

Posttransplant Lymphoproliferative Disorder

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Introduction

The use of immunosuppressive therapies in the setting of solid organ transplantation is associated with a 20- to 50-fold increased risk of lymphoma [1]. There are increasing evidences that the use of a more potent, multi-agent approach to immunosuppression, which has made possible improved graft survival in many types of organ transplantation, has accelerated the development of these lymphoproliferative disorders [2,3]. Posttransplant lymphoproliferative disorder (PTLD) is defined as *the presence of abnormal proliferation of lymphoid cells*. This term is preferred to lymphoma because the lesion may not meet the pathologic criteria for malignant lymphoma, although may have clinically a malignant fashion. Years of clinical and laboratory observations now support the view that most cases of PTLD are the result of failure of the host immune system to defend against infection with a common virus, Epstein-Barr virus (EBV) [3-5].

This article reviews what is currently known about PTLD, including evidence of EBV in the

pathogenesis of PTLD, risk factors for its development, clinical presentation, methods for diagnosis, pathology, treatment, and current and future preventive strategies.

Incidence

Nonrenal allograft recipients (such as heart or lungs) are much more likely to develop PTLDs than renal recipients are [6,7]. Heavy immunosuppressive therapy is often used in the former group to reverse rejection to save their lives, whereas with severe rejection of kidney allograft, physicians have the option to discontinue immunosuppression and return the patients to dialysis therapy. Thus, when 1,490 neoplasms in recipients of nonrenal organs in the Cincinnati Transport Tumor Registry were compared with 7,630 malignancies in renal allograft recipients, lymphomas constituted 45% of neoplasms in the former group compared with only 12% in the latter. These findings are reinforced by reports that whereas PTLD occurs in less than 1% of renal recipients, it involves

3% of heart–, 3% of liver–, 8% of lung–, and 19% of intestine– recipients. The risk of PTLD in bone marrow recipients is less than 2% at 4 years posttransplant but may reach levels as high as 24% in recipients of HLA mismatched T–cell depleted marrow.

Risk Factors and Pathogenesis

The known risk factors of the development of PTLD can be divided into two categories: immunosuppression and EBV infection (Table 1). As already stated, the incidence of PTLD is related to the type of organ transplanted, and is highest in the first posttransplant year[3,7]. A significant part of this increased risk can be attributed to the relatively inversed levels of immunosuppression used for the extrarenal organs and the amount of lymphoid tissue present in the transplanted organ may be important. Whether other features specific to the type of allograft are also contributing is not clear at this time. Intense immunosuppression is a major factor[8–10]. Often three, four, or even five immunosuppressive agents are administered over a short time span. Whenever a new immunosuppressive agent is introduced, there is a “learning curve” while we learn to use the

agent in appropriate doses, especially when it is added to the combinations with other immunosuppressive medications. An increased frequency of lymphoma was noted after the introduction of antilymphocyte globulin, then cyclosporine, then OKT3 and with thus far, tacrolimus and mycophenolate mofetil[9–11]. The role of EBV in the pathogenesis of PTLD has been well established[7]. Approximately 90 to 95% of PTLDs are positive for EBV, including some of PTLDs are seronegative states at the time of the transplantation. In one study, 11% of seronegative pediatric– and 5% of seronegative adult– recipients developed PTLD, whereas the corresponding figures in their seropositive counterparts were 0% and 2% respectively[12]. Several investigators have shown that PTLD after hematopoietic stem cell transplantation or solid organ transplantation is associated with a rise in EBV–DNA load detected by polymerase chain reaction (PCR)–based methods in peripheral blood samples[8]. Initial studies in recipients of T–cell depleted grafts suggested that an elevated EBV–DNA load was highly predictive of the development of EBV–PTLD. Primary EBV infection begins in oropharyngeal epithelial cells that allow viral replication. Early in the course of the infection the virus infects B lymphocytes, which are the main repository of latent virus and are important in the dissemination of EBV to other tissues. There is a broad immune response to the infection, mediated initially by natural killer cells and CD4+ suppressor T lymphocytes[13,14]. Later, class I HLA molecules and specific for EBV control the EBV–induced proliferation of latently infected B cell. Immunosuppression either acquired, as in AIDS, or therapeutic, as in transplantation, interferes with this important host defense mechanism and thus allows

Table 1. Risk factors for development of PTLD

Immunosuppression
Total burden of immunosuppression
Type of organ transplant
Immunosuppressive agents
Ebstein-Barr virus infection
Pretransplant seronegativity
Donor seropositivity

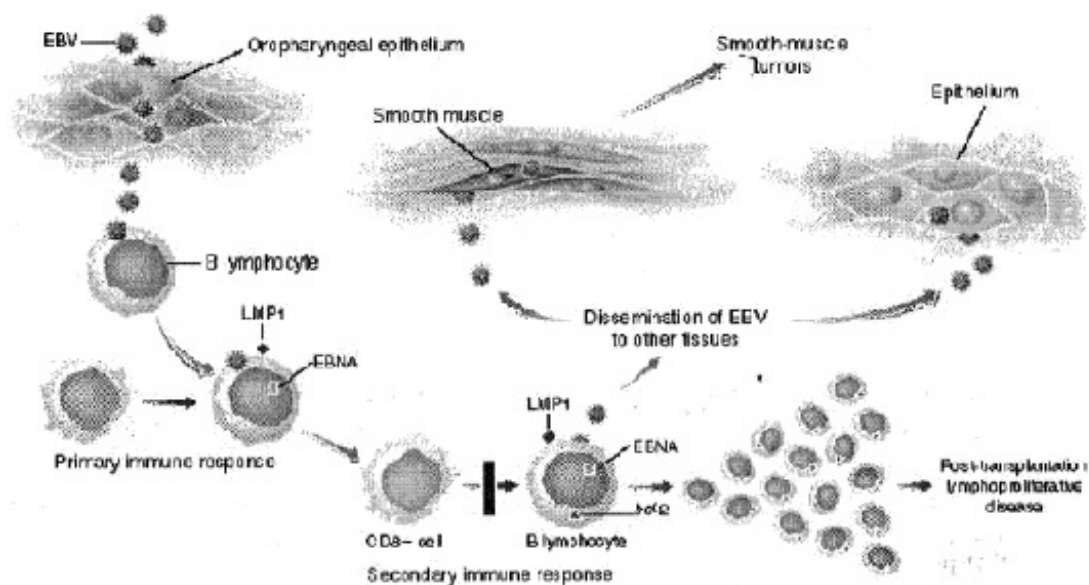


Fig. 1. Development of Epstein-Barr virus (EBV) related tumors in the immunosuppressed state

uncontrolled EBV-mediated proliferation of cells in susceptible patients (Fig. 1).

During acute infection, EBV infects oropharyngeal epithelial cells, where it is able to replicate and shed progeny that infect B lymphocytes in the area. The infected B lymphocytes express virally encoded EBV nuclear antigens (EBNAs) and latent membrane proteins (LMFs, specifically LMP1) that are the targets of the host's primary immune response by natural killer cells and CD4⁺ suppressor T lymphocytes. In a fraction of these EBV-infected B lymphocytes, the virus replicates and thus is disseminated to other sites. In the presence of immunosuppression, viral titers may be extraordinarily high. Later in the course of infection a secondary immune response occurs that is normally persists for the life of the host[9]; however, it may become impaired (black bar) in the setting of immunosuppression induced by agents such as the human immunodeficiency virus or drugs such as cyclosporine and tacrolimus. This allows

activated B lymphocytes, driven to proliferate by EBV, to replicate in an uncontrolled fashion and potentially leads to the development of post-transplant lymphoproliferative disorder. Furthermore, persistently high viral titers and impaired immune surveillance in the immunosuppressed state may allow the dissemination of EBV to distant epithelium and smooth muscle. Infected smooth muscle cells, presumably under the influence of EBV, may subsequently form tumors.

Clinical Manifestations

The common clinical presentations of PTLN are infectious mononucleosis-type illness, febrile illness with leucopenia, and focal organ system involvement. Focal organs involved in PTLN are gastrointestinal tract, central nervous system, allograft, other organs and disseminated disease. Whereas lymphomas in the general population frequently involves lymph nodes,

70% of PTLDs occurred in extranodal locations. The common signs and symptoms of PTLD in renal transplant patients are fever (52%), lymphadenopathy (28%), tonsillitis or pharyngitis (28%), intestinal perforation or obstruction (20%), central nervous system symptoms (16%), and weight loss (8%). The common sites of PTLD in renal transplant patients are lymph nodes (32%), kidney (32%), small intestine (32%), central nervous system (24%), bone marrow (20%), liver (20%), and large intestine (16%). Involvement of the allograft varies depending on the organ transplanted. Lungs were involved in 80% of heart–lung transplants, whereas one–third of patients with renal transplants developed lymphomas, as did those undergoing liver– and bone marrow– transplants [15]. Occasionally the presentation imitated allograft rejection and the diagnosis was made by finding an atypical lymphoblastic infiltrate in a biopsy specimen.

Diagnosis

The signs and symptoms of PTLD may be very nonspecific, and the diagnosis should be entertained early in patients who are doing poorly, particularly those who have the risk factors described previously. Disease is more likely to be extranodal than to be nodal [16,17], so extensive imaging, and deep tissue biopsies may be necessary to confirm the diagnosis. The key to diagnostic approach rests on the early recognition of PTLD [7]. Clinical suspicion must be raised whenever fever, pancytopenia, lymphadenopathy, encephalopathy, or appearance of extranodal tumors are encountered in the setting of graft dysfunction. Recently, it has been shown that semiquantitative and quantitative real–time PCR assay, detecting the increased levels of circulating EBV–DNA in the peripheral blood leukocytes, can complement the early diagnosis

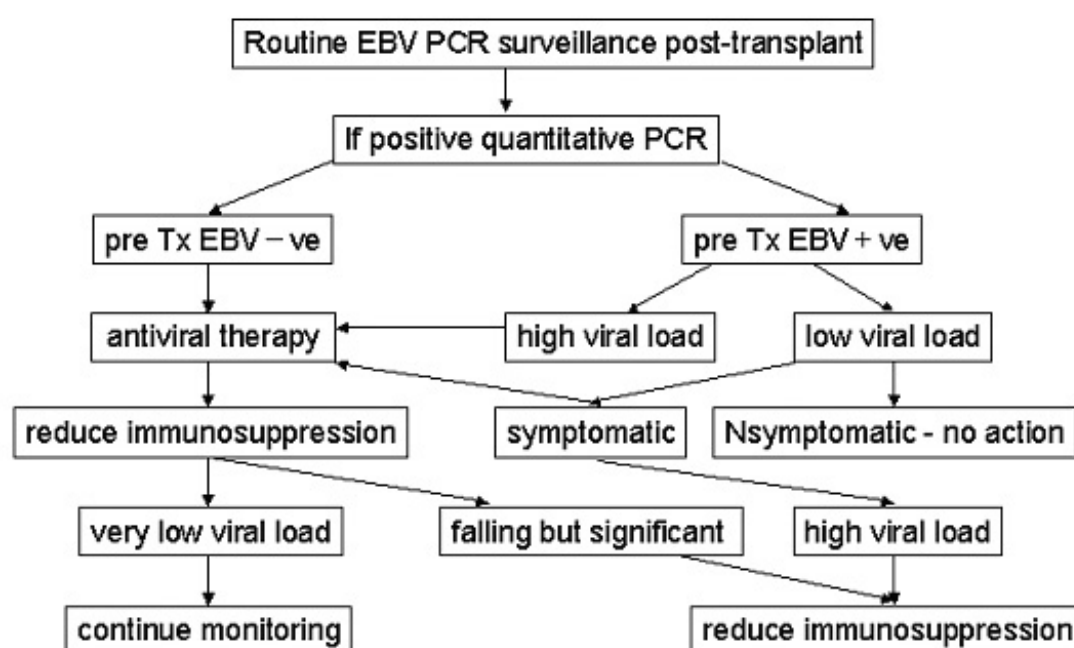


Fig. 2. Epstein-Barr virus (EBV) monitoring in posttransplant patients.

of PTLD and help monitor the effects of therapy [8] (Fig. 2). In contrast to the monitoring of EBV-DNA load in peripheral blood, measurements of EBV-specific T-cell responses are not routinely performed. Measurements can be made by interferon (IFN)- γ secretion assays using intracellular cytokine staining or Elispot assays, or by MHC class I-peptide tetrameric complexes for enumerating EBV-specific CTL. These studies indicate that the analysis of EBV-specific T-cell responses is feasible and may be useful in assessing the risk of PTLD development in patients with increased EBV-DNA load. However, for now, diagnosis of PTLD remains primarily dependent on timely provision of adequate biopsy processed for light microscopy, immuno-histology, and EBV in situ hybridization [18,19].

Classification

Three major PTLD classifications have been published over the last 15 years by Frizzera *et al.*, Nalesnik *et al.*, and Knowles *et al.* Modifications of both of the earlier classification schemes have also been reported. All recognize

a spectrum of lesions that range from those that appear more benign to others that have more features in common with traditional lymphomas. A simplified subclassification has been developed by Nalesnik *et al.* [14] (Table 2).

Prognosis and Outcome

Overall, the results of treatment have been disappointing [20–22], with mortality from PTLD or related complications reported in over 50% of patients. The survival statistics following the diagnosis of posttransplant lymphoma show a sobering 50% death with CNS lymphoma, involvement of three or more organs, T-cell PTLD, and late onset PTLD (usually EBV-negative) appear to do particularly poorly [23–25].

Treatment

Management of PTLD remains a challenge for physicians who are taking care of organ transplant recipients. There is no controlled trial with any of the treatment modalities. Currently, therapy consists primarily of reduction or cessation of immunosuppression with the

Table 2. Classification of posttransplant lymphoproliferative disorder

Microscopic features	Pathologic category
Hyperplasia	Infectious mononucleosis Plasma cell hyperplasia
Neoplasm	Polymorphic PTLD Lymphomatous (monomorphic) PTLD* Other (includes myeloma, plasmacytoma, B-cell lymphoma with Hodgkin's disease-like feature)

* include B-, T-, natural killer-, and null cell- lymphomas.

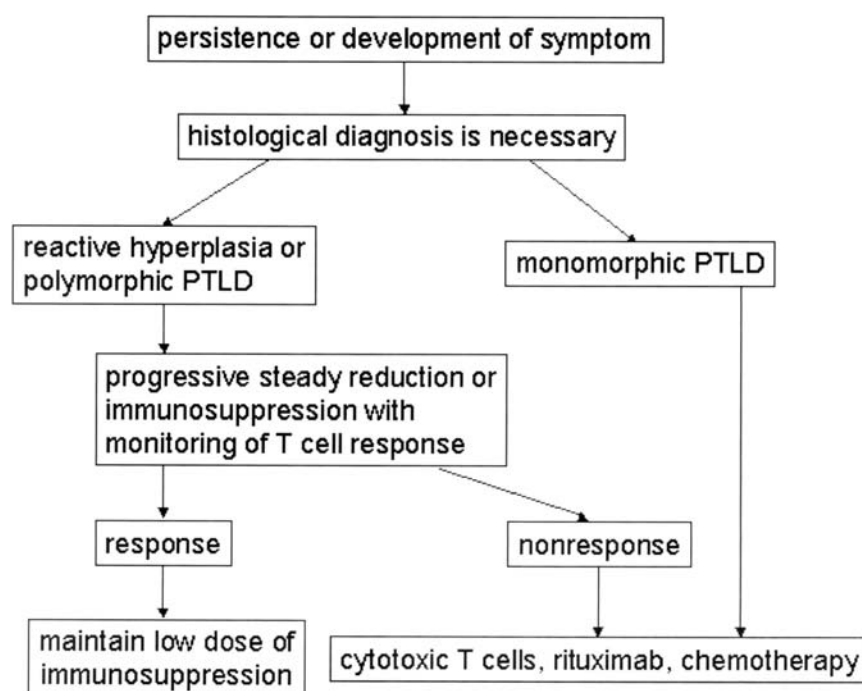


Fig. 3. The management of PTLD using EBV PCR screening.

attendant risk of graft loss because of rejection, and surgical excision of the tumor[10,11,26,27], if possible, when often includes allograft removal in renal transplant recipients. The treatment modalities for PTLD are reduction in immunosuppression, surgical resection or graftectomy, antiviral chemotherapy, radiotherapy, cytotoxic chemotherapy, interferon alpha, IVIG (intravenous immunoglobulin), anti-CD20 antibodies, IL-6 antibody, and EBV-specific Cytotoxic T Lymphocytes[28-30]. A suggested schema for the management of PTLD using EBV PCR screening when reduction of immunosuppression has failed is shown in Fig. 3.

Conclusion

PTLD is an uncommon but well recognized

complication of solid organ and hematopoietic stem cell transplantation and one of the adverse sequelae of immunosuppression for prevention of acute rejection.

With the rather grim survival prospects of patients who develop posttransplant lymphomas, prevention rather than treatment would seem to deserve the highest priority. This raises the dilemma of balancing too little against too much, that is, underimmunosuppression with resulting graft rejection against overimmunosuppression and lymphoma. Clearly, some risk of lymphoma must be accepted in organ transplant recipients. In general, because the risk of lymphoma is infinitely smaller than that of graft rejection, there is an understandable inclination of preserving a functioning graft even though this carries on increased risk of lymphoma. Nevertheless, it would seem prudent to aim at the 'smallest necessary' cumulative immuno-

suppressive regimen. A final word of caution would seem appropriate with respect to the new, even more powerful immunosuppressive drugs which are currently being used and introduced. While there is an understandable desire for stronger and better immunosuppression, the lymphoma issue should not be overlooked. It would be wrong to take an alarmist position and to argue against the introduction of new immunosuppressants. Nevertheless, care should be taken to carefully monitor the effect of any new drug on the incidence of lymphomas, a complication which fortunately affects a very small proportion of all transplant patients but which is associated with a high risk of death.

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