

# Posttransplant Lymphoproliferative Disease

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## Abstract

**Posttransplant lymphoproliferative disease include a wide spectrum of well-characterized disorders, from benign hyperplasia to invasive malignant lymphoma, with significant morbidity and mortality and characterized by abnormal lymphoid growth, most frequently B-cell type. Many factors have been associated with an increased risk of developing posttransplant lymphoproliferative disorder in transplant recipients, the most important being the degree and type of immunosuppressive treatment, younger age, and the type of organ transplanted. Despite the fact that the pathogenesis seems to be multifactorial, it is closely associated with Epstein-Barr virus serostatus, with non exposure to Epstein-Barr virus before transplantation being the most important risk factor.**

**The appearance of more potent immunosuppressive agents has lead to an increase in the incidence of posttransplant lymphoproliferative disorder. Treatment for posttransplant lymphoproliferative disorder includes reduction of immunosuppression and the administration of chemotherapy once posttransplant lymphoproliferative disorder is established. Strategies with (active or passive) immunoprophylaxis based in monitoring the Epstein-Barr virus viral load have failed to prevent posttransplant lymphoproliferative disorder. (Trends in Transplant. 2013;7:31-9)**

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## Key words

**Epstein-Barr virus infection. Lymphoproliferative disorder. Posttransplantation. PTLD. EBV.**

## Introduction

Posttransplant lymphoproliferative disorders (PTLD) are a severe and potentially fatal complication, particularly after solid organ

and hematopoietic cell transplantation. After skin cancer, PTLT is the second most common malignancy in adult solid organ transplant recipients, and the most common posttransplant malignancy in children<sup>1</sup>. The incidence of PTLT varies among transplant centers depending on allograft types, different immunosuppressive regimens used, the age of recipients, and geographic area. It includes a diverse group of lymphoproliferative disorders, from uncomplicated self-limiting "early lesions" to true malignant lymphoma, with nodal and/or extranodal involvement, restricted to the allograft or disseminated<sup>2</sup>. Epstein-Barr virus (EBV) infection has been

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identified as playing an important role in the pathogenesis of these disorders in up to 70-90% of cases<sup>3</sup>; non exposure to EBV before transplantation remains the most important risk factor for developing PTLT, as often occurs in pediatric solid organ transplant recipients<sup>4</sup>. The development of new immunosuppressive regimens to prevent rejection, such as belatacept which has already shown an increased risk of PTLT with central nervous system (CNS) involvement in EBV-seronegative recipients, has increased the interest in these disorders<sup>5,6</sup>.

According to the World Health Organization (WHO), PTLT has been classified into four continuum subtypes: early lesions, polymorphic PTLT, monomorphic PTLT, and classical Hodgkin's lymphoma<sup>7</sup>. Reduction of immunosuppression is the first line of therapy as it allows recovery of the appropriate T-cell regulation. Reported mortality from PTLT in case series exceeds 50%<sup>8,9</sup>, although this rate will possibly tend to decrease within the next years due to the extended use of immunotherapy<sup>10</sup>.

## Epidemiology and etiologic factors

The incidence of PTLT is difficult to define; among different series, the frequency of PTLT varies depending on time of observation and the scale of the studies. Nonetheless, in the United Network of Organ Sharing (UNOS) database (with 205,114 organ transplant recipients) PTLT was reported to have an overall frequency of 1.2% in transplant recipients<sup>11</sup>.

The incidence changes according to the type of transplanted organ. In adults, there is a high incidence of PTLT after multivisceral transplantation, small bowel (> 30%), heart (2-5%), lung (1.8-7.9%), liver (2-5%), pancreas (2%) and kidney (1%)<sup>12</sup> transplantation. However, kidney transplant recipients have the highest absolute number of PTLT; this is related to the higher number of kidney transplants performed. Different incidence depending on the organ

transplanted is explained by stronger immunosuppression needs in high-risk transplantations (e.g. bowel and lung) and by higher lymphoid tissue content in these organs<sup>13</sup>.

Children have a higher incidence of PTLT, mainly attributable to the fact that they are usually naive for EBV infection<sup>14</sup>. This infection is commonly transmitted via the donor organ<sup>15</sup> and seroconversion after transplantation increases the risk of PTLT in both children and adults<sup>2</sup>. Although PTLT may develop at any time, registry reports have shown bimodal peak incidence: in the first year posttransplantation (early PTLT) and in the later posttransplant period (late PTLT)<sup>11,16</sup>. Higher immunosuppression during the first year explains this observation. Late disease may be related to impaired immunological responses at the time of primary infection, better graft results (which increase exposure to immunosuppression), age, and probably to other infective agents such as cytomegalovirus (CMV)<sup>9</sup>. Early onset PTLT used to be more often reported than late onset PTLT; however late onset PTLT is currently the most frequently diagnosed, probably due to the longer survival of recipients and better knowledge of this disease<sup>13</sup>.

Risks factors for acute rejection, such as differences in HLA match, increase the risk for developing PTLT as they are associated with more potent immunosuppression<sup>16</sup>.

The vast majority of PTLT (> 90%) are of host origin in solid organ transplants, whereas, in stem cell transplantation the majority is of donor origin.

## Epstein-Barr virus-associated posttransplant lymphoproliferative disorder

The majority of PTLT cases (> 70%) are associated with EBV infection, representing a proliferation (of B-cells in most cases) that occurs in the setting of decreased T-cell

immune surveillance. In 30% of EBV-negative PTLD, the etiology is basically unknown.

Worldwide seroprevalence of EBV in adults is close to 95%<sup>17</sup>. In developed countries, 50% of children become seropositive at five years of age with a second peak of infection at 15-24 years old<sup>18</sup>.

Like other herpes viruses, EBV has various phases. During the lytic phase, viral proteins such as BZLF1 and BRLF1 are expressed, leading to activation, lytic replication, and destruction of host cells. During the latent phase, only few genes are expressed, including EBV antigens (EBNA) and latent membrane proteins (LMP), which are associated with oncogene activity<sup>19</sup>. The latent phase is characterized by interactions between viral mRNA and infected cells, resulting in the immortalization of infected B-cells<sup>18</sup>.

There are four EBV latency states; three of them are found in PTLD. Type 0: non-viral genes are expressed and appear in healthy persons. Type I: expression of EBNA-1; this is associated with Burkitt's lymphoma. Type II (default): expression of EBNA-1, LMP-1, LMP-2A; in Hodgkin's Lymphoma (HL)<sup>19</sup>. In type III latency (growth)<sup>10</sup>, all of these latency associated proteins are expressed and drive B-cell transformation and proliferation, resulting in PTLD and other immunosuppression-related lymphomas<sup>17</sup>. Tumors expressing type III develop early after transplantation, normally during periods of more intensive immunosuppression.

The response to early EBV infection in an immunocompetent host occurs through cytotoxic T lymphocytes (CTL), with more than 40% of circulating T lymphocytes directed against EBV. Intensive immunosuppression decreases the capacity to have an effective EBV CTL, with this explaining in part the increased risk for EBV disease and PTLD<sup>18</sup>. The balance between latently infected B-cells and

EBV CTL is altered by the effect of immunosuppression in recipients of solid organ transplants or hematopoietic cells.

Monitoring EBV viral load in high-risk groups is controversial. The method of determining EBV viral load has not been standardized among different laboratories. In addition, the optimal component of peripheral blood to do the test (whole blood or plasma) has not yet been defined. This is in contrast with the situation after allogeneic stem cell transplantation: high-risk patients should be systematically monitored for EBV load and treatment with rituximab is accepted only on the basis of significant increase of such viral load<sup>18</sup>.

### ***Human T lymphotropic virus***

Around 85% of PTLD have B-cell lineage; over 80% are related to EBV infection. About 10-15% have T-cell lineage and 30% of these are associated with EBV. However, in some parts of the world, such as the Far East, due to a higher prevalence of human T lymphotropic virus, the proportion of T lymphocyte PTLD is markedly elevated<sup>2</sup>.

### ***Cytomegalovirus***

Data are conflicting, but various studies indicate that a mismatch of donor/recipient CMV serostatus is not a risk factor for PTLD<sup>16,20</sup>. Nevertheless, CMV disease may be a risk factor for PTLD<sup>21</sup>.

### ***Hepatitis C virus***

The evidence supporting that hepatitis C virus (HCV) infection is a cofactor for PTLD is contradictory. In a French Registry (including 230 patients), HCV infection was associated with higher mortality from PTLD than in non-infected patients ( $p = 0.005$ )<sup>8</sup>. Nonetheless, in

the USRDS study, a relation between HCV serostatus and posttransplant HCV-related disease was not found<sup>16</sup>.

## Immunosuppressive regimens

Heavy immunosuppression increases the risk of developing PTLD<sup>22</sup> and, on the other hand, less immunosuppression implies lower risk of PTLD, but raises the risk of graft rejection episodes<sup>15</sup>. Immunosuppressive therapy not only diminishes the immune defenses against viral infections, but also decreases the immune surveillance over tumor cell proliferation<sup>23</sup>. The accumulative risk of developing PTLD seems to be closely related with the intensity and combination of induction immunosuppression, maintenance regimens, and acute rejection treatments. Induction therapy with monoclonal antibodies, such as OKT3, antithymocyte globulin for prophylaxis or treatment of acute rejection was associated with a three- to fourfold increase in the incidence of PTLD<sup>24</sup>. Cyclosporine and tacrolimus share the same mechanism of action; however, the immunosuppressive activity of tacrolimus is stronger, with this implying a higher risk of PTLD. On the other hand, cyclosporine can cause alterations in DNA reparation mechanisms, which might have a direct oncogenic effect. Opelz, et al. reported a twofold higher risk of developing PTLD in cadaveric kidney recipients treated with tacrolimus than those treated with cyclosporine<sup>25</sup>. Similar results were found by Bustami, et al., but only in those cases not receiving induction<sup>26</sup>.

A retrospective study in pediatric liver transplant recipients found a fivefold increase in lymphoma in the group treated with tacrolimus compared with the group treated with cyclosporine<sup>27</sup>.

Mycophenolate mofetil (MMF) and azathioprine are antimetabolites useful as immunosuppressive regimens. Several studies have established that MMF doesn't increase the risk

of PTLD but reduces it<sup>28</sup>. As MMF directly inhibits B-cell proliferation, this could explain these results<sup>29</sup>.

Inhibitors of the mammalian target of rapamycin (mTOR) pathway (sirolimus, also known as rapamycin) are immunosuppressors that have also demonstrated *in vitro* activity against tumoral cells<sup>30</sup>. Hence, they have been proposed as an alternative immunosuppressor to calcineurin inhibitors after diagnosis of PTLD, with few successful reported cases<sup>31,32</sup>.

Belatacept is an inhibitor of co-stimulation signaling between T-cell receptors and major histocompatibility complex on an antigen-presenting cell and has become a promising new immunosuppressor therapy. In the BENEFIT-EXTENT study, which compared belatacept versus cyclosporine in kidney renal transplant recipients, an increased number of PTLD with CNS involvement was found in the belatacept group<sup>33</sup>. This finding has led to the contraindication of belatacept in patients with seronegative EBV status<sup>6</sup>.

## Histologic classification

The pathological diagnosis of PTLD is currently based upon the WHO classification<sup>7</sup>, which includes four major categories: early lesions, polymorphic PTLD and monomorphic PTLD, probably representing a pathobiological continuum<sup>34</sup>, and classical Hodgkin's lymphoma-type PTLD (Table 1).

Early lesions are lymphoid proliferations, characterized by architectural preservation of the involved tissue. There are two histological patterns described: plasmacytic hyperplasia and infectious mononucleosis (IM)-like PTLD. They usually occur within the first year after transplantation<sup>2</sup> and at a younger age than other PTLD. Lymph node or tonsils and adenoids are more frequently involved than extranodal sites<sup>35</sup>.

**Table 1. Posttransplantation lymphoproliferative disorder: WHO classification**

WHO subtype	Age	Histology		Tumor localization	Ig gene clonality
		Architecture	Infiltrate		
Early lesions	Children or young adults	Usually preserved	Small lymphocytes (IM-like PTLTD), plasma cells (PH) ± immunoblasts	Tonsils or lymph nodes	Polyclonal
Polymorphic PTLTD	All age groups	Nearly complete effacement	Mixture of plasma cells, small lymphocytes, and large activated cells	Lymph nodes, GI tract, lung or allograft	Monoclonal B-cells, accompanying T-cells
Monomorphic PTLTD	All age groups	Complete effacement	Fulfills criteria for NHL (DLBCL, BL) or plasma cell neoplasm	Lymph nodes, any extranodal site including BM	Monoclonal B-and/or T-cells
Hodgkin's lymphoma type PTLTD	Young adults	Altered	Fulfills criteria for CHL	Lymph nodes	–

Ig: immunoglobulin; IM: infectious mononucleosis, PH: plasmacytic hyperplasia; PTLTD: posttransplant lymphoproliferative disorder; GI: gastrointestinal; NHL: non-Hodgkin's lymphoma; DLBCL: diffuse large B-cell lymphoma; BL: Burkitt's lymphoma; BM: bone marrow; CHL: classical Hodgkin's lymphoma.  
Adapted from Swerdlow, et al.<sup>7</sup>.

Plasmacytic hyperplasia is characterized by numerous plasma cells, small lymphocytes, and infrequent immunoblasts, while in the IM-like lesions the histology resembles that seen in IM, with numerous immunoblasts and a mixture of EBV-infected B-cells and reactive T-cells. Typically, immunoglobulin genes are polyclonal, although some IM-like PTLTD may have small monoclonal or oligoclonal populations<sup>7</sup>.

Polymorphic PTLTD is composed of a mixture of immunoblasts, plasma cells, small and intermediate-sized lymphocytes, and occasional Reed Sternberg-like cells that alter the normal architecture of lymph nodes or extranodal tissues. It is the most common type of PTLTD in children (frequently following primary EBV infection)<sup>36</sup> and adults (frequency varies from 20 to 80% depending on the institution)<sup>7</sup>.

Immunoglobulin heavy chain locus most frequently shows a clonal pattern, and the majority of the lesions exhibit EBV latency type II or III.

Monomorphic PTLTD resembles typical types of non-Hodgkin's lymphomas described

in immunocompetent hosts, either of B-cell or T-cell lineage. B-cell PTLTD (almost 85% of all monomorphic PTLTD) includes diffuse large B-cell lymphoma, Burkitt's lymphoma, and plasma cell neoplasms. This group is often seen many years after transplantation. Histologically, they disturb the normal architecture of the involved tissues, and fulfill the conventional criteria for diffuse large B-cell lymphoma (the most frequent type), Burkitt's lymphoma, or plasma cell neoplasms, although the term monomorphic can be somewhat confusing since it does not mean complete cellular monotony and cases with pleomorphism can be seen<sup>37</sup>. Almost all cases display a clonal pattern of immunoglobulin heavy chain locus rearrangement, and EBV-positive cases also show clonal episomal EBV genome. Burkitt's lymphoma cases have *myc* translocation. Regarding T-cell/natural killer-cell monomorphic PTLTD, this includes all disorders that fulfill the criteria for any of the T- or natural killer-cell lymphomas described in the WHO 2008 classification, with peripheral T-cell lymphoma being the most frequent<sup>38</sup>. Cases of T-cell origin have clonal T-cell receptor gene rearrangement.

Classical Hodgkin's lymphoma type is the least common type of PTLD. It is seen as a late complication, more frequently after kidney transplantation, and it is almost always EBV-positive. It should fulfill the criteria for classical Hodgkin's lymphoma type according to the WHO classification. The diagnosis must be based on morphological and immunophenotypic features because polymorphic PTLD and IM-like PTLD have cells that resemble Reed Sternberg cells, which usually lack CD15 expression.

In practice, a clear separation between the different morphologic categories of the WHO classification of PTLD is not always possible; overlap between categories may occur. Thus, this histological classification provides important information, although data about the biological context in which PTLD develops is missing, while on the other hand, the histological classification is only partially useful to decide treatment in these patients.

## Clinical features

In the current era of immunosuppression with calcineurin inhibitors, PTLD usually develops within the first year following transplantation of solid organs and within the first six months after stem cell transplantation<sup>39</sup>. Clinical presentation of PTLD is highly variable, and presentation symptoms frequently are non-specific, including fever (50%), malaise, weight loss, or lethargy<sup>40</sup>. Lymph node enlargement occurs in approximately 10-30% of cases<sup>41</sup>. Extranodal involvement is more frequent<sup>2</sup> and can occur at any site. Organ-specific dysfunction is another common presentation, such as intestinal perforation, obstructive symptoms of enlarged tonsils, or more rarely, solitary lesions in kidney, liver, lung, or CNS<sup>40,42,43</sup>. The CNS was involved in up to 30% of cases of PTLD in some reports in the 1990s<sup>37</sup>. However, the incidence of CNS PTLD appears to be decreasing with the new

immunosuppressive regimens<sup>44</sup>. Kidney was the organ most frequently associated with CNS involvement (11.9%)<sup>45</sup>. It should be noted that a fall in peripheral blood counts could be due to bone marrow infiltration as the sole manifestation<sup>37</sup>; a bone marrow aspirate would be then warranted.

## Diagnosis and staging

The diagnosis of PTLD should be based on histological examination of tissue biopsy, with excision biopsy being clearly preferred. Needle biopsy should only be performed where excision biopsy of affected tissue is not possible. For intrathoracic lesions (pulmonary masses or mediastinal nodes) a computed tomography (CT) scan-guided transthoracic needle biopsy may be useful<sup>46</sup>. If not diagnostic, an open lung biopsy should be performed. In cases of intraabdominal masses, laparoscopic lymph node biopsy is an effective approach<sup>47</sup>. Bone marrow biopsy should be performed in the rare cases limited to bone marrow. A lumbar puncture is the procedure of choice for suspected CNS disease, although masses that are not in contact with the meninges have often-normal spinal fluid and they can even contraindicate this procedure.

Morphology and standard immunostaining including studding (including the assessment of light chain class restriction and basic lymphoid subsets) are the basis of the PTLD diagnosis. Epstein-Barr virus detection (EBER *in situ* hybridization and EBV-LMP1 stain) is mandatory.

Staging of PTLD should be similar to that of any type of lymphoma. Thus, in addition to anamnesis and physical exam, blood cell count and serum biochemistry (including LDH and B<sub>2</sub>-microglobulin), and CT scan of thorax, abdomen, and pelvis should be performed.

A CT scan is useful for identifying areas for biopsy, staging, and treatment response.

However, CT is not able to identify affected lymph nodes of normal size, nor can it distinguish enlarged nodes due to non-malignant causes. In this regard, <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET) can provide more information. In a recent publication, the use of FDG-PET was analyzed, showing an overall sensitivity of 89%, specificity of 89%, positive-predictive value of 91%, and negative-predictive value of 87% for detecting PTLD<sup>48</sup>. Magnetic resonance imaging is particularly useful in the diagnosis of bone and CNS involvement. Finally, bone marrow biopsy is also part of standard staging of lymphomas.

## Treatment

The management of PTLD is a major challenge; therefore, expert hematologists or oncologists should ideally direct it. There is no standard treatment and many approaches have been proposed, with some agreement about overall principles.

Reduction of immunosuppression is the initial step to treat PTLD in solid organ transplant patients.

These approaches search for improving the reconstitution of the host's immune system and have been reported to be successful in 40-86% of cases of PTLD in pediatric recipients and 25-63% of adults<sup>2,49</sup>. The patients treated with reduction of immunosuppression should be closely monitored<sup>50</sup>. The majority of patients who have some response can show clinical evidence within 2-4 weeks of reduction<sup>18</sup>. In the Reshef, et al. experience with 67 solid organ transplant recipients diagnosed with PTLD treated with reduction of immunosuppression alone, the response rate was 45%, with 37% complete responses. The authors recommended that reduction of immunosuppression alone might be useful in low-risk PTLD patients. The presence of bulky disease (> 7 cm), advanced stage, late onset

PTLD, organ dysfunction, multiorgan involvement, and age > 50 years were associated with lack of response to reduction of immunosuppression<sup>10,50</sup>.

Polyclonal tumors often respond well to reduction of immunosuppression when onset is in the first year posttransplantation (early disease). Of note, there was better prognosis of PTLD in pediatric recipients because of the greater frequency of this type of tumor in them, which could regress after lowering immunosuppression<sup>16</sup>.

In immunotherapy, monoclonal antibody against CD20 (rituximab) has been shown to be effective when associated with a reduction of immunosuppression, given for four weekly doses, although experience is limited. In a series of 26 patients, this approach achieved a complete remission in 15 patients (58%)<sup>51</sup>, while in another series, seven out of eight patients achieved a complete remission<sup>52</sup>. Of note, the use of rituximab appears to be less effective in late PTLD<sup>53</sup>.

Chemotherapy combinations of cyclophosphamide, vincristine, adriamycin and prednisone (CHOP) and rituximab are most frequently used when reduction in immunosuppression was not effective. However, there is concern about treatment-related toxicity<sup>54</sup>, such as cytopenia and infectious complications. In order to minimize toxicity, regimens with rituximab and lower doses of chemotherapy have been used with promising results (complete remission in 5/6 pediatric patients), although more studies are needed<sup>55</sup>. Recently, Trappe, et al. published the results of a prospective, international, multicentre phase II PTLD-1 trial. They showed that sequential first-line treatment with rituximab followed by CHOP is more efficacious than first-line rituximab monotherapy followed by chemotherapy at progression or relapse<sup>56</sup>.

Adoptive T-cell therapy, i.e. the use of EBV-specific CTL, is a promising approach

and has already been shown to be effective as prophylaxis for PTLD<sup>57</sup>. Recent publications have demonstrated it to be highly effective with use of hematopoietic stem-cell transplantation in the treatment of PTLD, but could be necessary optimizing manufacturing processes<sup>58</sup>.

Other agents have been used with little evidence, such as interferon- $\alpha$ , anti-interleukin-6, and antiviral agents against EBV, but more studies are needed to determine their place in the treatment algorithm.

## Prognosis

One-year survival after PTLD diagnosis has been reported to be from 56 to 73%, five-year survival is around 50%, and estimated 10-year survival is estimated to be around 37%<sup>8,9</sup>. However, these data may not reflect the present mortality rates as the impact of rituximab in the outcome of PTLD has not been defined yet<sup>10</sup>.

## Conclusions

Lymphoproliferative disorders are rare complications after transplantation, difficult to diagnose because the clinical presentation is often non-specific, and the morphology of these lesions is heterogenic (there is no adequate consensus for their diagnosis). A high level of suspicion is fundamental in the transplanted patient. Epstein-Barr virus plays a key role in the development of lymphomas in the immunocompromised patients, although EBV-negative PTLD is seen (other viruses could be implicated). The treatment of these disorders is controversial, but there is some agreement that reduction of immunosuppression should be the first step, followed by rituximab alone or in combination with chemotherapy. New therapies such as adoptive T-cell therapy are promising, but more studies are needed to definitely include them in the management of PTLD.

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