

Clinical Issues

Case 3 : Posttransplant Lymphoproliferative Disorder

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The use of immunosuppressive therapies in the setting of solid organ transplantation is associated with a 20-fold to 50-fold increased risk of lymphoma. There is increasing evidence 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 disorder

Posttransplant lymphoproliferative disorder (PTLD) is defined as *the presence of an abnormal proliferation of lymphoid cells*. This term is preferred to lymphoma because these lesions may not meet the pathologic criteria for malignant lymphoma, although they may behave clinically in 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).

This article reviews what is currently known about PTLD, including evidence for 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. Heavy immunosuppressive therapy is often used in the former group to reverse rejection to save their lives, whereas with severe rejection of kidney allografts, physicians have the option to discontinue immunosuppression and return the patients to dialysis therapy. Thus, when 1490 neoplasms in recipients of nonrenal organs in the CTTR were compared with 7630 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 intestinal 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 for 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. A

Table 1. Risk Factors for Development of PTLD

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

significant part of this increased risk can be attributed to the relatively increased levels of immunosuppression used for the extra-renal organs. Whether other features specific to the type of allograft are also contributing is not clear at this time.

Intense immunosuppression is a major factor. 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 agents in appropriate doses, especially when it is added

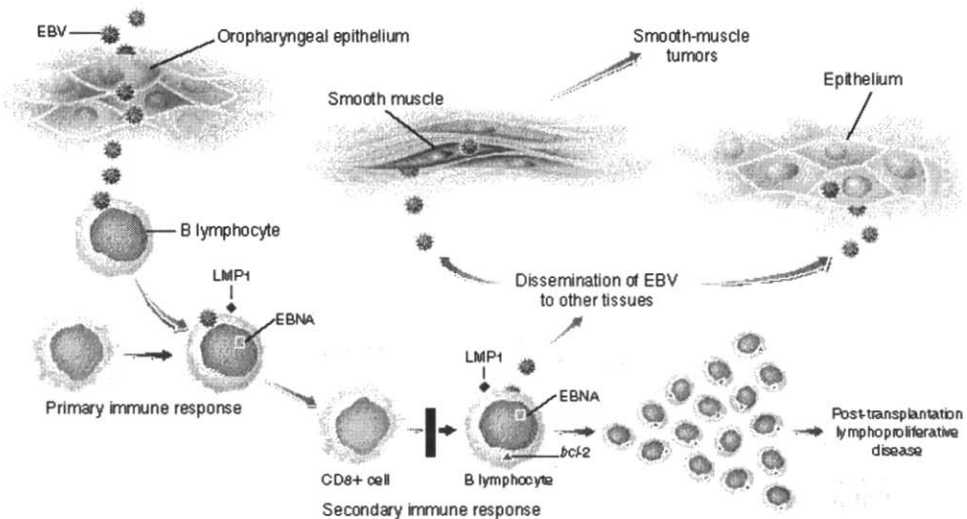


Fig. 1. Development of EBV-Related Tumors in the Immunosuppressed State. During acute infection EBV infects oropharyngeal epithelial cells, where it is able to replicate and shed progeny that infect B lymphocytes in the area. The infected B lymphocytes express virally encoded EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs, 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 mediated by HLA-restricted CD8+ cytotoxic T lymphocytes specific for EBV. The secondary immune response normally persists for the life of the host; 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-transplantation 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.

to combinations of other immunosuppressive medications. An increased frequency of lymphoma was noted after the introduction of antilymphocyte globulin, then cyclosporin, then OKT3 and with limited experience gained, thus far, tacrolimus and mycophenolate mofetil.

The role of EBV in the pathogenesis of PTLD has been well established. Approximately 90% to 95% of PTLDs are positive for Epstein-Barr virus (EBV), including some T cell PTLDs. A risk factor for the development of PTLD is seronegative status at the time of the transplantation. In one study, 11% of seronegative pediatric and 5% of seronegative adults recipients developed PTLD, whereas the corresponding figures in their seropositive counterparts were 0 and 2%, respectively. Some investigators suggest that high viral loads of EBV in the peripheral blood may presage the onset of 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. Later, CD8⁺ cytotoxic T lymphocytes restricted to 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 uncontrolled EBV-mediated proliferation of cells in susceptible patients (Fig 1).

CLINICAL MANIFESTATIONS

The common clinical presentations of PTLD

are as follows :

- Infectious mononucleosis-type illness
- Febrile illness with leukopenia
- Focal organ system involvement
 - GI tract
 - Central nervous system
 - Allograft
 - Other organs
- Disseminated disease

Whereas lymphomas in the general population frequently involve 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. 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 nodal, so extensive imaging and deep tissue biopsies may be ne-

cessary to confirm the diagnosis.

The key to diagnostic approach rests on the early recognition of PTLD. 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 polymerase chain reaction assay detecting the increased levels of circulating EBV DNA in the peripheral blood leukocytes can complement the early diagnosis of PTLD and help monitor the effects of therapy. However, for now, diagnosis of PTLD remains primarily dependent on timely provision of adequate biopsy processed for light microscopy, immunohistology, and EBV in situ hybridization

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

Table 2. Classification of Posttransplant Lymphoproliferative Disorder

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

* Includes B, T, natural killer, and null cell lymphomas

been developed by Nalesnik (Table 2).

PROGNOSIS AND OUTCOME

Overall, the results of treatment have been disappointing, 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 rate within a year of diagnosis. Patients with CNS lymphoma appear to do particularly poorly.

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 attendant risk of graft loss because of rejection, and surgical excision of the tumor, if possible, when often includes allograft removal in renal transplant recipients.

The treatment modalities for PTLD are as follows:

- Reduction in immunosuppression
- Surgical resection or graftectomy
- Antiviral chemotherapy
- Radiotherapy
- Cytotoxic chemotherapy
- Interferon plus Ig
- Anti B cell antibodies
- Infusion of donor cytotoxic T cell, autologous LAK cells or allogenic leukocytes
- Genetically engineered antibodies or antibody-toxin conjugates
- Anti-idiotypic antibodies specific for patient's B cell
- Cloned cytotoxic T cells specific for patient's MHC and EBNA epitopes

CONCLUSION

Posttransplant lymphoproliferative disorder is an uncommon but well recognized complication of solid organ and bone marrow 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 may carry on increased risk of lymphoma. Nevertheless, it would seem prudent to aim at the 'smallest necessary' cumulative immunosuppressive regimen.

A final word of caution would seem appropriate with respect to the new, even more powerful immunosuppressive drugs which are currently being 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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