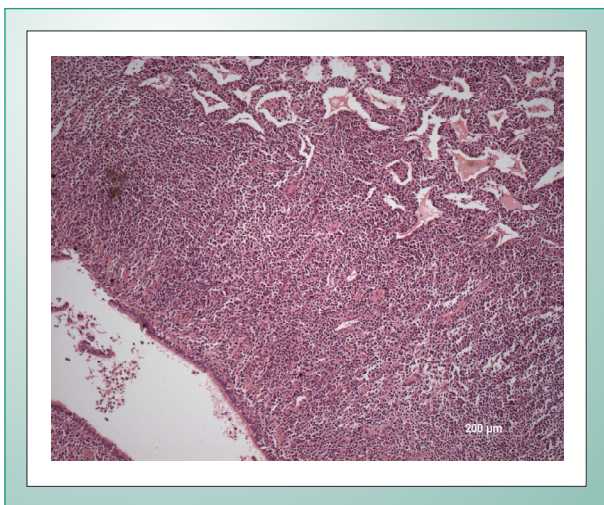


Fig. 2 - Microphotography of a lung diffusely infiltrated by mononuclear cells. In the right upper corner some remaining alveoli with edema in the lumen and enlarged septa can be observed. In the left lower corner we can observe a bronchial wall, which is also infiltrated. Hematoxylin and eosin staining. Magnification: x10.

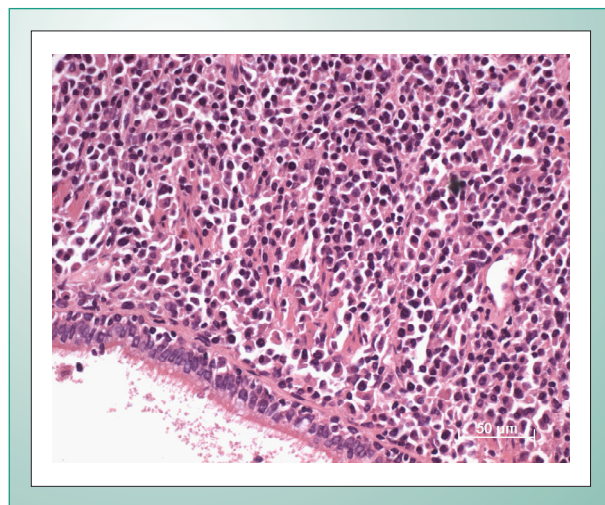


Fig. 3 - Micrograph showing a detail of the bronchial wall infiltrated by mononuclear cells. Note that some have characteristics of plasmacytes. Hematoxylin and eosin staining. Magnification: x40

phenotype are known to be more prevalent, whereas those with T cell phenotype are less frequent, more aggressive, and are associated with late complications in the transplanted organs⁶.

The chest imaging findings in individuals with PTLD usually include: multiple (more common) and enlarged pulmonary nodules, alveolar consolidation with central necrosis or isolated mediastinal involvement (rare, occurring only in heart transplant patients)⁵.

Chest CT scans performed in our patient revealed thickened interlobular septa in the lung base, pulmonary nodules with irregular borders in right upper and left upper lobes, pulmonary opacities with consolidation appearance in the middle lobe, lingula and upper lobes – more evident at the left side, and lymph node conglomerate in the retrocaval and periaortic regions.

Our initial treatment included the reduction of immunosuppressive therapy, adenotonsillectomy and use of ganciclovir, which was discontinued due to neutropenia, with further initiation of acyclovir.

Studies have shown that the optimal immunosuppressive therapy would be one using the minimum dose able to suppress rejection, since an excessive treatment would allow the development of PTLD^{3,4,6,10}. Reduction of immunosuppression, however, may lead to a regression of PTLD, because it enables the reactivation of T lymphocytes against EBV expression⁹.

Successful treatment of PTLD with acyclovir and ganciclovir have been demonstrated, both by increasing survival rates of patients and by preventing acute rejections^{4,6}. However, some authors have shown that the administration of these antiviral drugs is inefficient because they only suppress EBV replication in its linear form, but not in its latent form⁸.

The major risk factors associated with the development of PTLD are: primary post-transplantation EBV infection¹⁰,

high number of rejections, and the fact that the patient is a child⁴. Pediatric patients have a higher probability of being serologically negative for EBV and of acquiring primary infection^{4,10}.

By means of endomyocardial biopsies, foci of grade II and III acute cellular rejection were found in our patient, and were controlled with the initiation of a corticosteroid until signs of rejection could no longer be observed.

The use of anti-CD20 monoclonal antibody (rituximab) has proven effective in the treatment of PTLD in heart transplant patients^{8,9}. We chose to use this medication for four weeks. No alterations were observed in immune globulins and control blood counts.

Other treatment modalities, such as surgery, chemotherapy, radiotherapy, or α -interferon and high doses of immunoglobulins have been used with varying results⁸. Left pulmonary nodulectomy was successfully performed in our patient, using a video-assisted anterolateral minithoracotomy and wedge resection, enabling the confirmation of the diagnosis.

Despite the advances in the treatment of transplanted patients, which enabled the development of countless therapeutic modalities, we could say that no significant alterations in the incidence of PTLD have been observed in the past few years⁴. Perhaps, with more comprehensive studies, we will come to a better understanding of the etiopathogenesis of this process and will be able to establish an early efficient strategy of treatment.

The serial follow-up on an outpatient basis of this child with EBV enabled the diagnosis of a pulmonary nodule and PTLD by nodulectomy, thus allowing an adequate treatment and favorable outcome.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Case Report

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