Post-Transplant Lymphoproliferative Disorders

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Learning Objectives
After completing this course, the reader will be able to:

1. Discuss the incidence and pathologic classification of PTLD.
2. Define the etiology and risk factors for PTLD.
3. Discuss the presenting clinical features and diagnostic evaluation of PTLD.
4. Describe treatments and reported outcomes for PTLD.

Abstract
Post-transplant lymphoproliferative disorder is the most common malignancy, with the exception of skin cancer, after solid organ transplantation in adults. The incidence varies according to the transplanted organ and is often associated with Epstein-Barr virus. Prognosis is variable, due in part to the heterogeneity of the disease, which ranges from reactive plasmacytic hyperplasia to aggressive monoclonal disease. The Oncologist 2006;11:674–680

Introduction
Post-transplant lymphoproliferative disorder is the most common malignancy, with the exception of skin cancer, after solid organ transplantation in adults and occurs in up to 10% of patients. The incidence varies according to the transplanted organ, and in the majority of cases, particularly those occurring less than 1 year after transplantation, are associated with Epstein-Barr virus.

Pathologic Classification
The most commonly used pathologic classification of post-transplant lymphoproliferative disorder (PTLD) is the World Health Organization (WHO) classification, which divides PTLD into three categories: early lesions, polymorphic PTLD, and monomorphic PTLD [5, 6] (Table 1). Early lesions are characterized by reactive plasmacytic hyperplasia. Polymorphic PTLD may be either polyclonal or monoclonal and is characterized by the destruction of underlying lymphoid architecture, necrosis, and nuclear atypia. In monomorphic PTLD (Fig. 1), the majority of cases (>80%) arise from B cells, similar to non-Hodgkin's lymphoma in immunocompetent hosts [7, 8]. The most common subtype is diffuse large B-cell lymphoma, but Burkitt's/Burkitt's-like lymphoma and plasma cell myeloma are also seen. Rarely T-cell variants occur, which include peripheral T-cell lymphomas and, rarely, other uncommon types, including gamma/ delta T-cell lymphoma and T-natural killer (NK) cell varieties. Hodgkin's disease-like lymphoma is very unusual.
A recent study found that cytogenetic abnormalities are rare in early lesions and uncommon in polymorphic PTLD (15%), but they occur commonly in monomorphic PTLD (72% of B-cell and 100% of T-cell lymphomas). The most frequent chromosomal abnormalities include trisomy 9 and 11, which are associated with EBV and have favorable outcomes. Rearrangements involving the \textsc{myc} gene (8q24.1) are associated with poor survival. Rearrangements involving 3q27 and 14q32 were also reported [9].

**INCIDENCE**

PTLD occurs more commonly in pediatric patients than in adults. The higher incidence in children is thought to result from the fact that they have a greater likelihood of being EBV-naïve recipients. In adults, rates range from 1%–3% in kidney and liver transplants, 1%–6% in cardiac transplants, 2%–6% in combined heart–lung transplants, 4%–10% in lung transplants, and in up to 20% of small intestine transplants [2, 7, 8, 10–14]. The variation in rates among the types of organ transplanted is likely related to the degree and duration of immunosuppression as well as the number of EBV-positive donor lymphocytes in the graft. PTLD is more common in lung and small bowel transplants [2]. Duration of the post-transplant period is important because PTLD is most likely to develop in the first year following transplantation, with an incidence of 224 per 100,000, but falls to 54 per 100,000 in the second year and 31 per 100,000 in the sixth year [15].

**ETIOLOGY/RISK FACTORS**

The majority of cases of PTLD are of recipient origin, though donor-derived lymphomas can occur, particularly in the transplanted organ [16]. Most cases of PTLD are associated with EBV infection from grafted B lymphocytes, which in the setting of immunosuppression, can induce a transformation to a lymphoproliferative disorder. EBV-negative lymphomas typically occur late, more than 1 year post-transplantation.

EBV is incorporated into B lymphocytes during primary infection and establishes lifelong latency [17]. Immunocompetent hosts mount an antibody response and, more importantly, a cellular immune response consisting of CD4- and CD8-positive T cells [18]. Latent EBV infection is associated with a number of different malignancies, including PTLD, HIV-associated lymphomas, endemic Burkitt’s lymphoma, and a subset of Hodgkin’s lymphoma. In PTLD, EBV-latent membrane protein 1 (LMP1) has been implicated in the transformation of B lymphocytes through a receptor in the tumor necrosis factor receptor family [19].

The molecular pathogenesis has been studied in a series of 52 patients. Somatic hypermutation of immunoglobulin variable (\textit{IgV}) genes confirms that most are derived from post-germinal center B lymphocytes. \textit{bcl-6} mutations, which are noted in the majority of diffuse
large cell or Burkitt’s lymphoma, occur only in 25% of polymorphic PTLD cases. There is a variable positivity for MUM1 (multiples myeloma oncogene 1 protein) and CD138 [20].

Patients who are EBV negative and receive grafts from EBV-positive individuals typically acquire the infection from the donor and are at highest risk for developing PTLD. In a series from the Mayo Clinic of 381 adult nonrenal transplant recipients, the rate of developing PTLD was 24 times higher in EBV-negative than in EBV-positive recipients [21]. The development of cytomegalovirus (CMV) disease, particularly in serologically negative patients receiving positive grafts, was also identified as a risk factor [22].

The degree and duration of immunosuppression are major factors in the development of PTLD in part by decreasing host cytotoxic T cells directed against grafted EBV-infected B lymphocytes. Prior to the use of cyclosporine, PTLD was extremely rare, and the incidence rose significantly after the introduction of the triple therapy of cyclosporine, OKT3 antibody, and antithymocyte globulin (ATG) [11]. Induction therapy has been associated with increased risk in several studies since the dose and duration of OKT3 exposure have been shown to be critical [14]. OKT3 and ATG were associated with a three- to fourfold higher incidence of PTLD in a study of 200,000 solid organ transplants [15]. In that study, there was no greater incidence in recipients of interleukin (IL)-2 receptor antibodies. Therapy with the immunosuppressive agent tacrolimus in kidney recipients was associated with a twofold greater risk, and there was no added risk in patients receiving cyclosporine versus azathioprine and steroids. Two studies, in 41,000 and 25,000 renal transplant patients, also found a higher risk associated with tacrolimus than with cyclosporine [23, 24].

Clinical Presentation

The most common presenting features of PTLD are fever and lymphadenopathy, though extranodal involvement occurs in more than two thirds of cases and may also involve the allograft, particularly in lung and small bowel transplant recipients [25]. The central nervous system (CNS) is frequently involved (in up to 30% of cases) and can be the only site of disease [2, 26].

An excisional biopsy, if possible, is important in order to obtain adequate tissue for standard histology, immunophenotyping/flow cytometry, and evaluation of EBV status. If an excisional biopsy cannot be performed, multiple core needle biopsies may provide adequate tissue for diagnosis. A bone marrow biopsy and computed tomography scans of the chest, abdomen, and pelvis are necessary for staging, and positron emission tomography may be useful in evaluating response to therapy. For patients presenting with disease involving the CNS, magnetic resonance imaging of the brain and spinal cord and a spinal fluid evaluation are essential.

Prognosis

Reported rates of disease-free and overall survival in PTLD are variable, partly because of the heterogeneity of the disease, ranging from early disease, EBV-negative large cell lymphoma, to Burkitt’s/atypical Burkitt’s lymphoma. Estimated survival rates range from 25%–60% [27]. A recent study of 107 cases from the Mayo Clinic proposed a multivariate prognostic model in which a performance status score of 3–4, monomorphic disease, and grafted organ involvement predicted poor outcome [28]. Other negative risk factors that have been implicated include EBV-negative status of the recipient, late onset of disease, disease involving multiple sites, advanced age, stage, elevated lactate dehydrogenase (LDH), severe organ dysfunction, and CNS disease [29–31].

Therapy

The management of PTLD is based primarily on the experience of retrospective case series with no clear consensus on therapy. Significant comorbidities in this patient population may limit the intensity of therapy.

Reduction of Immunosuppression

The initial management in all patients involves reduction of immunosuppression. In a patient with early lesions or polymorphic PTLD, complete regression of the disease commonly occurs as a result. Although no standard formula exists, decreasing cyclosporine or tacrolimus by 50% and discontinuing azathioprine or mycophenolate mofetil is often recommended [32]. In renal transplant patients, discontinuing all agents except prednisone may be feasible, but for heart, lung, and liver transplant recipients, the risk for allograft rejection must be taken into consideration. Approximately 25%–50% of patients respond to reduction in immunosuppression alone [33–35].

Antiviral Therapy

The role of antiviral therapy with acyclovir or gancyclovir has been controversial. Antiviral agents may be effective in patients with early or polymorphic disease, but there has been no clear benefit for antiviral therapy demonstrated in monomorphic disease in which transformed B lymphocytes do not have actively replicating EBV infection [35]. Arginine butyrate is an agent that can induce EB viral thymidine kinase in latently infected lymphoma cells with the purpose of activation. In a preliminary study of six patients treated with that antiviral agent, five responded, including
four complete remissions. Confirmation of this observation is needed [36].

**Antibody Therapy**

Anti-B-lymphocyte antibodies, including rituximab, an antibody directed against CD20 expressed on B lymphocytes, have been used as monotherapy and in combination with chemotherapy for B-cell PTLD [7, 37, 38]. Rituximab has a relatively benign toxicity profile, with the exception of infusional reactions, and this makes it an attractive agent in immunosuppressed patients. In a recent multicenter, prospective study that treated 46 patients who had failed reduction in immunosuppression alone, 44% of the patients responded with 12 complete remissions. At approximately 1 year, 68% of responders remained disease free. Normal LDH was the sole predictor of response [39].

**Interferon**

Interferon alpha has been evaluated in isolated case reports of clinical remissions. The largest series included only 16 patients, but half of them responded. The therapy, however, can be poorly tolerated and has been associated with an increased risk for rejection [40]. It is not generally included in the primary therapy of PTLD.

**Chemotherapy**

Combination chemotherapy is used in patients who fail to respond to reduction in immunosuppression or rituximab infusion and in most patients with advanced disease at presentation. Regimens include anthracycline-based therapy typically used in aggressive lymphoma, including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), PROMACE-CYTABOM (cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, methotrexate, leucovorin), DHAP (dexamethasone, cytarabine, cisplatin), and VAPEC-B (doxorubicin, etoposide, cyclophosphamide, methotrexate, bleomycin, vincristine) [2, 41–43]. Response rates are variable but approached 70% in one study [41]. The main toxicity of cytotoxic chemotherapy in such patients is neutropenia and secondary sepsis. CHOP or CHOP plus rituximab is now the most widely used regimen.

**Radiation Therapy**

This modality is typically used to treat CNS disease [26]. The role of rituximab in these patients is unclear and most are not candidates for high-dose methotrexate-based approaches used in non-PTLD patients given baseline renal dysfunction or other comorbidities. Isolated lesions in patients with generalized disease may also benefit from involved-field radiotherapy.

**Hemopoietic Transplantation**

Case reports of successful autologous stem cell transplants in patients with chemotherapy-sensitive PTLD at relapse have been reported with preservation of graft function [44]. Most patients with refractory PTLD, however, are not candidates for salvage high-dose chemotherapy with stem cell support because of refractory disease and/or the comorbidities associated with organ dysfunction.

**Cellular Therapy**

Donor T cells that are EBV specific have been used in stem cell transplantation procedures whereby normal donor lymphocytes are expanded ex vivo. In contrast to solid organ transplantation, lymphoma seen following allogeneic bone marrow is derived from donor, not recipient, B lymphocytes and thus the tumor cells are HLA identical to the donor lymphocytes being infused [45]. For solid organ recipients, however, the donor may not be available for collection of cytotoxic T cells. Some studies have shown that using HLA-matched T cells from normal EBV-positive donors or recipient-derived natural killer cells and lymphocytes activated ex vivo may be a feasible alternative approach [46].

**Early Detection**

There has been an advocacy for serial monitoring of serum EBV viral loads and IL-10 levels, which in some studies have correlated with the development of EBV-positive PTLD [46–48]. Others have not found a reliable association [49]. Another biologic marker may be the presence of a unique monoclonal protein on serum protein electrophoresis, which has been reported in patients who developed PTLD [50–53].

**Prevention**

Limiting the levels of immunosuppression and avoiding OKT3 and ATG are important in preventing PTLD. Early studies also suggest that tacrolimus may confer a higher risk than cyclosporine. Rapamycin has recently been introduced as a new immunosuppressive agent, which is used most commonly in stem cell transplantation but has also been used in solid organ transplantation. In vitro, rapamycin has activity against B-cell PTLD cell lines. Successful treatment of PTLD has been reported in several cases treated with rituximab and rapamycin, but the contribution of the latter agent is unclear [54]. There are some reports of patients treated with rapamycin for immunosuppression who subsequently developed PTLD [55].

Vaccination against EBV may provide protection against PTLD, particularly in EBV-naïve pediatric patients. A vaccine directed against gp350, a viral membrane
protein, is currently under development [56]. Antiviral prophylaxis is another strategy that has been examined in a number of studies with variable results. A recent case control study with 100 cases of PTLD and 375 matched controls demonstrated an 83% reduction in risk with gancyclovir or acyclovir [57]. In that study, there was no correlation with pretransplant EBV status. A second study reported a prophylactic antiviral strategy for 40 pediatric liver transplant patients [58]. High-risk individuals were EBV-negative recipients who received EBV-positive grafts and were treated with i.v. gancyclovir for 100 days. All others received gancyclovir during their initial hospitalization, followed by oral acyclovir. EBV viral loads were monitored monthly with reduction in immunosuppression for increasing viremia. No cases of PTLD occurred in 18 such high-risk patients. Two cases, which resolved after discontinuing immunosuppression with tacrolimus, occurred in 22 low-risk patients. Overall, the incidence of PTLD using this strategy was 5% compared with 10% in comparable historical controls [58].

A similar phenomenon has been noted in patients with rheumatoid arthritis treated with methotrexate—namely, the occurrence of lymphoma, some of which is EBV associated. One series of 25 patients collected over 3 years yielded 18 cases of non-Hodgkin’s lymphoma (three with EBV) and seven cases of Hodgkin’s lymphoma (five were EBV positive). Methotrexate withdrawal was undertaken in eight patients with three clinical remissions, one of which was long term [59].

**Conclusion**

PTLD represents a heterogeneous group of diseases that occur after solid organ transplant. Early disease is typically EBV related, and other risk factors include degree and duration of immunosuppression, type of organ transplanted, and CMV status. Early lesions and polymorphic PTLD often respond to withdrawal of immunosuppression, but the prognosis of monomorphic and EBV-negative disease is much more variable. Patients who do not respond to reduction in immunosuppression or have advanced disease at presentation may benefit from antibody-based therapy with rituximab, often in combination with anthracycline-based chemotherapy. Efforts to improve early detection and define the role of antiviral prophylaxis and other preventative strategies are under investigation. Randomized controlled trials are critical to better define the optimal management of these patients, both in terms of prophylaxis and therapy.

**Disclosure of Potential Conflicts of Interest**

The authors indicate no potential conflicts of interest.