Seminars in Pediatric Surgery 26 (2017) 257–266

Contents lists available at ScienceDirect

Seminars in Pediatric Surgery

journal homepage: www.elsevier.com/locate/sempedsurg

Post-transplant lymphoproliferative disorder after solid-organ transplant in children

Michael J. Absalon, MD, PhD*, Ruby A. Khoury, MD, Christine L. Phillips, MD

Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 7018, Cincinnati, Ohio 45229

ARTICLE INFO

Keywords:
PTLD
Post-transplant lymphoproliferative disorder

ABSTRACT

The post-transplant lymphoproliferative disorders (PTLD) are a diverse group of potentially life-threatening conditions affecting organ transplant recipients. PTLD arises in the setting of an attenuated host immunologic system that is manipulated to allow a foreign graft but then fails to provide adequate immune surveillance of transformed malignant or premalignant lymphocytes. The diversity of biological behavior and clinical presentation makes for a challenging clinical situation for those involved in the care of children with PTLD occurring after solid-organ transplantation. This review details a large transplant center's multidisciplinary approach to monitoring for PTLD and systematic approach to intervention, which has been essential for early recognition and successful treatment.

Introduction

Solid-organ transplantation has led to significant improvement in survival and quality of life of children experiencing organ failure from a wide variety of health conditions.[1–4] An essential contribution to this success emerged from a basic understanding of immunology that allowed manipulation of the immune system so that a foreign graft can be tolerated while not leaving the patient prohibitively vulnerable to infections. However, current strategies to suppress immune surveillance of foreign tissue also lead to suppression of a monitoring system for virus-transformed cells and malignant or premalignant entities. The post-transplant lymphoproliferative disorders (PTLD) are a diverse group of potentially life-threatening malignant or premalignant conditions that arise within the hematopoietic system in this attenuated host immune system. Appreciating the epidemiology, biology, and diverse clinical presentations of PTLD in solid-organ recipients can assist in developing a systematic approach to the management of children at risk for PTLD.

PTLD subtypes

The 2016 revision of the World Health Organization classification of lymphoid neoplasms describes six categories of PTLD: plasmacytic hyperplasia, florid follicular hyperplasia, infectious mononucleosis, polymorphic, monomorphic, and classical Hodgkin lymphoma PTLD.[5] The first three categories are often referred to as "early PTLD". The term "early" PTLD is not meant to imply that the other more lymphomatous forms of PTLD necessarily stem from these lesions, but rather refers to the preserved architecture of the lymph tissue albeit with expansion of specific cell types occurring within the tissue. The lesions are typically polyclonal and are nearly universally associated with EBV.[6] In contrast to the "early" lesions, the polymorphic form of PTLD describes proliferations of plasma cells and other B-lineage lymphocytes of small and large sizes that do disrupt the lymph node architecture (Figure 1). Polymorphic lesions are often monoclonal but polyclonal lesions may also occur.[7] The monomorphic PTLDs are monoclonal B-lineage processes that are most commonly histologically indistinguishable from diffuse large B-cell lymphoma (DLBCL),[8] but the category also includes entities such as Burkitt lymphoma, NK/T-cell lymphomas.[9–12] Hodgkin lymphoma occurring in the solid-organ recipient is histologically and immunohistologically indistinct from classical Hodgkin lymphoma that occurs in the nontransplant population, although expression of CD20 and evidence of EBV involvement by *in situ* studies is more commonly observed.[13]

PTLD occurring in children is most commonly associated with EBV. EBV is a double-strand DNA human herpes virus that infects the epithelial cells of the nasopharynx where it exists in its lytic phase, is highly contagious, and is the cause of infectious mononucleosis.[14] It also infects lymphocytes (predominately B-cells) where it most commonly resides in a latent phase.[15] During the latent phases of the virus replication cycle, EBV exists as a circular DNA episome distinct from host DNA. Whereas the gene products necessary for viral replication are inactive, other viral gene products in latently infected lymphocytes may activate signals for cell proliferation and survival. Serologic evidence of prior EBV infection is ubiquitously found in healthy adults, but circulating

* Corresponding author.
E-mail address: Michael.absalon@cchmc.org (M.J. Absalon).

http://dx.doi.org/10.1053/j.sempedsurg.2017.07.002
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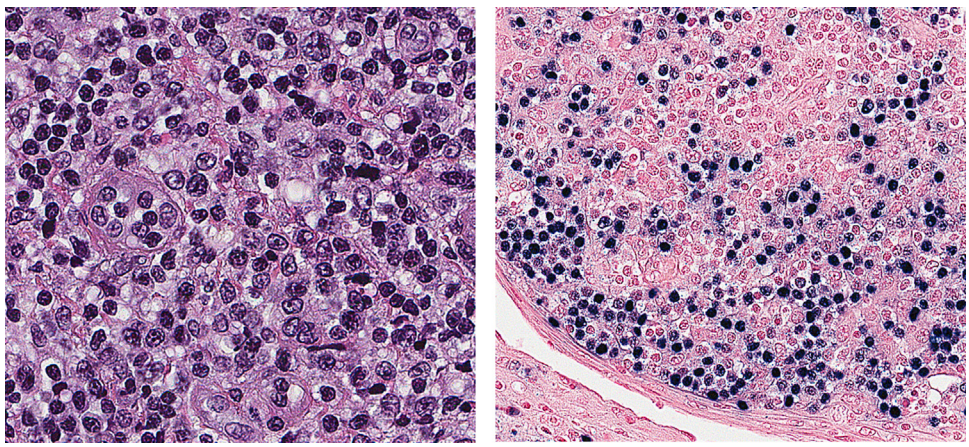

Fig. 1. Polymorphic EBV-associated PTLD. *Left panel*: H&E stain of a palatine tonsil from a liver transplant recipient shows effacement of the nodal architecture with a mixed proliferation of predominantly lymphocytes, few immunoblasts, and plasma cells. Lymphocytes are small to medium in size with slightly irregular nuclei and conspicuous nucleoli. *Right panel*: *in situ* hybridization for EBER shows numerous positive cells.

B-cells with episomal EBV is typically not detected in peripheral blood due to immune surveillance by cytotoxic T-cells that keep proliferating EBV-infected B-cells in check. The epidemiology of EBV infection is such that young children are frequently EBV-naïve at the time of solid-organ transplantation.[16] These children become EBV infected either through community acquired means, or through infection that occurs through EBV-reactivation[17,18] in donor lymphocytes that accompany the graft. Reactivated EBV infects other recipient lymphocytes leading to latently infected (host) B-cells often without showing signs of mononucleosis or other symptoms of EBV disease. Proliferation of EBV-infected lymphocytes occurring in solid-organ recipients is therefore usually of host-origin.[7] In either mechanism of EBV exposure, the child solid-organ recipient encounters EBV in the setting of immunosuppression that may not allow adequate subsequent immune surveillance against aberrant lymphoproliferation.

Risk factors

The reported incidence of PTLD varies considerably among transplant centers and likely depends upon the predominant age of the patient population, the organ transplanted, and the center's approach to immunosuppression. Variability in the clinical threshold in which PTLD is recognized and confirmed by biopsy may also account for reported differences. These caveats aside, the incidence of PTLD appears to be highest among recipients of intestine[19,20] and lung,[21–23] followed by heart,[24–27] liver,[28–31] and then kidney.[32–35] The incidence of PTLD is higher in the pediatric population than in adults and is primarily accounted for by EBV-positive disease.[36] EBV-positive disease tends to occur early after transplantation while EBV-negative PTLD more commonly occurs late (median onset 3.3 vs 6.6 years).[36] The 100-day mortality from any cause after development of PTLD in a population including children and adults is historically high (23.3%).[36]

Risk factors for the development of EBV-associated PTLD are shown in Table 1. Young age and negative EBV-serologic status of the recipient at time of transplant are likely related risk factors. EBV infection and seroconversion increase with age in the general population,[16] therefore older organ recipients are more likely to have developed adequate immunologic surveillance for EBV at the time of transplant that may be functional in the post-transplant period. The degree of immunosuppression clearly contributes to the development of PTLD. Patients that require a relatively high level of calcineurin inhibitor or those that receive T-cell depleting antibody therapy have a higher incidence.[37–41] The degree of immunosuppression is often greatest during the period immediately following organ transplant, therefore less time from organ transplantation increases the risk for PTLD as does receiving a graft from an EBV-positive donor.[42,43] Multiple episodes of graft rejection may also contribute to the development of PTLD presumably because of a subsequent need for increased immunosuppression.[30] While the difference in PTLD incidence between organs transplanted is partially explained by the degree of immunosuppression required for graft tolerance, a contributing factor may also be the donor lymphocyte load accompanying the graft which then increases the risk of EBV infection of recipient B-cells. Previous history of PTLD is associated with an 11–13% risk of subsequent PTLD and likely reflects an inability to achieve or maintain a significant reduction in the overall level of immunosuppression following the initial occurrence.[24,36,44]

EBV monitoring

Monitoring for EBV in peripheral blood can be a useful but sometimes confusing tool for assessing patients at risk for PTLD. The detection of EBV in blood can be used to support a diagnosis of EBV-associated PTLD or to identify patients at sufficient risk for PTLD often prompting further evaluation or alteration of the immunosuppression regimen. The success of this approach has been illustrated by several groups that have reported a significant decrease in incidence of PTLD by monitoring and reducing the degree of immunosuppression in those deemed high risk for PTLD.[29,30,45,46] Monitoring is perhaps particularly useful early after organ transplantation to capture when an organ recipient converts from an EBV-undetectable state to a high detectable state.

Table 1
Risk factors for the development of EBV-associated PTLD

- Young age at time of organ transplantation
- EBV naïve at time of organ transplantation
- Donor EBV-positive in EBV serologically negative recipients
- Organ transplanted (incidence of PTLD)
  - o Lung (1.8–23%)
  - o Intestine (14–19%)
  - o Heart (5–10%)
  - o Liver (2.8–8%)
  - o Kidney (0.005–9%)
- Extent of immunosuppression
  - o Use of T-cell depleting antibodies
  - o Calcineurin inhibition
- Time from transplantation less than 1 year
- Previous development of PTLD (11–13% incidence)