Posttransplant Hodgkin Lymphoma Preceded by Polymorphic Posttransplant Lymphoproliferative Disorder

Report of a Pediatric Case and Review of the Literature

Gabriela Gheorghe, MD,* Edythe A. Albano, MD,† ‡ Christopher C. Porter, MD,† ‡ Loris McGavran, PhD,*§ Qi Wei, BS,§ Lynne Meltzer, BA,* Susan M. Danielson, BS,§ and Xiayuan Liang, MD*§

Summary: Epstein-Barr virus-mediated posttransplant lymphoproliferative disorder (PTLD) is a well-recognized complication of immunosuppression in transplant patients and has broad clinical manifestations and pathologic features ranging from reactive lymphoid proliferation to malignant lymphoma. The category of Hodgkin lymphoma and Hodgkin lymphomalike PTLD is an uncommon variant of PTLD. Development of Hodgkin lymphoma subsequent to other subtypes of PTLD in the same patient is even more unusual, especially in pediatric patients. In this report, we describe a pediatric case of Epstein-Barr virus-associated posttransplant Hodgkin lymphoma developing several years after the patient was diagnosed with polymorphic PTLD and review the literature of the previously reported cases in children to further help characterize the clinical features, histopathologic appearances, biology, and treatment strategies of this uncommon entity.

Key Words: Hodgkin lymphoma, posttransplant lymphoproliferative disorders, lymphoma, EBV


Posttransplant lymphoproliferative disorder (PTLD) is primarily an Epstein-Barr virus (EBV)-mediated uncontrolled B-cell proliferation that occurs with decreased T-cell immune surveillance as a result of immunosuppression for graft survival.1 The clinical manifestations vary from infectious mononucleosis to malignant neoplasia. The morphologic spectrum of these conditions varies from reactive process such as mononucleosis type EBV infection to an intermediate group of lesions labeled “polymorphic PTLD” to a monomorphic PTLD/malignant lymphoma according to the World Health Organization (WHO) Classification.

In the WHO Classification, there is an additional miscellaneous group of malignant lymphomas in transplant recipients that includes the category of Hodgkin lymphoma and Hodgkin lymphomalike PTLD.2 These entities are uncommon variants of PTLD. Only a very limited number of reported cases are found in the literature.3 Most cases are seen in adults. Development of Hodgkin lymphoma subsequent to other subtypes of PTLD in the same patient is even more unusual. There is insufficient published information and experience with respect to the pathology, clinical characters, and management of these patients. We report a case of EBV-associated posttransplant Hodgkin lymphoma that preceded by polymorphic PTLD in a pediatric liver transplant patient and review the literature of the previously reported cases in children.

REPORT OF A CASE

A 1-year-old boy received a liver transplant for biliary atresia, after which he remained in relatively good health on immunosuppressive medications. In 1996, at 10 years of age, 102 months posttransplant, the patient developed chronic otitis media, adenotonsillar hypertrophy, and enlarged right cervical lymph nodes. The tonsils, adenoid, and right cervical nodes were resected. Pathologic evaluation revealed EBV-associated polymorphic PTLD. He was treated with reduction of immunosuppression and acyclovir therapy. Three months postresection, he developed a brief episode of liver rejection, and cyclosporine was reinstituted. The patient was followed by his local pediatrician for 6 years and remained in stable condition.

In 2003, at age 16, 82 months after resolution of polymorphic PTLD, he presented with chronic fatigue, persistent cough, fever, night sweats, and significant weight loss of 3 weeks duration. Laboratory studies showed a white blood cell count of 2200/mm3, hemoglobin 9.1 g/dL, lactate dehydrogenase 190 IU/L, and normal electrolytes and liver function. Computed tomography scans of head, neck, chest, and abdomen demonstrated a mediastinal mass and an enlarged spleen. Biopsy of the mediastinal mass was performed, and a diagnosis of EBV-associated posttransplant classic Hodgkin lymphoma,
stage IIIB was made. The immunosuppressive drugs were
discontinued. The patient received 6 cycles of Cytoxan,
Oncovin, Prednisone, and Procarbazine/Adriamycin,
Bleomycin, and Vinblastine chemotherapy with excellent
response. He has remained in complete remission for
3 years.

PATHOLOGY FINDINGS

The histology sections of the tonsils, adenoid, and
cervical nodes from 1996 revealed effacement of normal
lymphoid tissue architecture by a diffuse infiltrate which
was composed of a spectrum of polymorphous cell
populations including plasma cells, plasmacytoid lym-
phocytes, small lymphocytes, histiocytes, immunoblasts,
and rare scattered large Reed-Sternberg (RS)-like cells
(Fig. 1A). The mitotic rate was focally brisk. Immunob-
lasts and large RS-like cells were CD15– (Fig. 1B),
CD20– (Fig. 1C), CD30+, and CD45+ by immunohis-
tochemical staining. In situ hybridization for EBV early
RNA (EBER) showed strong reactivity in both large and
small lymphoid cells (Fig. 1D). In contrast, the biopsy of
the mediastinal mass from 2003 showed numerous large
malignant cells in the background of small lymphocytes
and histiocytes. The large malignant cells were composed
of RS cells and variants with large eosinophilic nucleoli
(Fig. 2A). These cells were CD15+ (Fig. 2B), CD20+
(Fig. 2C), CD30+, and CD45+. Strong EBER signals were
detected primarily in RS cells and variants by EBER in
situ hybridization (Fig. 2D).

Conventional cytogenetic analysis showed
47,XY,+X,t(3;22)(q27;q11.2)[4]/47,XY,+X[8]/46,XY[10]
karyotype in the tonsils adenoid and 47,XY,+X[17]/
46,XY[3] in lymph nodes from 1996, and normal male
karyotype in the specimens of the mediastinal mass and
bone marrow from 2003. Fluorescent in situ hybridization
(FISH) study using a dual color probe set for enumera-
tion of X and Y chromosome copy number was
performed on the sample of the mediastinal mass did
not show extra X chromosome. Polymerase chain

FIGURE 1. Polymorphic PTLD of lymph node from 1996. A, A spectrum of lymphoid cell proliferation composing of small and
medium sized lymphocytes with rare large RS-like cells (hematoxylin and eosin, ×1000). B, The large RS-like cells were negative
for CD15 (×1000). C, The large RS-like cells showed CD20 reactivity (×1000). D, In situ hybridization for EBER exhibited positive
signals in both large RS-like cells and small lymphocytes (×1000).

© 2007 Lippincott Williams & Wilkins
reaction (PCR) detected an IgH gene rearrangement in the lymph node biopsy from 1996. The signal of the PCR product from the mediastinal mass was too low to interpret.

**DISCUSSION**

Not including the patient described here, only 3 well-defined cases of posttransplant Hodgkin lymphoma developing after other subtypes of PTLD in childhood are found in the English literature.\(^3\)\(^-\)\(^5\) The clinical information of our case plus the 3 previously reported cases reviewed in this report is summarized in Table 1. Three were male and 1 was female. All patients were solid organ recipients. The interval between the organ transplantation and the onset of the primary PTLD ranged from 3 to 8 years, and the interval between primary PTLD and Hodgkin lymphoma was from 1 to 6 years. EBV was detected in both the primary PTLD and subsequent Hodgkin lymphoma in all cases in which the tests were performed. All patients underwent withdrawal or reduction of immunosuppression with or without antiviral therapy for the primary PTLD and received chemotherapy for the posttransplant Hodgkin lymphoma with 1 patient (case 3) having additional radiation therapy. All patients achieved complete remission.

PTLD is a well-known complication of bone marrow transplantation, and occurs more frequently in children than adults. The role of EBV in PTLD is well recognized.\(^6\) Morphologically PTLD has a wide range of appearances. Currently, the WHO classifies PTLD into 4 major categories: early lesions (reactive plasmacytic hyperplasia and infectious mononucleosis-like lesions), polymorphic PTLD, monomorphic PTLD (B-cell and T-cell lymphomas), and a category of Hodgkin lymphoma and Hodgkin lymphomaliike PTLD.\(^2\) The last category constitutes a very small portion of PTLD, with only 3 cases in 273 PTLDs reported in one series.\(^7\) Development of posttransplant Hodgkin lymphoma subsequent to other entities of PTLD in the same patient is even rarer, with only infrequent scattered case reports found in the literature.\(^3\)\(^-\)\(^5\) Among 4 cases in this
TABLE 1. Clinical Information of Posttransplant Hodgkin Lymphoma Subsequent to Other Subtypes of PTLD in Pediatric Patients

<table>
<thead>
<tr>
<th>Case No. and Diagnosis</th>
<th>Age/Sex</th>
<th>Organ Transplant</th>
<th>Clinical Presentation</th>
<th>Intervals</th>
<th>Treatment</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Polymorphic PTLD</td>
<td>9 y/M</td>
<td>Liver</td>
<td>Cervical adenopathy, enlarged tonsils, adenoïd</td>
<td>8 y from transplant</td>
<td>↓ Immunosuppression, cyclosporine</td>
<td>CR for 6 y</td>
<td>Current case</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>15 y</td>
<td></td>
<td>Mediatinal mass</td>
<td>6 y 10 mo from transplant</td>
<td>Chemotherapy (COPP/ABV)</td>
<td>CR for 3 y</td>
<td></td>
</tr>
<tr>
<td>2. Hodgkin-like PTLD</td>
<td>10 y/M</td>
<td>Kidney</td>
<td>Lymphadenopathy (mediastinal, cervical, axillary, intrathoracic, abdominal)</td>
<td>4 y from transplant</td>
<td>Withdrawal of immunosuppression</td>
<td>Partial response, relapsed, rituximab</td>
<td>3</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>11 y</td>
<td></td>
<td>Same as above</td>
<td>1 y from Hodgkin-like PTLD</td>
<td>Chemotherapy (not specified)</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>3. Polymorphic PTLD</td>
<td>7 y/F</td>
<td>Kidney</td>
<td>Bone marrow</td>
<td>70 mo from transplant</td>
<td>↓ Immunosuppression, interferon-α</td>
<td>CR for 13 mo</td>
<td>4</td>
</tr>
<tr>
<td>Hodgkin (MC)</td>
<td>10 y</td>
<td></td>
<td>Lymphadenopathy (cervical, mediastinal, abdominal, pelvic)</td>
<td>3 y from PTLD</td>
<td>Chemotherapy (COPP/ABV), involved field radiation</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>4. Polymorphic PTLD</td>
<td>15 y/M</td>
<td>Kidney</td>
<td>Lymphadenopathy (retroperitoneal, pelvic)</td>
<td>3 y from transplant</td>
<td>Withdrawal of immunosuppression</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Hodgkin (MC)</td>
<td>18 y</td>
<td></td>
<td>Lymphadenopathy (para-aortic, retroperitoneal)</td>
<td>3 y from PTLD</td>
<td>Chemotherapy (MOPP)</td>
<td>CR for 9 mo</td>
<td></td>
</tr>
</tbody>
</table>

COPP/ABV indicates Cyclophosphamide, Oncovin, Prednisone, and Procarbazine/Adriamycin, Bleomycin, and Vinblastine; CR, complete remission; F, female; M, male; MC, mixed cellularity; MOPP, Mustard, Oncovin, Prednisone, and Procarbazine; PTLD, posttransplant lymphoproliferative disorders; ↓, reduce.

report, 3 of 4 patients (cases 1, 3, and 4) had polymorphic PTLD and 1 patient (case 2) had Hodgkin lymphoma-like PTLD before Hodgkin lymphoma. Although RS cells are the hallmark of Hodgkin lymphoma, cells morphologically similar to RS cells are seen in a variety of lymphoid conditions. Occasional RS-like cells may be part of polymorphic PTLD, but when they form a significant proportion of reactive immunoblastic proliferation, then the term Hodgkin lymphoma-like PTLD is appropriate. Unlike classic Hodgkin lymphoma, neither polymorphic PTLD nor Hodgkin lymphoma-like PTLD has mixed infiltrate of eosinophils and neutrophils. Immunophenotypically, the difference in staining patterns in large RS-like cells and smaller lymphocytes of the background between polymorphic PTLD/Hodgkin lymphoma-like PTLD and true Hodgkin lymphoma is also evident. The large RS-like cells in polymorphic PTLD and Hodgkin lymphoma-like PTLD are B-cells. They share CD20 (B-cell marker), CD45 (leukocyte common antigen), and EBV staining with the smaller lymphocytes of the background, and they are negative for CD15. This staining pattern was seen in all primary PTLD cases in which the tests were performed (Table 2). In contrast, in the subsequent lesions of Hodgkin lymphoma of these patients, the RS cells uniformly marked for CD15 and CD30, markers of classic Hodgkin lymphoma cells, and were negative for CD45 in cases in which the tests were performed. CD20 showed weak reactivity in rare RS cells.

TABLE 2. Immunoprofile of the Cases

<table>
<thead>
<tr>
<th>Case No. and Diagnosis</th>
<th>CD3</th>
<th>CD15</th>
<th>CD20</th>
<th>CD30</th>
<th>CD45</th>
<th>EBV Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RS</td>
<td>BG</td>
<td>RS</td>
<td>BG</td>
<td>RS</td>
<td>RS</td>
</tr>
<tr>
<td>1. Polymorphic PTLD</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2. Hodgkin-like PTLD</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>-</td>
<td>+</td>
<td>Rare+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3. Polymorphic PTLD</td>
<td>+</td>
<td>+</td>
<td>Rare+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>+</td>
<td>+</td>
<td>Rare+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

BG indicates background cells; LMP, latest membrane protein; RS, Reed-Sternberg-like cells; w, weak.
+ , positive; −, negative; + + , method not specified.
in cases 2 and 3 and was negative in case 1. EBV was mainly confined to the large RS cells (cases 1 and 2). Taken together, the pathologic and immunophenotypic features indicated that the primary and subsequent lesions of these 4 patients are distinct pathologic entities.

The clonal relationship between primary PTLD and subsequent Hodgkin lymphoma in allograft recipients has not been well established in the literature. Given that the neoplastic cells in Hodgkin lymphoma is usually of B-cell origin, and approximately 50% of Hodgkin lymphoma in immunocompetent patients is related to EBV, neither B-cell markers like CD20 nor EBER test for EBV serves as a good clonality marker between primary PTLD and subsequent Hodgkin lymphoma. To assess the clonal connection between the primary polymorphic PTLD and subsequent Hodgkin lymphoma in our patient (case 1), we performed cytogenetic analysis and/or FISH, and PCR IgH gene rearrangement in both specimens from 1996 to 2003. An abnormal karyotype 47,XX,+X and monoclonal IgH gene rearrangement were detected in the tonsil adenoid and lymph nodes with polymorphic PTLD from 1996. However, both standard cytogenetic analysis and FISH study showed a normal male karyotype in the specimen of Hodgkin lymphoma from 2003. The fluorescence signal of the PCR product for IgH gene rearrangement from the same specimen was too low to draw any conclusions. Possible explanations of the discrepancy of the karyotypes between the primary PTLD and subsequent Hodgkin lymphoma include: (1) the primary polymorphic PTLD and subsequent Hodgkin lymphoma arose from different clones; (2) RS cells carrying cytogenetic abnormalities failed to grow in the cell culture, and the normal male karyotype was the result of growth of the small “bystander” lymphocytes; or (3) too few RS cells were left on the FISH study slides after extensive immunophenotype work-up by immunohistochemical stains may have resulted in the failure of detection of extra X chromosome in RS cells. Although it is known that RS cells of Hodgkin lymphoma contain monoclonal Ig gene rearrangement in greater than 98% of cases, the monoclonal rearrangements are usually not detectable in whole tissue DNA but only in the DNA of isolated single RS cells. The PCR test on the Hodgkin lymphoma specimen of our patient was performed on whole tissue DNA, which is not sensitive enough to detect Ig gene rearrangement in RS cells. Furthermore, the low fluorescence signal may have been attributable to DNA degradation. Larger series of patients, adequate tissues, and single RS cell isolation technique are needed to determine if polymorphic PTLD can subsequently evolve to become classic Hodgkin lymphoma.

The mainstay of treatment of PTLD is generally withdrawal of immunosuppression, however, this is effective in only 20% to 50% of patients. All patients in this report were treated with reduction or withdrawal of immunosuppression with additional antiviral therapy in some cases. All patients with polymorphic PTLD (cases 1, 3, and 4) responded to immunosuppression reduction or withdrawal. The patient with Hodgkin-like PTLD (case 2) had a partial response and subsequent relapse. He was then treated with rituximab and antiviral therapy and went into complete remission. All patients in this report received chemotherapy for their subsequent Hodgkin lymphoma and remained in complete remission from 9 months to 3 years of follow-up.

In conclusion, occurrence of Hodgkin lymphoma subsequent to other entities of PTLD in the same patient is an unusual form of EBV-mediated PTLD in children. An immunohistochemical panel including CD15, CD20, CD30, and CD45 as well as EBV staining can be used to distinguish the 2 categories. Our case and available data from previous cases suggest that posttransplant Hodgkin lymphoma occurring after other subtype of PTLD in the same patient represents a distinct clinical entity, rather than the evolution and relapse of the primary PTLD.

REFERENCES
