Pediatric T-Cell Post-Transplant Lymphoproliferative Disorder After Solid Organ Transplantation

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Post-transplant lymphoproliferative disorder (PTLD) is the most common treatment related malignancy that occurs after solid organ transplantation (SOT). PTLD has extended from its initial description as an Epstein–Barr virus (EBV)-driven B-cell proliferation to include EBV-negative and non-B lineage cases. T-cell PTLD (T-PTLD) is rare in both adults and children. We report two cases of pediatric T-PTLD after SOT (liver and lungs) and review cases reported in the literature. Both patients had a bimodal response to therapy with initial eradication of bulky nodal disease with regimens typically used to treat leukemia, but persistence of low-level clonal T-cells in marrow, which were eradicated by organ transplantation. Both patients have maintained long-term neutroptenic remission.

Key words: flow cytometry; T-cell PTLD; T-cell receptor V-beta

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) was first described in 1981 as an Epstein–Barr virus (EBV)-associated polymorphic B-cell proliferation with either rapidly fatal or relatively slower progressive clinical course arising in patients receiving immunosuppressive therapy following solid organ transplantation (SOT) [1]. A critical step in the pathogenesis of PTLD is believed to be a disruption of the host’s immune response to EBV and impaired immune surveillance against subsequent cell proliferation. PTLD spans a continuum from reversible lymphoid proliferation to irreversible high-grade lymphoma, with corresponding morphological changes ranging from polymorphous to monomorphous and clonality evolution from polyclonal to oligoclonal and monoclonal. The causative connection between PTLD and immunosuppression is supported by the fact that many PTLDs respond to reduction or cessation of immunosuppressive therapy.

EBV-negative PTLD and proliferations of T-cell or other lineages also occur following SOT, and now are typically included under the umbrella term PTLD. Ambiguity about the pathogenesis of T-PTLD, and the lack of accepted diagnostic criteria may contribute to the rarity and inconsistent characterization of T-PTLD in the literature. Of the 100–200 reported cases of T- and NK-cell PTLD most were single case reports, and very few included more than three cases [2–7]. We report two cases of T-PTLD in children after SOT.

MATERIALS AND METHODS

Patient Data and Specimen Collection

Two recent cases of pediatric T-PTLD prompted us to review the experience at our center, which has a large volume of pediatric

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Morphological Evaluation and Immunohistochemistry

Morphological evaluation was based on light microscopy. All tissue stains, including hematoxylin and eosin (H&E), immunohistochemistry, and in situ hybridization (ISH) were performed on formalin-fixed tissue according to standard laboratory procedures.

Flow Cytometric Analysis

Sample preparation from tissue, bone marrow (BM) or cerebrospinal fluid (CSF) was performed as described elsewhere [8]. T-Cell Receptor V\(\beta\) analysis was performed according to manufacturer’s instructions. Expression of a single V\(\beta\) antigen in the majority of T-cells (>40%) is a direct indication of T-cell clonality, while non-reaction to any of the 24 antibodies in the majority of T-cells (>60%), after exclusion of gamma/delta T-cells, is considered indirect evidence of T-cell clonality [13].

Polymerase Chain Reaction (PCR) for TCR-\(\gamma\) Gene Rearrangement

T-cell receptor \(\gamma\) gene rearrangements were evaluated using primers for the four T-gamma gene families (1–4) in a multiplex PCR reaction with a portion of the \(\beta\)-globin gene amplified to ensure DNA integrity [13].

RESULTS

Case Reports

Case 1. This patient underwent bilateral lung transplant at 4 months of age for congenital surfactant C deficiency. Post-transplant immunosuppression included tacrolimus and prednisone. Thirty-two months following lung transplant, a CT scan revealed multiple mesenteric and retroperitoneal masses, with the largest approximately 10 × 8 × 4 cm. Biopsy of the mesenteric mass showed T-cell PTLD. A low level (approximately 1%) of T-cells with the same aberrant immunophenotype present in the abdominal tumor was detected in the marrow. She was EBV-seropositive pretransplant, but had also received multiple red blood cell transfusions. Quantitative PCR for EBV was performed after the transplant and reported as negative. Following diagnosis of T-PTLD, the patient was treated with three cycles of cyclophosphamide (600 mg/m\(^2\)) plus a 5-day pulse of prednisone (2 mg/kg/day) given every 21 days with continuation of reduced dose tacrolimus [9]. She had an initial significant decrease in size of the abdominal masses, but re-evaluation after cycle #3 showed regrowth of the abdominal adenopathy. She then received four-drug acute lymphoblastic leukemia (ALL)-like induction chemotherapy with vincristine, daunorubicin, PEG asparaginase and prednisone with intrathecal methotrexate [10]. She had a dramatic response to this therapy with complete disappearance of abdominal disease. She continued to receive chemotherapy as given in the augmented BFM regimen [11], but persisted with low-level presence of the abnormal T-cell population in BM specimens 9 months following diagnosis. Therapy was complicated by multiple infectious and gastrointestinal complications. The family elected to discontinue intensive chemotherapy. She received several brief pulses of high dose steroids and was continued on reduced doses of immunosuppression.

Fig. 1. Abdominal masses from Case 1 (left panel) and Case 2 (right panel) show similar morphological features with diffuse lymphoid proliferation effacing normal nodal architecture (top panels 100×; insets 400×). Immunohistochemical stains (bottom panels) show that both tumors are composed of CD3+ CD4+ T-cells that lack expression of CD8 and CD79a (case 1 400×; case 2 200×).
with tacrolimus and prednisone with addition of sirolimus. Twenty months following diagnosis of PTLD, she has ongoing problems with lung rejection and gastrointestinal problems with intermittent low-level persistence of clonal T-cells in the marrow and liver, but no mass disease.

**Case 2.** At age 4 years, a previously healthy girl had a cadaveric liver transplant for end stage liver disease due to idiopathic Budd–Chiari syndrome. She received tacrolimus for post-transplant immunosuppression, without significant episodes of rejection. Five years post-transplant, she developed abdominal pain, and hepatosplenomegaly; imaging studies revealed multiple abdominal masses, including one of 11 x 8 x 4 cm. Retroperitoneal lymph node and liver biopsies showed T-PTLD with low-level presence of the same T-cell clone in the marrow and CSF, and clinical and radiological evidence of interstitial lung involvement. Her pre-transplant EBV status was unknown. ALL induction therapy, as given in case #1 [10], was complicated by pancreatitis, and posterior reversible encephalopathy syndrome. Following completion of induction chemotherapy she had complete resolution of abdominal nodal disease, but the abnormal T-cell clone persisted at a low-level in the marrow and CSF in conjunction with interstitial lung disease. Following 4 weeks of augmented BFM consolidation therapy (without asparaginase) [11], she had persistent disease in the BM, CSF, and biopsy-proven lung involvement. She then received two 4-day courses of fludarabine (30 mg/m²/day) and high dose Ara C (2 g/m²/day), and attained a complete remission. She continues to receive ALL maintenance therapy and remains in complete remission 10 months following diagnosis of T-PTLD.

**Diagnosis of T-PTLD**

The histological appearance of the abdominal masses from both patients is very similar, with diffuse lymphoid proliferation effacing normal nodal architecture (Fig. 1). The proliferating cells were predominately small to medium size lymphocytes with slightly irregular nuclei, inconspicuous nucleoli and abundant pale stained cytoplasm. Prominent vascular proliferation was present in both cases (Fig. 1 insets). These proliferating cells are almost exclusively CD4 (+) T-cells with dim CD3 and negative for CD8 and the pan-B-cell marker CD79a. The liver biopsy in Case 2 demonstrated a similar T-cell proliferation (not shown). Both tumors were EBV-negative based on in-situ hybridization with EBV-encoded RNA (not shown).

Phenotypically abnormal T cells in Case 1 and Case 2 exhibited similar aberrant antigen expression pattern via FCM, namely down-regulated CD3, partial loss of CD7, up-regulated CD2 and aberrant expression of HLA-DR (data not shown). Clonal T-cell proliferation was suggested by FCM analysis of TCR VB usage either directly (Case 1), or indirectly (Case 2). Clonality was confirmed by amplification of distinct products via TCR-γ chain gene PCR in both cases (not shown).

**DISCUSSION**

Pediatric T-cell PTLD is very rare, with only 17 other cases previously described in the literature. We report two cases of T-PTLD with large abdominal nodal masses arising in children following SOT. The T-cell lineage was established based on immunohistochemistry and FCM analysis with T-cell monoclonal antibodies. The clinical course and response to therapy of these two cases are presented in Table I. The data are compared with other reported cases of pediatric T-PTLD.

**TABLE I. Pediatric T-Cell PTLD After Solid Organ Transplant**

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Age and sex</th>
<th>Immu. supp</th>
<th>Disease type</th>
<th>Location</th>
<th>EBV status</th>
<th>Clonality assay</th>
</tr>
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<tbody>
<tr>
<td>Kidney</td>
<td>10 Y</td>
<td>MTX</td>
<td>Diffuse large cell</td>
<td>BM, liver</td>
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ality confirmed by FCM analysis of Vβ family usage and by PCR analysis of TCR-γ chain gene rearrangement. In contrast to most cases of B-lineage PTLD, these two T-PTLD cases were EBV-negative. This is consistent with data from the literature, with 42 of 69 (60%) T-PTLD cases being EBV-negative based on Southern blot hybridization with a fragment of the EBV genome or in-situ hybridization or EBV RNA. Table I shows characteristics of the 14 cases of pediatric T-PTLD that arose following SOT, including the cases described herein.

While there is a general impression that T-PTLD is very difficult to cure, several recently reported cases, including those described in this report, demonstrate that these tumors can be very treatment responsive. This may be due to use of different chemotherapy regimens than those typically used to treat B-PTLD, such as the intensive ALL-type treatments we employed, and/or the use of different strategies for immunosuppression. Most T-PTLDs are not EBV-driven; thus, reduction of immunosuppression may not be effective as a sole treatment strategy, and may be less critical for management of T-PTLD than it is in EBV-driven B-PTLDs. However, the follow-up on several cases, including those we describe, is short and it will be important to gather information on a larger number of cases with longer follow-up to make definitive conclusions regarding the outcome of T-PTLD.

It is important to note that both of our pediatric T-PTLD cases exhibited a bimodal response to therapy, with initial eradication of the bulk nodal disease with regimens typically used to treat ALL, but persistence of low level clonal T-cells in marrow, CSF and lung (1 case). Case #1 showed prolonged disease control with modification of immunosuppression, including introduction of sirolimus, which may have anti-tumor activity [12]. While we are cautious to make conclusions based on small patient numbers, different strategies of treatment may be needed in patients with T-PTLD than those that are often successful in treatment of B-lineage-PTLD. Multi-institutional trials are needed to define the optimal diagnostic evaluation and management strategy for T-PTLD.

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REFERENCES


