Post-transplant lymphoproliferative disorders: a simplified overview

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Abstract

Post-transplant lymphoproliferative disorders comprise a spectrum of reactive to neoplastic lymphoid proliferations that occur in organ transplant recipients as a result of the iatrogenic immunosuppression. They usually appear within 1 year after the transplant, although they can sometimes occur after a long interval. Most cases are B-cell proliferations that are driven by Epstein-Barr virus, and the major types are 1. early lesions (plasmacytic hyperplasia and infectious mononucleosis-like lesion), which are usually polyclonal; 2. polymorphic post-transplant lymphoproliferative disorders, which are usually oligoclonal or monoclonal; and 3. monomorphic post-transplant lymphoproliferative disorders, which are morphologically identical to conventional lymphomas, are monoclonal, and commonly exhibit structural alterations in oncogenes and tumor-suppressor genes. Early lesions and a proportion of polymorphic post-transplant lymphoproliferative disorders regress with reduction in immunosuppressants, whereas almost all monomorphic post-transplant lymphoproliferative disorders progress and require lymphoma-type treatment.

Key words: B-lymphocytes/pathology, Immunosuppression, Lymphoma, Lymphoproliferative disorders, Transplantation

中文摘要

移植後淋巴細胞增生性疾病指現於器官移植患者中，由腫瘤性免疫抑制所引起的一系列反應性至腫瘤性淋巴細胞增生。移植後淋巴細胞增生性疾病通常於器官移植後一年內出現，但部份亦會在移植一段較長時間後發生。大部分病例屬由Epstein-Barr病毒所引起的B細胞增生，主要類型為：一、早期損害（壟細胞過度增生及感染性單核細胞病棧損害），一般屬多克隆；二、多形性移植後淋巴細胞增生性疾病，通常為寡克隆或單克隆；及三、單形性移植後淋巴細胞增生性疾病——在形態學上與傳統淋巴瘤沒有分別，屬單克隆，通常呈腫瘤性及腫瘤抑制基因的結構變化。早期損害和部分多形移植後淋巴細胞增生性疾病在減少免疫抑制劑後出現改善；而絕大部份單形移植後淋巴細胞增生疾病則繼續進展，需視為淋巴瘤治療。

INTRODUCTION

Organ transplant recipients are at an increased risk of developing malignancies, in particular lymphomas (lymphoproliferative disorders), skin cancer, and Kaposi sarcoma. The emergence of malignancies results from reduced host immune surveillance because of the inevitable need to take immunosuppressants to prevent graft rejection. It is important to recognize post-transplant lymphoproliferative disorders (PTLDs) because some lesions can show dramatic regression with reduction or cessation of immunosuppression, and thus do not require aggressive treatment as used for lymphomas (1).

WHAT IS POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER?

Post-transplant lymphoproliferative disorder is a lymphoid cell proliferation affecting organ transplant recipients (2). The majority of cases is of B lineage, and is driven by Epstein-Barr virus (EBV). The designation “lymphoproliferative disorder” is used instead of an...
Post-transplant lymphoproliferative disorders

Post-transplant lymphoproliferative disorders can also occur in recipients of bone marrow transplant (5). The differences from PTLDs occurring in solid organ transplant recipients include the following (6,7): 1. younger age group; 2. shorter interval between transplantation and development of PTLD (median, 52-101 days); 3. almost consistent association with EBV; 4. lack of correlation between histologic appearance and molecular evidence of clonality; and 5. very aggressive clinical course. The risk of developing PTLD is particularly high for those who receive T cell-depleted allogeneic grafts (8).

The literature on PTLD is confusing because different terms and classifications have been used by different authors (3,9,10). Some authors used the term PTLD as an umbrella term to encompass the entire spectrum of lymphoid proliferations in the post-transplant setting, and this is also the recommended terminology of the latest World Health Organization classification of hematopoietic and lymphoid tumors (11). Some restricted the term for lymphoid hyperplasias and polymorphic lymphoproliferations; and still others used the term for polymorphic lymphoid proliferations only.

HOW HIGH IS THE RISK OF DEVELOPING POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER IN AN ORGAN TRANSPLANT RECIPIENT?

The overall risk of developing PTLD in organ transplant recipients is approximately 1.7%. However, it is difficult to estimate the risk for an individual patient because many factors can influence the magnitude of the risk, such as the following:

1. Nature of transplant (Table 1) (12)—the reported risk of developing PTLD varies with the nature of transplant, and is low for renal transplant (approximately 1%). The high risk seen in patients with heart-lung transplant is probably attributable to the relatively high intensity of immunosuppressive regime, propensity to develop severe infections and/or rejection, and frequent occurrence of primary EBV infection.

2. Immunosuppressive regimes—the more profound the immunosuppressive regime, the higher the risk. For example, adding OKT3 to treat graft rejection episodes is associated with a particularly high risk of PTLD, which can develop after a remarkably short interval. When cyclosporin was first used as an immunosuppressive agent for organ transplant recipients, the incidence of PTLD increased to 9% to 13%; but with the use of lower doses through close monitoring of the cyclosporin blood levels, the incidence has dropped dramatically to 1% to 2% in recent years. The use of tacrolimus as an immunosuppressant seems to be associated with a higher risk of developing PTLD compared with the use of cyclosporin, but perhaps careful monitoring of the drug level can help to bring down the incidence (13,14).

3. Age of patient—children are at higher risk of developing PTLD, probably because they are more often sero-negative for EBV before transplantation (12,14,15).

4. Primary infection of EBV (first exposure) after transplantation—thus, seronegativity for EBV before transplantation is a high-risk factor for development of PTLD (16,17).

WHEN DOES POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER OCCUR?

Most PTLDs develop within several months to 1 year after the transplant, with the reported median interval being 4.5 to 11 months. Use of cyclosporin is associated with the development of PTLD at a shorter time interval after transplantation. Rarely, PTLD can develop late; such late-occurring PTLDs are more likely than early-occurring PTLDs to be EBV negative (11,12).

WHAT ARE THE PREDILECTION SITES?

The preferred sites of involvement in PTLD are the allograft and various extranodal sites, such as the gastrointestinal tract, central nervous system, liver, and lung (Fig. 1) (12). Lymph nodes can also be involved.

The pattern of organ involvement may differ according to the immunosuppressive regime. In patients receiving an azathioprine-based regime, PTLDs often involve extranodal sites, such as the allograft and central nervous system. In patients receiving cyclosporin or tacrolimus, the PTLDs tend to involve lymph nodes and gastrointestinal tract (11).

Table 1. Overall risks of developing post-transplant lymphoproliferative disorder in transplant recipients.

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<thead>
<tr>
<th>Type of organ transplant</th>
<th>Reported risk of developing PTLD (%)</th>
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<tbody>
<tr>
<td>Kidney</td>
<td>1</td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
</tr>
<tr>
<td>Heart</td>
<td>1.8-9.8</td>
</tr>
<tr>
<td>Heart and lung</td>
<td>4.6-9.4</td>
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<tr>
<td>Bone marrow</td>
<td>0.6-7.4</td>
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PTLD = post-transplant lymphoproliferative disorder
HOW DOES POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER MANIFEST CLINICALLY?

Patients with PTLD usually present with one of the following three clinical patterns (18): 1. infectious mononucleosis-like, characterized by prominent cervical lymphadenopathy, pharyngitis, and fever. This presentation is most often seen in young patients, and occurs soon after transplantation. The disease is usually self-limiting, but some cases can prove fatal; 2. effects or complications of mass lesions, such as in the allograft, gastrointestinal tract, liver, lung, and central nervous system; and 3. allograft failure because of involvement of the allograft by PTLD. This presentation of PTLD can mimic that of graft rejection.

WHAT ARE THE PATHOGENETIC MECHANISMS?

To understand the pathogenesis of PTLD, it is essential to know the immune regulation of infectious mononucleosis, which is a self-limiting EBV-associated lymphoproliferative disorder. As a primary infection, EBV infects and immortalizes B cells, causing them to proliferate profusely. The host mounts an EBV-specific T-cell response to control the B-cell proliferation, with the cytotoxic T cells killing the B cells. As a result, the lymphoproliferative process subsides (Fig. 2).

Post-transplant lymphoproliferative disorders can be imagined as infectious mononucleosis gone astray (19). Primary infection by EBV or reactivation of latent EBV infection results in marked B-cell proliferation. In organ transplant recipients, the T-cell response is attenuated because of the inevitable use of immunosuppressants. As a result, there are insufficient host T cells to control the B-cell proliferation, which then proceeds unchecked (Fig. 3). The EBV-positive B cells can accumulate in various sites of the body and form mass lesions. The process progresses from a polyclonal proliferation, to an oligoclonal proliferation, and eventually to a monoclonal proliferation (neoplasm) (Fig. 4). In the early phases, restoration of the immune competence (such as by reduction or cessation of immunosuppressive therapy) can lead to reversal of the process, because the increased cytotoxic T cells can recontrol the B-cell proliferation. However, with subsequent emergence of subclones that have growth advantage because of mutations in the various proto-oncogenes and tumor suppressor genes, that is, development of frank lymphoma with autonomous growth, even restoration of immune competence will not be able to reverse the lymphoproliferative process. Thus, like other malignant neoplasms, the genesis of PTLD is a multistep process (20).

When a patient develops multiple PTLD lesions in the same organ, in several anatomic sites, or at different time
points, the lesions can represent the same clonal process or multiple independent distinct clonal processes (21,22).

**IS EPSTEIN-BARR VIRUS ESSENTIAL FOR DEVELOPMENT OR DIAGNOSIS OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER?**

Although EBV takes a key role in the development of PTLD, 10% to 20% of PTLDs are negative for EBV (11, 20,23). Of interest, the proportion of EBV-negative PTLDs seems to have increased in recent years (24,25). Such PTLDs have the following characteristics (23,24): 1. occurring at a longer interval after transplantation (median, 50 months vs 10 months for EBV-positive cases); 2. more likely to show a monomorphic morphology (67% vs 42% for EBV-positive cases); and 3. generally more aggressive, that is, poor response even with aggressive therapy.

Nonetheless, some (approximately 23%) patients with EBV-negative PTLDs do show remission with reduction of immunosuppression (24). Thus, EBV positivity is neither a prerequisite for the diagnosis of PTLD, nor can it predict whether a lesion will or will not respond to reduction of immunosuppression. Of interest, human herpesvirus type 8 has recently been implicated in an example of PTLD (25). Further studies are needed to determine its role, if any, in the genesis of PTLDs.

**IS THE LYMPHOPROLIFERATIVE DISORDER OF DONOR OR HOST ORIGIN?**

The donor-versus-host origin of PTLD arising in solid organ transplant recipients remains a controversial issue. Whereas some studies suggest that the majority of PTLDs are of host origin (26,27), recent studies suggest that most cases are of donor origin (28-31).

**WHAT ARE THE PATHOLOGIC FINDINGS?**

The histologic findings are variable, depending on the type of PTLD. The latest World Health Organization classification scheme of hematolymphoid neoplasms is listed in Table 2 (11). The clinicopathologic features of the major types of PTLDs are listed in Table 3 (Figs. 5 and 6) (32). One form of PTLD can progress to another, for example, polymorphic PTLD can transform to monomorphic PTLD.

It is important to realize that the term “polymorphic” refers to the presence of a spectrum of lymphoid cells that recapitulate the development of B lymphocytes (lymphocyte ⇒ immunoblast ⇒ plasmablast ⇒ plasma cell), but not a pleomorphic population of atypical cells with significant variation in size and shape. In the latter circumstance, the lesion should be classified as a “monomorphic PTLD” (33). Earlier studies indicate that only approximately half of the cases of polymorphic PTLDs are monoclonal (9,34), but more recent studies have shown that the great majority of cases are monoclonal (20,32,35). Monomorphic PTLDs are almost always monoclonal.

Rare types of PTLDs include plasmacytoma, Hodgkin lymphoma, peripheral T-cell lymphoma, and natural killer-cell lymphoma (36-41). Peripheral T-cell lymphomas usually develop after a long latent interval (median, 5 years), rarely involve the allograft, show association with EBV in only approximately 50% of cases, and only infrequently respond to decreased immunosuppression (11,20,42).
WHAT INFORMATION CAN BE EXPECTED FROM PATHOLOGIC EXAMINATION OF LESIONS SUSPECTED TO REPRESENT POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER?

Pathologic examination of the biopsy or excision specimen is required to determine the histologic diagnosis. The major diagnostic possibilities are: 1. PTLD; 2. graft rejection. Histologically, it is not always easy to make a distinction between graft rejection and early involvement of the allograft by PTLD (Fig. 7A). In general, B cells predominate in PTLD, whereas T cells (mostly cytotoxic T cells) predominate in graft rejection. In situ hybridization for EBV early RNAs usually shows numerous positive cells in PTLD, whereas there are no or few positive cells in graft rejection (Fig. 7B); 3. infection; 4. other immunosuppression-associated neoplasms, such as Kaposi sarcoma and EBV-positive post-transplant smooth muscle tumor; and 5. other incidental pathologic processes unrelated to the immunosuppression.

If a diagnosis of PTLD is confirmed, the following information will help to predict the outcome and guide the treatment:

1. Type of PTLD (Tables 2 and 3)—according to one study, no patients with plasmacytic hyperplasia died.

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<th>Table 2. Post-transplant lymphoproliferative disorders (World Health Organization classification of tumors of hematopoietic and lymphoid tissues, 2001).</th>
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| 1. Early lesions  
  - Reactive plasmacytic hyperplasia  
  - Infectious mononucleosis-like  
  2. Polymorphic PTLD  
  3. Monomorphic PTLD (classify according to conventional lymphoma classification)  
  - B-cell neoplasms (eg, diffuse large B-cell lymphoma, Burkitt lymphoma, plasma cells myeloma, plasmacytoma-like lesions)  
  - T-cell and natural killer cell neoplasms (eg, peripheral T-cell lymphoma not otherwise specified, hepatosplenic γδ T-cell lymphoma, natural killer cell lymphoma)  
  4. Hodgkin lymphoma and Hodgkin lymphoma-like PTLD  |
| PTLD = post-transplant lymphoproliferative disorder |

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<th>Table 3. Clinicopathologic features of major types of post-transplant lymphoproliferative disorder (2,32).</th>
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<tr>
<td><strong>Type</strong></td>
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| Early lesions (plasmacytic hyperplasia and infectious mononucleosis-like) | Usually affects children and young adults not previously exposed to EBV  
Often appears soon after transplantation  
Involves lymph nodes and tonsils  
Lesion often regresses spontaneously or with minimal reduction in immunosuppressant | Tissue architecture at least partially preserved  
Proliferated cells do not exhibit atypia  
Plasma cells and lymphanphocytoid cells predominate in plasmacytic hyperplasia; and more immunoblasts and plasmablasts are seen in infectious mononucleosis-like lesion | Polyclonal Ig gene in most cases  
EBV usually nonclonal |
| Polymorphic PTLD | Affects all age groups  
Disease involves lymph node, lung, gastrointestinal tract, or allograft  
A proportion of cases regresses with reduction of immunosuppression, but some cases do progress | Tissue architecture effaced  
Mixture of small lymphocytes, plasma cells, and large activated cells recapitulating the full spectrum of B lymphocyte maturation.  
Large cells may show atypia.  
Necrosis is variable | Ig gene usually monoclonal, but sometimes oligoclonal or polyclonal  
EBV clonal  
Usually no structural alterations in oncogenes and tumor suppressor genes |
| Monomorphic PTLD | Affects all age groups  
Disease involves lymph node, bone marrow, or various extranodal sites  
Disease often disseminated at presentation  
Most cases show rapid progression, and only rare cases respond to reduction in immunosuppression | Tissue architecture effaced  
Monotonous infiltrate similar to the usual lymphomas, most commonly large B-cell lymphoma  
Geographic necrosis is common | Monoclonal Ig gene in all cases  
EBV clonal  
Frequently shows structural alterations in various oncogenes and tumor suppressor genes, such as c-myc, p53, and N-ras. |

EBV = Epstein-Barr virus; Ig = immunoglobulin; PTLD = post-transplant lymphoproliferative disorder
Figure 6. Monomorphic post-transplant lymphoproliferative disorder (large B-cell lymphoma) involving the brain. (A) There is a monotonous population of abnormal large lymphoid cells. (B) Geographic necrosis is a common feature.
whereas death occurred in 20% and 67% of patients with polymorphic PTLD and monomorphic PTLD, respectively (43). Nonetheless, there can be variability in the nature of the lesions at different sites in the same patient; for example, biopsy at one site may show polymorphic PTLD, whereas biopsy at another site may reveal monomorphic PTLD (33). Thus, multiple-site biopsies are advisable if there are multiple lesions, unless one biopsy already shows a “worst” lesion (monomorphic PTLD).

2. Oncogene mutations—it is difficult to predict precisely in an individual patient whether the PTLD will regress with reduction of immunosuppression. According to one study, the presence of bcl-6 gene mutation (found in 0% of early lesions, 45% of polymorphic PTLDs, and 90% of monomorphic PTLDs) predicts shortened survival and lack of regression after reduction in immunosuppression and/or surgical excision, irrespective of the morphologic category (44). However, another study reports bcl-6 mutation in only 25% of polymorphic PTLDs and 25% of monomorphic PTLDs, and lack of significant impact on survival (45). More studies are required to determine the clinical and biologic significance of bcl-6 mutation.

Increased age, elevated LDH level, severe organ dysfunction, presence of B symptoms (fever, night sweats, and weight loss), and multiorgan involvement by PTLD at the time of diagnosis have been shown to be independent indicators for poor survival (14,46).

**HOW CAN POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER BE TREATED?**

In the early phases of development, restoration of the T-cell response by various means can potentially reverse the process because the proliferated B cells can still be controlled by the T cells. This can be achieved by the reduction or cessation of immunosuppression (46), infusion of autologous lymphokine-activated killer cells (47-49), or infusion of unirradiated donor leukocytes (to supply cytotoxic T cells presensitized to EBV). The latter is effective in treating PTLD in allogeneic marrow transplant recipient (50).

Simultaneous antiviral therapy can also be helpful (51). The reported complete response rate to reduction of immunosuppression ranges from 30% to 80% (14).

However, when the process is more advanced, with alterations of oncogenes and tumor suppressor genes, the B-cell proliferation becomes autonomous, and restoration of the host immune system will not be able to reverse the process. In such circumstance, the PTLD
has to be treated as for conventional lymphoma, such as surgical excision, chemotherapy, and radiotherapy. There have also been some successes with the use of the humanized anti-CD20 antibody Rituximab, other anti-B cell monoclonal antibodies, or interferon alpha (52-57).

In summary, in the management of PTLD, the best results are obtained if an early diagnosis can be made, and appropriate treatment is given accordingly (11). In practical terms, except for monomorphic PTLD showing rapid tumor progression, the patient can be observed for 1 or 2 weeks to see whether there is disease regression upon withdrawing or decreasing the immunosuppressant (21). This plan of treatment can be continued if there is evidence of regression. If the disease progresses, aggressive therapy as for lymphoma has to be initiated.

**CAN POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER BE PREVENTED?**

Only a small fraction of organ transplant recipients develops PTLD. The incidence can potentially be reduced by targeting the known high-risk group. Careful adjustment of the immunosuppressant dose to a low level just sufficient to prevent graft rejection can reduce the risk. Prophylactic antiviral therapy (such as ganciclovir and acyclovir) can be considered whenever antilymphocyte globulin has to be used to treat episodes of graft rejection (58). Careful monitoring of the EBV load, such as using quantitative polymerase chain reaction technique, can potentially help in identifying early development of PTLD, especially for patients that are seronegative for EBV before transplantation (59).

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Post-transplant lymphoproliferative disorders


