New Developments in the Diagnosis and Management of Posttransplantation Lymphoproliferative Disorders in Solid Organ Transplant Recipients

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Posttransplantation lymphoproliferative disorders (PTLDs) have emerged as important causes of morbidity and mortality in solid organ transplant recipients. Epstein-Barr virus (EBV) plays a major pathophysiologic role in the development of many, if not most, of the highly diverse disease states, which span the spectrum from infection to malignancy, encompassed by the term “PTLD.” Clinical presentation and biological behavior associated with PTLD are highly variable; patients experiencing primary EBV infection in the immediate posttransplantation period are most vulnerable. New insights into PTLD pathogenesis provide exciting opportunities for rational and targeted approaches to the diagnosis, prevention, and treatment of PTLD. This article highlights some of these developments and outlines unresolved and controversial issues in PTLD management.

NEW INSIGHTS INTO PTLD PATHOGENESIS

The primary—and perhaps exclusive—target of EBV in the immunocompetent host is the B cell. EBV has usurped normal physiologic B cell responses to persist in the host, establish latency, and transmit infection [4, 5]. During the course of naive B cell infection, EBV-coded proteins substitute for antigen, T cell help, B cell receptor, and other signals that result in cellular activation, proliferation, differentiation, and survival, mimicking pathways followed when naive B cells encounter antigen, with the end result of establishing EBV latency in memory B cells. Here, EBV persists in a transcriptionally silent state that is invisible to the immune system. The lytic EBV cycle is triggered and infectious virus is produced when B cells differentiate into plasma cells. While this is happening, additional EBV-induced factors down-regulate normal immune responses to virus-infected cells. All EBV-infected B cells, except memory cells, express antigens recognized by EBV-specific cytotoxic T cells, and antibody neutralizes the virus. An equilibrium between virus and host is established. A number of controversial and unresolved issues in this theoretical model have recently been discussed elsewhere [4, 5].

What goes wrong in the immunosuppressed allograft recipient that leads to PTLD (figure 1)? Naive EBV-infected B cells express a repertoire of latent EBV proteins known as “the growth program,” which results in polyclonal cellular proliferation. The local microenvironment (cytokine milieu) may

Posttransplantation lymphoproliferative disorders (PTLDs) have emerged as important causes of morbidity and mortality in solid organ transplant (SOT) recipients in an era in which an increasing variety of powerful new drugs are available for immunosuppression, in which rates of patient and graft survival have significantly improved, and in which transplantation is often the treatment of choice for organ failure in pediatric populations. The epidemiology of PTLD, risk factors for development, approaches to the diagnosis, prevention, and treatment were recently reviewed elsewhere [1–3]. Epstein-Barr virus (EBV) plays a major pathophysiologic role in the development of many, if not most, of the highly diverse disease states encompassed by the term “PTLD.” New insights into PTLD pathogenesis provide exciting opportunities for rational and targeted approaches to the diagnosis, prevention, and treatment of PTLD. This article highlights some of these developments and outlines unresolved and controversial issues in PTLD management.

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Figure 1. How Epstein-Barr virus (EBV) might give rise to posttransplantation lymphoproliferative disorders (PTLDs). This model is adapted from that outlined by Thorley-Lawson and Gross [4]. Naive EBV-infected B cells express a repertoire of latent EBV proteins known as "the growth program," resulting in polyclonal cellular proliferation. Specific clones may have a growth advantage resulting in oligoclonal or monoclonal proliferation. These cells would be cleared by a combination of differentiation into memory cells and killing by EBV-specific cytotoxic T lymphocytes (CTLs). The differentiation to memory cells involves down-regulation of latent EBV gene expression from the growth program through a "default program" to a transcriptionally silent state in the memory cell. In the presence of an impaired immune response, rates of proliferation may exceed rates of clearance and differentiation, leading to clinical PTLD presentations. Differentiation of EBV-infected B cells into plasma cells results in lytic viral replication, thereby continuing to recruit newly infected cells into the process. Mutations may occur during the lymphoproliferation process. If this occurs during the activated B cell blast stage, it results in PTLD with a naive B phenotype. Cells may be stuck at the germinal-center stage, resulting in Hodgkin disease (constitutive expression of the default program), or c-myc activation may cause the cell to get stuck as the germinal-center cell is entering the memory compartment (Burkitt lymphoma). In the presence of high levels of infectious virus, "bystander" cells, such as germinal-center and memory B cells, that are not normally infected with EBV may become infected. These cells will express the growth program, be unable to differentiate out of the cell cycle, be dependent on the T cell response for destruction, and be vulnerable to mutation events resulting in clinical PTLD.
give growth advantage to specific clones, resulting in oligoclonal or monoclonal proliferation. Normally, these cells would be cleared by both differentiation into memory cells and EBV-specific cytotoxic T lymphocytes (CTLs) that recognize antigens expressed. In the presence of an impaired immune response, rates of proliferation may exceed rates of clearance and differentiation, leading to clinical presentations with morphology, such as plasmacytic hyperplasia and polymorphic PTLD. Cytogenetic abnormalities may also occur, resulting in a more “malignant” form of PTLD. Patients experiencing primary infection are at highest risk, not only because of delays in the development of the CTL response, but also because, in the absence of neutralizing antibody, newly infected B cells are continually recruited into the process by infectious virus produced in the lytic cell cycle.

Recently, a surprising unexpected observation was made in 3 studies of V-gene sequences of PTLD cases that has dramatically changed theories of disease pathogenesis (reviewed by Kuppers [5]). Pre-B cells, naive B cells, and immature B cells do not carry somatic hypermutations, which are a hallmark of antigen-selected germinal-center B cells and their descendants. Although some PTLD cases occurring early after transplantation are derived from naive B cells, most PTLD cases (particularly those occurring late after transplantation) have their origin from germinal center and post–germinal center B cells. Although further validation is required, PTLD cases with this B cell lineage may have a worse prognosis than those involving naive B cells. It has been suggested that infection of these “bystander” cells is an accidental event [4]. When infected with EBV, these cells will express the growth program, will be unable to differentiate out of the cell cycle, and will depend on the T cell response for destruction. EBV-positive germinal-center B cells may be particularly vulnerable to additional transforming mutation events, because this is the site at which somatic hypermutation and class-switching occur. Moreover, EBV may be able to rescue and clonally expand post–germinal center B cells with crippling mutations that would normally result in apoptotic cell death, and ongoing somatic hypermutation can occur in the absence of the usual dendritic and T cell signals. It is interesting to speculate that the high levels of infectious virus in an immunocompromised host, particularly one experiencing a primary infection, significantly increases the probability of “accidental” infection of cells that would only very rarely be infected in the immunocompetent host (i.e., memory and germinal center B cells, T cells, and NK cells). Failure of a vigorous CTL response to rapidly destroy these expanding clones sets the stage for secondary transforming events to which B cells in germinal centers are particularly vulnerable.

### Identifying the High-Risk Patient

Risk factors for PTLD development have recently been reviewed elsewhere [1, 6]. Primary EBV infection, usually as a result of infection transmitted from EBV-seropositive donors to EBV-seronegative recipients, is a major risk factor for early (occurring in the first year after transplantation) PTLD, increasing the risk by 10–76-fold. Disease risk is also dependent on the type of organ allografted, partially because of the intensity of the immunosuppression used, but also likely because of the biological characteristics of the allografted organ (table 1). Although global immunosuppression, rather than any single immunosuppressive agent, is most important in determining PTLD risk, potent antilymphocyte antibodies for the induction or treatment of acute rejection increases risk, particularly when administered in prolonged or repeated doses. Cytomegalovirus (CMV) mismatch and CMV disease act as cofactors for PTLD disease development, as does hepatitis C virus infection. Although antigenic mismatching has been identified as a major risk factor in stem cell recipients, this is less apparent in SOT recipients. In SOT recipients, antigenic stimulation by autoimmune disorders or chronic infections, as are found in patients with cystic fibrosis, may increase risk. Preliminary evidence suggests that cytokine gene polymorphisms may also affect PTLD development. Although young age and its associated risk of primary EBV infection are risk factors for early PTLD, older recipient age appears to be a risk factor for the development of PTLD after the first posttransplantation year. This may reflect the impact of immunosuppression on a senescent immune system.

### How Does PTLD Present Clinically?

Cases of PTLD represent a highly diverse spectrum of disease states that vary greatly with respect to clinical presentation and behavior (reviewed in [1, 2]). The disease may be nodal or extranodal, localized, or widely disseminated. The gastrointestinal tract is a common site of extranodal disease. CNS disease may also occur. Disease limited to the allograft is a common manifestation of early PTLD. Its differentiation from allograft

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Percentage of patients</th>
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<tbody>
<tr>
<td>Kidney</td>
<td>1.0</td>
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<tr>
<td>Liver</td>
<td>2.2</td>
</tr>
<tr>
<td>Heart</td>
<td>3.4</td>
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<tr>
<td>Lung</td>
<td>1.8–7.9</td>
</tr>
<tr>
<td>Heart-lung</td>
<td>9.4</td>
</tr>
<tr>
<td>Intestinal</td>
<td>7.0–11.0</td>
</tr>
<tr>
<td>Multivisceral</td>
<td>13.0–33.0</td>
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</tbody>
</table>

**NOTE.** Adapted from [6]
rejection in this situation is critically important. Patients may be symptomatic or asymptomatic. Lesions may be limited and progress slowly, or the patient may present with a fulminant, multiple-system, sepsis-like syndrome. PTLD may resemble a self-limited infection or be indistinguishable from non-Hodgkin lymphoma.

A STANDARDIZED APPROACH TO CLASSIFICATION IS KEY

The “gold standard” for PTLD classification is pathological examination [1, 7]. A standardized approach to pathological analysis is essential for interinstitutional comparison of the epidemiology, prevention, and treatment of this complication. An updated classification system for PTLD was recently published under the auspices of the World Health Organization and is recommended for use (table 2) [8]. Although the role of EBV is firmly established in the development of B cell PTLD, EBV may also be pathogenic in a subset of T cell lymphomas occurring after receipt of an SOT that account for ~13% of post-transplantation cases of lymphoma (20%–38% of patients are EBV positive; reviewed in [9]). Over the past decade, the proportion of EBV-negative patients with PTLD appears to have been increasing (21%–32% of patients). These cases generally have a worse prognosis than their EBV-positive counterparts and may be the predominant form of late PTLD [7]. The pathogenic role of EBV early in the course of this disease with subsequent genome loss cannot be excluded.

There are intrinsic weaknesses in the purely histological classification of PTLD. Additional pathological tools may be useful for developing more effective and targeted therapies, as outlined in table 3 [1, 7]. In the future, it is hoped that comprehensive molecular profiling might be used to guide therapy.

HOW USEFUL ARE EBV LOAD ASSAYS IN PTLD MANAGEMENT?

B cell PTLDs occurring early after transplantation are often associated with high EBV loads measured in peripheral blood samples obtained from patients, and these high loads often precede clinical symptoms. These assays have been used as diagnostic and surveillance tools and to monitor response to therapy. Despite their potential power, they have significant limitations, as reviewed by Stevens et al. [10].

It is extremely important to differentiate the use of these assays for surveillance (frequent repetitive monitoring of individual patients) from their use as a diagnostic tool for a single sample in the presence of established disease. Virus load assays appear to be most useful when used for surveillance for patients who are EBV seronegative before receiving a transplant. The sensitivity, specificity, and positive and negative predictive values of the assays used for diagnosis or surveillance may be highly dependent on the type of population studied (e.g., adult versus pediatric, type of organ transplanted and pretransplantation EBV serostatus [11]). In general, in surveillance studies involving pediatric patients receiving an SOT, high virus loads have been found to be sensitive but not specific predictors of PTLD development. It must be noted, however, that EBV-associated PTLDs have been described in patients with low or undetectable EBV loads [12]. This may reflect practical limitations with respect to the frequency with which monitoring can occur. Episodes of “high virus loads” that are triggering events for PTLD may be missed and may no longer present when clinical disease is apparent. In contrast, when high EBV loads were used to diagnose PTLD in an adult population, they were found to be highly specific but to lack sensitivity [13].

EBV load assays also suffer greatly from lack of standardization [10]. The optimal assay technique, type of sample (e.g., lymphocytes vs. whole blood samples vs. plasma samples), and sampling schedule have not been determined. Proficiency testing of laboratories for these assays are currently not available, and quantitative values are not cross-referenced between laboratories. Data regarding the natural history of EBV load in the absence of intervention are limited, preventing the clear definition of “trigger points” that are predictive of PTLD and at which preemptive intervention should take place. Clearly, significantly more work needs to be done to realize the full potential of these laboratory tools.

A number of investigators studying both stem cell recipients and SOT recipients have attempted to improve the specificity of EBV load monitoring by combining it with serial monitoring of EBV-specific CTL responses [14–16]. Persistently high EBV

![Table 2. Categories of posttransplantation lymphoproliferative disorders (PTLDs).](cid:2004:39 (1 October) 1019)
loads are sometimes seen in the absence of symptoms and PTLD development. This may represent a high “set point” for equilibrium between host and virus in the presence of a suboptimal immune response. Recently, investigators observed that high virus loads were predictive of PTLD development only when associated with undetectable or low-level CTL responses. The dual-assay approach was associated with positive predictive values for PTLD of 100%. Although associated with increased complexity and cost, this approach may distinguish patients who are able to spontaneously control virus-induced lymphoproliferation from those who require specific and early preemptive intervention.

Serial measurement of quantitative EBV load has been used to monitor response to therapy. A decrease and “clearance” of EBV load is usually associated with clinical response after treatment. However, in one study, when rituximab, a chimeric antibody directed against the CD20 antigen expressed on B cells, was used, decreases in EBV load did not predict clinical response [17]. Rebound of EBV load often occurs after clinical remission has been achieved. Preliminary data suggests that high viral loads in this setting do not appear to be predictive of recurrent disease [10]. The utility of ongoing monitoring of patients who have survived PTLD is uncertain.

**CAN PTLD BE PREVENTED THROUGH UNIVERSAL PROPHYLAXIS OR PREEMPTIVE STRATEGIES?**

Antiviral agents (such as intravenous immunoglobulin containing neutralizing antibody or acyclovir, ganciclovir, and foscarnet) that target neutralizing steps in the lytic virus cycle are sometimes used for PTLD prevention. The potential efficacy of these agents depends on the relative importance of EBV-driven lymphoproliferation (which is not influenced by these agents) and the lytic virus cycle (which is) on EBV-induced lymphomagenesis. There is an increasing body of evidence suggesting that the role of lytic virus in the pathogenesis of PTLD may have been seriously underestimated. The recruitment of large numbers of newly infected cells into the lymphoproliferative process—including those that, under normal circumstances, would not be infected—may be a crucially important first step in PTLD development. The majority of EBV DNA detected in peripheral blood is found in transcriptional silent memory B cells, even in immunosuppressed patients with high virus loads. Data regarding EBV gene expression and the detection of lytic virus in peripheral blood is inconsistent and often involves obtaining a single sample from small numbers of patients (reviewed by Hopwood et al. [18]). However, a recent study of EBV gene expression in peripheral blood samples obtained from a large number of asymptomatic cardiovascular transplant recipients who were observed serially found surprisingly frequent expression of “growth pattern” transcripts and lytic replication in patients with high virus loads who did not develop PTLD, although this expression was transient [18]. Similar patterns of expression were often found in peripheral blood samples from patients with PTLD. In further support of the importance of lytic infection, the cytotoxic T cell response is quantitatively dominated by a response specific for EBV lytic antigens during the acute phase of infection and switches to a response directed to latent antigens during recovery from PTLD and during persistent infection [19, 20]. Tissue samples obtained from approximately 40%–80% of patients with PTLD contain linear replicative virus, although only a small minority of cells actually progress through the entire lytic cycle [1].

Can EBV replication be effectively shut down using antiviral agents in transplant recipients, and does this reduce the risk of acquiring PTLD? PTLD has been documented in patients receiving acyclovir and/or ganciclovir prophylaxis. However, historical comparisons of the incidence of PTLD among patients receiving and patients not receiving ganciclovir prophylaxis, either immediately after transplantation or during antilymphocyte antibody therapy, suggest that prophylactic anti-viral therapy may be of some benefit [1]. A multicenter, randomized controlled trial of CMV immunoglobulin prophylaxis in EBV-seronegative, pediatric SOT recipients was inconclusive with respect to PTLD prevention. This was likely the result of immunosuppression modification by clinicians in response to EBV load data, resulting in an overall reduction over time in the incidence of PTLD, irrespective of the prophylactic regimen used [21]. Antiviral agents may have indirect benefit on PTLD risk by eliminating other viral infections, such as CMV infection, that act as cofactors in PTLD development. For this reason, the use of ganciclovir may be preferred over the use of acyclovir. Antiviral agents may also influence global immunosuppression by preventing the expression of EBV immunomodulatory proteins expressed during the lytic cycle. There is an urgent need for additional multicenter controlled trials that evaluate the efficacy of agents used alone and together for prophylaxis.

An alternative approach to prevention employs a preemptive strategy in which intervention (usually in the form of reduction
in immunosuppression and/or the use of antiviral drugs, with or without immunoglobulin) is administered in response to "trigger points," usually high EBV loads. This approach has been used in both intestinal transplant recipients and pediatric liver transplant recipients [1, 2]. Although the simultaneous use of multiple interventions makes it difficult to determine the efficacy of any single approach, the incidence of PTLD decreased in these populations, compared with historical controls, when preemptive strategies were applied.

In patients undergoing allogeneic stem cell transplantation, rituximab therapy has been used preemptively when serially monitored EBV loads have reached levels historically documented to be associated with a high risk of PTLD [22]. Although preemptive rituximab therapy has not been reported in SOT recipients, it has the advantage of targeting cells latently infected with EBV. A major disadvantage is its high cost. It is perhaps most appropriately used when the more conservative approaches of modifying immunosuppression and administering antiviral agents fail to decrease the virus load.

Adoptive immunotherapy has also been used preemptively by infusion of autologous-cloned CTL or HLA-matched CTL lines (reviewed by Straathof et al. [23]). The experience using this approach is greatest for stem cell transplantation, in which PTLD is most often derived from the donor. However, preliminary infusion of HLA-matched CTL into SOT recipients was associated with a decrease in the EBV load and an increase in EBV-specific CTL frequency, suggesting that this approach is feasible.

**WHAT IS NEW IN PTLD TREATMENT?**

The means of PTLD management have been based on clinical outcomes described in case reports, limited studies of patients, and phase 1 and 2 clinical trials. No controlled trials with therapeutic intervention have been performed. The options available (table 4) and the evidence for their use were recently reviewed elsewhere [1–3]. Below, I will highlight some newer immunomodulatory approaches to PTLD treatment, including the use of anti–B cell therapy, anti–IL-6 therapy, and adoptive immunotherapy.

The goal of PTLD treatment is to cause disease regression with minimum patient morbidity while preserving graft function. The preferred approach, whenever possible, is to use reconstitution of the immune response to clear disease—often the first step in the management of early PTLD (B cell lesions occurring in the first year after transplantation that are EBV positive). Clinicians are often reluctant to discontinue immunosuppression, particularly in patients who have received vital organ transplants, such as heart and lung transplants. However, patients with PTLD (particularly when disease is not localized and virus loads are high) are profoundly immunosuppressed, and immunosuppressive drugs can be safely withdrawn with careful monitoring to maximize opportunities for spontaneous disease regression.

These strategies may have limited application in the setting of PTLD occurring after the first year after transplantation in non–B cell and EBV-negative lesions. In these cases, approaches involving cytokotoxic chemotherapy may be appropriate. Modified, less-aggressive regimens that incorporate antitumor activity with antirejection effects have been advocated by some investigators [24].

When reduction in immunosuppression fails, B cell monoclonal antibody therapy represents an attractive second-line therapeutic option because of its low toxicity. Preliminary data from prospective multicenter trials document response rates of 61%–76% in SOT recipients with PTLD, confirming the complete remission rates of 62.5% found in the largest retrospective review of anti-CD20 treatment of PTLD [25]. When this approach is being considered, it is important to document the presence of CD20 on PTLD tissue. Clonal anti–CD20–negative escape mutants have been described in relapse events associated with this therapy in nonimmunosuppressed hosts. Although it is an unusual side effect in persons who are not transplant recipients, profound and protracted hypogammaglobulinemia has been reported in transplant recipients receiving anti-CD20 therapy, as has severe CMV reactivation disease and intestinal perforation. Hepatitis B and C reactivation, parvovirus-induced RBC aplasia, and enterovirus meningoencephalitis have also been reported in immunocompetent patients receiving this agent.

Modulation of cytokine responses presents an opportunity for both therapeutic and preemptive intervention. In a single phase 1 clinical trial using an anti–IL-6 monoclonal antibody, investigators observed a PTLD response rate of 41% in some cases of early PTLD [26]. Unfortunately, this antibody is not commercially available.

The reconstitution of the CTL response by adoptive immunotherapy is an elegant example of correction of the most

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**Table 4. Treatment options for posttransplantation lymphoproliferative disorders.**

<table>
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<tr>
<th>Treatment Option</th>
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<tr>
<td>Reduction or withdrawal of immunosuppression</td>
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<tr>
<td>Antiviral agents (i.e., ganciclovir, acyclovir, and foscarnet)</td>
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<tr>
<td>Passive antibody (i.e., intravenous immunoglobulin)</td>
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<tr>
<td>Surgical resection</td>
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<tr>
<td>Local irradiation</td>
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<tr>
<td>Anti–B cell (CD20) monoclonal antibody therapy (i.e., rituximab)</td>
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<tr>
<td>IFN-α</td>
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<tr>
<td>Anti–IL-6 monoclonal antibody (not commercially available)</td>
</tr>
<tr>
<td>Adoptive immunotherapy (i.e., autologous cloned CTL or HLA-matched CTL)</td>
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<tr>
<td>Cytotoxic chemotherapy</td>
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**NOTE.** CTL, cytotoxic T lymphocytes.
significant immunologic defect leading to PTLD [21]. Early approaches used autologous lymphokine-activated killer cells and unfractionated HLA-matched leukocytes. Adoptive immunotherapy with donor-derived, cloned, EBV-specific cytotoxic T cells has been successfully used for both the prevention and the treatment of PTLD in stem cell transplant recipients. Cloning and using these lines in SOT recipients has proven to be challenging, because the incidence of infection is often lower than that among high-risk stem cell transplant recipients, PTLD lesions are most often recipient in origin, and the highest-risk patients are EBV seronegative. The obstacles have largely been overcome, but in vivo data using these clones for PTLD treatment in SOT recipients are limited, although preliminary results of tests are positive. HLA-matched banked cell lines in this setting have been used as an alternative to autologous cloned lines. Use of adoptive immunotherapy requires confirmation of the origin of the lesion (recipient vs. donor). Escape mutants, cost, time required to clone cell lines, and regulatory issues may limit how widely this approach is adopted.

CAN STUDYING PTLD IN TRANSPLANT RECIPIENTS IMPROVE OUR UNDERSTANDING OF LYMPHOMAGENESIS IN IMMUNOCOMPETENT HOSTS?

SOT involves bypassing normal mucosal barriers and placing B cells latently infected with EBV into an environment with intense antigenic stimulation at a time when immune responses—particularly T cell responses—are profoundly crippled. An equilibrium that has evolved over several million years between a virus and its host that ensures survival for both is dramatically disrupted. There is increasing evidence to suggest that pathogenesis of PTLD may be similar to the pathogenesis of Hodgkin disease and other types of lymphoma in the immunocompetent host [4, 5, 27]. What we may be seeing in the transplantation scenario is that highly improbable events that initiate lymphomagenesis have become much more probable, perhaps because levels of lytic virus are extraordinarily high. The clinical consequences of those events evolve much more rapidly when the immune system is impaired. Although EBV-associated PTLD is a significant problem in transplant recipients, it is also presents a unique opportunity to study time-compressed events in a high-risk population before the clinical appearance of symptoms. Understanding pathogenesis gives us opportunities for improved diagnostic testing and more specifically targeted and novel approaches to prevention and treatment of EBV-induced disease and malignancy that may benefit not only the transplant population but, perhaps, the general population as well.

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Conflict of interest. J.K.P.: No conflict.

References


