Post-Transplant Lymphoproliferative Disorder after Lung Transplantation: The Portuguese Experience

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Abstract

Introduction: Post-Transplant Lymphoproliferative Disorders (PTLD) is a well-recognized and potentially fatal complication after solid organ transplantation. Reports of the incidence and characteristics of PTLD in Lung Transplant (LT) recipients are few, and risk factors and treatment approaches have been postulated, although more research is needed.

Methods: We report a retrospective analysis of patients who developed PTLD after lung transplant in the Portuguese lung transplant center between 2008 and 2018.

Results: Of 193 patients submitted to lung transplant five (2.6%) developed PTLD. At the time of LT, the mean age was 43.4 years (range, 20 to 63 yrs) and the median time between LT and PTLD diagnosis was 41 months (range, 8 to 120 months). All patients had reduction of immunosuppression at the time of diagnosis. Only one patient died four months after the diagnosis due to infectious complications.

Conclusion: Our small experience shows a variable sample, although with a trend to later occurrence. Despite treatment effectiveness is better in early stages, in our sample outcome remained well.

Keywords: Post-transplant lymphoproliferative disorders; Lung transplant; Epstein-Barr virus

Introduction

Post-Transplant Lymphoproliferative Disorder (PTLD) is a serious, often fatal complication after solid organ transplantation [1,2]. Patient's age, transplanted organ, Epstein-Barr Virus (EBV) status of the donor and recipient before transplantation and the dosage of immunosuppression drugs are considered risk factors [1,2]. EBV is closely involved in the pathogenesis of PTLD, although it is important to notice that not all cases of PTLD are associated with EBV viral replication [3].

PTLD in the setting of LT has some specificity, such as a higher incidence when compared with transplantation of most other organs [4-6], a frequent involvement of the grafted lung [6], and the risk of dysfunction or loss of a vital graft if immunosuppression is importantly reduced [7].

The incidence of PTLD after LT varies among the studies but ranges around 4.2% to 10% [3]. Although PTLD may occur at any time after LT, the risk is higher within the first year and these patients with early onset PTLD seems to have a better prognosis than those who developed late onset disease [1,3].

Clinical presentation is highly variable, as well as its pathologic characteristics. PTLD can virtually affect any organ system and can present with nodal and extra nodal involvement [2,7,8]. The clinical presentation can vary from simple lymphoid hyperplasia to aggressive disease that closely resembles Non-Hodgkin Lymphomas (NHL) [8]. PTLD encompasses a wide spectrum of lymphoproliferative disorders [3]. Pathologically, there are two major subtypes of PTLD. Polymorphic PTLD is characterized morphologically by nuclear atypia, tumor necrosis and destruction of the underlying lymphoid architecture [3,8]. It is the most common type of PTLD and may occur at any time after transplantation [3]. Monomorphic PTLD is a sub-type of NHL that appears as homogeneous sheets of transformed, monoclonal B cells, often with cytogenetic abnormalities [9]. This type of PTLD is often seen several years after transplantation [3]. The etiologic factors that underlie these different sub-types, as well as the implications for differential therapy and survival are unknown [8].

SPSS® Statistics (version 24) was used to analyze all data collected. Repeat imaging of the abdomen, and pelvis were obtained in all patients. The disease was confirmed in all patients by biopsy specimen. The records of all lung transplant recipients diagnosed with PTLD between 2008 and 2018 at Hospital de Santa Marta-Centro Hospitalar Universitário Lisboa Central were reviewed.

The disease was confirmed in all patients by biopsy specimen. Most patients were sub-classified by histologic subtype as polymorphic, monomorphic, or non-classified morphology. Immunohistochemical staining for CD20 and in situ hybridization for EBV-Encoded RNA (EBER) was performed as indicated. Serum chemistries and Computed Tomography (CT) scans of the chest, abdomen, and pelvis were obtained in all patients. The disease was staged according to the Ann Arbor staging system. The median time between LT and PTLD diagnosis was 41 months (range, 8-120 months). The diagnostic site of PTLD included bone marrow (n=1), gastrointestinal tract (n=1), native lung (n=1), transplanted lung (n=1) and lymphatic nodes (n=1). The disease was closely related to immunosuppression. Most patients were sub-classified by histologic subtype as polymorphic, monomorphic, or non-classified morphology.

The median time between LT and PTLD diagnosis was 41 months (range, 8-120 months). The diagnostic site of PTLD included bone marrow (n=1), gastrointestinal tract (n=1), native lung (n=1), transplanted lung (n=1) and lymphatic nodes (n=1). Ann Arbor staging classification was applied and two patients were in stage IB, one in stage IIB, and two in stage IVB. Clinical presentation was nonspecific, mainly presenting with fatigue (n=5), weight loss (n=3) and gastrointestinal symptoms (n=2). Characteristics of our PTLD patients are summarized in (Table 1).

**Table 1: Patients characteristics.**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age at LT</th>
<th>Indication for LT</th>
<th>IS at diagnosis</th>
<th>LT-PTLD diagnosis (months)</th>
<th>Organs involved</th>
<th>Histology</th>
<th>CD20</th>
<th>EBV</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>63</td>
<td>IPF</td>
<td>TAC, AZA, Pred</td>
<td>62</td>
<td>BM</td>
<td>Poly</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>23</td>
<td>OB</td>
<td>TAC, MMF, Pred</td>
<td>9</td>
<td>GI</td>
<td>Mono</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>20</td>
<td>BCNF</td>
<td>TAC, Pred</td>
<td>8</td>
<td>Lung</td>
<td>Poly</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>55</td>
<td>COPD</td>
<td>TAC, Sir</td>
<td>41</td>
<td>Lung</td>
<td>Mono</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>56</td>
<td>Sarcoïdosis</td>
<td>TAC, Pred</td>
<td>120</td>
<td>LN</td>
<td>Mono</td>
<td>+</td>
<td>NA</td>
<td>-</td>
</tr>
</tbody>
</table>

Pt: Patient; M: Male; F: Female; LT: Lung Transplant; IPF: Idiopathic Pulmonary Fibrosis; OB: Obliterans Bronchiolitis; BCNF: Bronchiectasis Non-Cystic Fibrosis; COPD: Chronic Obstructive Pulmonary Disease; IS: Immunosuppression; Pred: Prednisone; TAC: Tacrolimus; MMF: Mycophenolate Mofetil; BM: Bone Marrow; GI: Gastrointestinal Tract; LN: Lymph Nodes; Poly: Polymorphic Morphology; Mono: Monomorphic Morphology; NA: Not Assessed; EBV status (determined by EBV-encoded RNA [EBER] transcripts/latent membrane protein-1) determined at the time of PTLD diagnosis; CMV: Cytomegalovirus status determined before lung transplant

Immunosuppression is one of the main risk factors for the development of PTLD [3]. Some reports showed that after cyclosporine introduction the incidence of PTLD increased and the same happens after introduction of Tacrolimus which was associated with a two- to five-fold increase in the risk of developing PTLD [3,10]. Also, the use of Anti-Thymocyte Globulin (ATG) for prophylaxis against or treatment of acute rejection was associated with a three- to four-fold increase in the incidence of PTLD [3]. The disease is closely related to the overall severity immuno-suppression over time, so Reduction of Immunosuppression (RI) remains the cornerstone of treatment [8]. Rituximab has become the standard treatment for CD20-expressing tumors since it has significantly increased the response rate of therapy [11,12]. All these approaches however come with risks as a result of direct toxicity, as well as the risk of organ rejection that arises from RI [8].

**Materials and Methods**

The records of all lung transplant recipients diagnosed with PTLD between 2008 and 2018 at Hospital de Santa Marta-Centro Hospitalar Universitário Lisboa Central were reviewed.

The disease was confirmed in all patients by biopsy specimen. Most patients were sub-classified by histologic subtype as polymorphic, monomorphic, or non-classified morphology. Immunohistochemical staining for CD20 and in situ hybridization for EBV-Encoded RNA (EBER) was performed as indicated. Serum chemistries and Computed Tomography (CT) scans of the chest, abdomen, and pelvis were obtained in all patients. The disease was staged according to the Ann Arbor staging system. Repeat imaging was performed to monitor the clinical progression of the disease. SPSS Statistics (version 24) was used to analyze all data collected.

**Results**

**Characteristics of PTLD patients**

Between February 2008 and November 2018, 193 patients underwent lung transplantation at Hospital de Santa Marta-Centro Hospitalar Universitário Lisboa Central and five (2.6%) of them developed PTLD. At the time of LT, the mean age was 43.4 years (range, 20 to 63 yrs). Three patients were male and two were female. Primary disease of these patients was idiopathic pulmonary fibrosis, obliterans bronchiolitis, bronchiectasis non-cystic fibrosis, chronic obstructive pulmonary disease and sarcoidosis. Single lung transplant was performed in two patients and double lung transplant in three patients. All patients had received induction immunosuppression with ATG and at the time of PTLD diagnosis they were at least with two different classes of immunosuppressive drugs: Prednisone (n=5), tacrolimus (n=5), sirolimus (n=1), mycophenolic acid (n=1) and azathioprine (n=1). One patient had had previously few episodes of acute rejection that required transient increases in immunosuppression.

The median time between LT and PTLD diagnosis was 41 months (range, 8-120 months). The diagnostic site of PTLD included bone marrow (n=1), gastrointestinal tract (n=1), native lung (n=1), transplanted lung (n=1) and lymphatic nodes (n=1). Ann Arbor staging classification was applied and two patients were in stage IB, one in stage IIB, and two in stage IVB. Clinical presentation was nonspecific, mainly presenting with fatigue (n=5), weight loss (n=3) and gastrointestinal symptoms (n=2). Characteristics of our PTLD patients are summarized in (Table 1).

**Morphologic and immunophenotypic features**

According to the WHO classification of lymphoid neoplasms, we identified three monomorphic and two polymorphic PTLD. The monomorphic cases were characterized by atypical large lymphoid cells, and a spectrum of small lymphocytes was characteristic of polymorphic disease. All cases were B-cell lineage and expressed CD20.

**EBV and CMV analysis**

Before LT, all candidates are tested for EBV and CMV status. Three patients had EBV- VCA-IgG and anti-CMV-IgG positivity.
After the PTLD diagnosis, EBER-ISH was performed in all patients and was positive in four cases.

**Outcome**

At the time of PTLD diagnosis, all patients were submitted to reduction of immunosuppression at the lower acceptable levels. This included the suspension of anti-proliferative agents, the reduction in the dose of the calcineurin inhibitor and the maintenance of steroids doses. The first patient of this series was treated with chemotherapy according to the recommendations at that time, and died four months after the diagnosis due to infectious complications. The other four patients were treated with rituximab and had a good response being under surveillance with no signs of recurrence of the disease (Figure 1).

**Discussion**

Solid organ transplantation is a well-known risk factor for malignancy, possibly due to immunosuppression. PTLD remains a rare, but a well-recognized complication after lung transplant with a higher incidence when compared with other solid organs.

We describe the results of our experience with this small series of cases. We had a very heterogeneous sample of PTLD patients, with an incidence lower than described in the other series. Although the association between EBV infection and the risk to develop PTLD is well described, we did not find any differences to the risk of PTLD regarding to the EBV status before LT. We had a trend toward later occurrence that did not influence the final outcome. However, our data should highlight the importance of a careful monitoring of these patients, since it’s established that the prognosis is better for earlier stages. Reduction of immunosuppression is the cornerstone of the treatment, and it may be sufficient for disease remission for most cases of early stages [13-15]. Rituximab with reduction of immunosuppression is the standard approach, being chemotherapy reserved for non-responding cases. Our experience shows a very good response with this approach, since all patients treated with rituximab persist with no signs of recurrence.

In summary, our series report points some important issues. It gives more information about this rare disease that can present with a variable clinical scenario. Since the prognosis is better for early stages, it is important to be aware of this disease and systematically screen these patients for it. Finally, more research in treatment approaches is needed and should continue to be explored to ensure new diagnostic techniques and management tools.

**References**


