Epstein-Barr Virus–Induced T Cell Lymphoma in Solid Organ Transplant Recipients

David H. Dockrell, John G. Strickler, and Carlos V. Paya

From the Division of Infectious Diseases and the Department of Pathology, Mayo Clinic, Rochester, Minnesota

Epstein-Barr virus (EBV) infection in transplant recipients can lead to lymphomas termed post-transplantation lymphoproliferative disorders (PTLDs). Most PTLDs are malignancies of B lymphocytes and are linked to EBV infection, but the rare T lymphocyte PTLDs have been inconsistently linked to EBV infection. Although the B lymphocyte is the main host cell of EBV, it has been suggested that T lymphocytes may also become infected by EBV. A review of EBV-induced PTLDs at our institution identified one of 61 cases that was restricted to T lymphocytes. Of 36 cases of T cell PTLD identified through a literature review, 21 were investigated for the presence of EBV, and eight (38%) were documented to be EBV-induced. We compared the features of EBV-positive and EBV-negative T cell PTLDs and concluded that cases of EBV-positive T cell PTLD have some distinctive clinical features.

Posttransplantation lymphoproliferative disorders (PTLDs) are a heterogenous group of lymphoid proliferations distinguished by specific histological, phenotypic, and genotypic features [1]. Most PTLDs are B cell malignancies, and a clear relationship between B cell PTLD and infection with Epstein-Barr virus (EBV) has been demonstrated [1]. Other B cell lymphoproliferative disorders associated with EBV infection include endemic Burkitt’s (African) lymphoma and high-grade B cell lymphomas in HIV-positive individuals [2]. However, EBV may also infect T lymphocytes and has been linked with T cell proliferations such as angiocentric immunoproliferative T cell lymphoma (clinically presenting as lethal midline granuloma), angioimmunoblastic lymphadenopathy, and anaplastic large cell lymphoma [3, 4]. T cell PTLDs are rare; the relationship of T cell PTLDs to EBV infection has been inconsistently documented, and the exact relationship between T cell PTLD and posttransplantation immunosuppression remains speculative. Therefore, we investigated our experience with T cell PTLDs and reviewed the literature to determine if EBV is linked to cases of T cell PTLD and if differences exist between EBV-positive and EBV-negative cases.

A total of 61 cases of PTLD in 2,498 solid organ transplant recipients at our institution were identified. Of 61 cases of PTLD, only one (2%) was a T cell PTLD.

Case Report

A 46-year-old man presented 9 years after receiving an orthotopic liver transplant because of primary sclerosing cholangitis complicating chronic ulcerative colitis. Before transplantation, the patient was EBV-seropositive, and 1 year after transplantation, he received OKT3 treatment for allograft rejection. Maintenance immunosuppressive therapy included prednisone and cyclosporine. The patient had fever, night sweats, diarrhea, and stomal ulceration that led to medical evaluation. Physical examination demonstrated a febrile patient with 0.5- to 1.0-cm inguinal lymph nodes and ulceration of his ileostomy site. Biopsy of the stomal ulceration revealed T cell PTLD (figure 1A). Resection of the distal 14 cm of the ileum was performed, which demonstrated a 6-cm mass with transmural involvement of the ileal wall.

The PTLD had morphological findings of malignant lymphoma that was defined as an immunoblastic lymphoma (polymorphous T cell type) according to the Working Formulation or a peripheral T cell lymphoma (unspecified) according to the REAL (revised European American lymphoma) classification. Immunohistochemical analysis of frozen tissue samples indicated that the neoplastic cells reacted with antibodies to the pan T cell markers (CD2, CD3, CD4, CD5, and CD7), while the neoplastic cells in paraffin-embedded tissue samples reacted with antibodies to CD3 and CD45RO. The neoplastic cells did not react with B lineage markers (CD20, CD22, CD23, CD45RA, κ, λ).

Southern blot hybridization of the T cell receptor genes and immunoglobulin genes performed on fresh (snap-frozen) tissue samples demonstrated rearrangement of the T cell receptor genes (β and γ) but not of the immunoglobulin genes (μ, κ, λ). In situ hybridization with EBER (EBV-encoded RNA) probes to noncoding nonpolyadenylated EBV RNA demonstrated EBV RNA in the neoplastic cells. Southern blot hybridization with an EBV terminal repeat probe showed that EBV had a clonal configuration (figure 1B). The same clone of EBV was found in both the biopsy specimen of the stomal ulceration and the resected ileal specimen, thus proving monoclonality of the PTLD.

Complete staging of the disorder revealed only abdominal adenopathy. The patient was treated with decreased immuno-
suppressive therapy and one cycle of chemotherapy with cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone. He refused further chemotherapy and died 1 month after diagnosis.

Discussion

Literature review revealed 35 other previously reported cases of T lymphocyte PTLD [5–9]. In this series of 36 cases, T lymphocyte PTLDs frequently involved the lung (13 cases [36%]), skin (5 cases [14%]), and bone marrow (6 cases [17%]). The most frequent morphological classification was large cell lymphoma in 13 cases (36%), and in only 13 cases (36%), monoclonal T cell receptor rearrangements were documented.

The presence of EBV was examined in 21 cases, and EBV was demonstrated in eight (38%). We defined probable EBV-positive T cell PTLDs as cases with morphology consistent with PTLD, a clonal T cell receptor rearrangement, the absence of any evidence of clonal expansion of B lymphocytes, the presence of EBV DNA or RNA, and the absence of other pathological causes of lymphoproliferative disorders in a population without endemic EBV-associated malignancies. Only our index case and the two cases reported by Waller and colleagues (reviewed in [5]) fulfilled all these criteria. In addition, Southern blot hybridization with an EBV terminal repeat probe specific to the terminal region of circular latent viral episomes demonstrated clonality in our case.

When rigid pathological criteria are applied, only a few EBV-positive T cell PTLDs are strongly associated with EBV infection, although the significance of other documented EBV-positive cases is speculative. To further explore this relationship, future studies should attempt to apply these criteria. Nevertheless, despite the limitations in case definitions in the literature, we compared previously reported EBV-positive and EBV-negative cases of T cell PTLD. Some differences were noted, and these differences are summarized in table 1. The small numbers result in none of these trends reaching statistical significance. Age, duration after transplantation, morphological classification of tumor type, and cyclosporine use were similar between the two groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EBV-positive cases (n = 8)</th>
<th>EBV-negative cases (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female ratio</td>
<td>6.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Transplanted organ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>4 (50)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Heart</td>
<td>3 (38)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (13)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Organ involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>3 (38)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Lung</td>
<td>1 (8)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>0</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Use of antilymphocyte globulin</td>
<td>1 (13)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Survival of 1 year (if followed up for 1 year)</td>
<td>3/6 (50)</td>
<td>2/12 (17)</td>
</tr>
</tbody>
</table>

NOTE. Unless stated otherwise, data are no. (%) of cases. EBV = Epstein-Barr virus; PTLD = posttransplantation lymphoproliferative disorder.
Our findings suggest that few T cell PTLDs are related to EBV infection. However, the extent of this association is limited by the variable case definitions encountered in the literature, and we suggest that these definitions should be standardized. EBV infects B lymphocytes via CD21 and induces oncogenesis through its gene products, Epstein-Barr nuclear antigen 2 and latent membrane protein 1 [2]. Recent reports suggest that a subset of T lymphocytes may also express CD21 and become infected with EBV [10]. Alternatively, unidentified receptors may mediate EBV infection of T lymphocytes.

Therefore, T lymphocytes may also undergo malignant transformation following EBV infection. The relative infrequency of EBV infection of T lymphocytes and possibly a lower viral burden of infected cells may explain why only few T lymphocyte malignancies and T cell PTLDs have so far been related to EBV infection. Other viruses such as human T-lymphotropic virus I, human herpesvirus 6, human herpesvirus 7, and human herpesvirus 8 should be studied in these cases of EBV-negative T cell PTLD.

Our index case and the few other EBV-positive T cell PTLDs may reflect a subtype of PTLD with a pathogenesis different from that of the more frequent EBV-negative cases. A better understanding of this relationship and its clinical consequences should enable the design of more effective diagnostic and therapeutic strategies for this often fatal complication of solid organ transplantation.

References
6. Ghorbani RP, Shokouh-Amiri H, Gaber L. Intragraft angiotropic large-cyte malignancies and T cell PTLDs have so far been related to EBV infection. Other viruses such as human T-lymphotropic virus I, human herpesvirus 6, human herpesvirus 7, and human herpesvirus 8 should be studied in these cases of EBV-negative T cell PTLD.

Our index case and the few other EBV-positive T cell PTLDs may reflect a subtype of PTLD with a pathogenesis different from that of the more frequent EBV-negative cases. A better understanding of this relationship and its clinical consequences should enable the design of more effective diagnostic and therapeutic strategies for this often fatal complication of solid organ transplantation.

References
6. Ghorbani RP, Shokouh-Amiri H, Gaber L. Intragraft angiotropic large-cyte malignancies and T cell PTLDs have so far been related to EBV infection. Other viruses such as human T-lymphotropic virus I, human herpesvirus 6, human herpesvirus 7, and human herpesvirus 8 should be studied in these cases of EBV-negative T cell PTLD.

Our index case and the few other EBV-positive T cell PTLDs may reflect a subtype of PTLD with a pathogenesis different from that of the more frequent EBV-negative cases. A better understanding of this relationship and its clinical consequences should enable the design of more effective diagnostic and therapeutic strategies for this often fatal complication of solid organ transplantation.