Autopsy Pathology of Pediatric Posttransplant Lymphoproliferative Disorder

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ABSTRACT. Objectives. Posttransplant lymphoproliferative disorder (PTLD) causes significant morbidity and mortality, is related to Epstein-Barr virus (EBV) infection, and is more common in children than in adults. We reviewed autopsies of children who died with PTLD to compare postmortem with antemortem PTLD histology, to assess the extent of PTLD, to document associated pathology, and to identify cause of death.

Methods. Postmortem examinations were performed on 7 patients after bone marrow (n = 3) or liver (n = 4) transplant. PTLD was classified histologically as hyperplasia or lymphoma. In situ hybridization for EBER1 messenger RNA was performed on tissue samples from all cases. EBV serologies were used to categorize infections as negative, primary, or reactive.

Results. PTLD was diagnosed in 5 children 12 to 35 (mean: 22) days before death, and 1.5 to 4 (mean: 3) months after transplant; PTLD was diagnosed in 2 cases at autopsy 2.5 and 4 months after transplant. Postmortem PTLD histology resembled antemortem histology. 5 PTLDs were lymphoma, 1 was hyperplasia, and 1 contained both lymphoma and hyperplasia. EBER1 messenger RNA was detected in 6 B-cell PTLDs, including lesions from patients who did not have EBV serology that indicated active infection. Complete autopsy of 4 patients who died with biopsy-proven PTLD revealed widely disseminated disease, and lymph node, brain, gastrointestinal tract, and kidney were involved in all 4 patients. Cases diagnosed at autopsy were 1 widely disseminated PTLD that had been suspected but not proven antemortem, and 1 PTLD confined to abdominal lymph nodes that was not suspected antemortem. Severe organ dysfunction (renal failure, gastrointestinal hemorrhage) was caused by massive PTLD infiltration in 2 patients. The conditions other than PTLD that contributed to morbidity and death were organ infection (5 cases), infarcts (4 cases), and diffuse alveolar damage (3 cases).

Conclusions. PTLD may occur within weeks after transplant in children. The distribution of PTLD comprises a spectrum from localized and subclinical to widely disseminated and symptomatic. PTLD may cause demise quickly after the onset of signs and symptoms, through massive organ infiltration or associated conditions, such as diffuse alveolar damage. EBV serology may not accurately reflect the presence or extent of PTLD. Autopsy studies of transplant patients are necessary to identify the true incidence, natural history, and response to treatment of PTLD. Pediatrics 2001;107(6). URL: http://www.pediatrics.org/cgi/content/full/107/6/e89; posttransplant lymphoproliferative disorder, autopsy, pediatric pathology, Epstein-Barr virus, lymphoma, mortality.

ABBREVIATIONS. PTLD, posttransplant lymphoproliferative disorder; EBV, Epstein-Barr virus; CHOP, Children’s Hospital of Philadelphia; LMP, latent membrane protein; Ig, immunoglobulin; VCA, viral capsid antigen; GI, gastrointestinal; PCR, polymerase chain reaction.

Posttransplant lymphoproliferative disorder (PTLD) is related to Epstein-Barr virus (EBV) infection and is estimated to occur in 2% to 5% of all transplant recipients. However, PTLD is more common in children, because many children are EBV-naïve at the time of transplant. Manifestations of PTLD are protean and include signs and symptoms of both focal disease, such as graft dysfunction, as well as systemic disease, eg, viral illness. Mortality rates reported for children who develop PTLD are high and range from 36% to 69%. However, detailed autopsy reports of series of PTLD patients have not been reported. We present the pathology found at autopsy of 7 children who died with PTLD.

METHODS

Cases of PTLD were retrieved from surgical pathology and autopsy files at the Children’s Hospital of Philadelphia (CHOP). Clinical information was obtained from chart review. Necropsy was performed at Penn State Hershey Medical Center on a patient who had received a bone marrow transplant and had a craniotomy at CHOP, and on another patient who had a liver transplant performed at CHOP.

Antemortem biopsies were reviewed and classified as hyperplasia, polymorphic lymphoma, or monomorphic lymphoma using the criteria of Frizzera et al.10,11 Immunohistochemical stains for B cells (CD20) and T cells (CD45RO, Dako, Carpinteria, CA) were the basis to designate lesions as B or T cell. Flow cytometry and gene rearrangement studies (B/T Blue Gene Rearrangement Test System, Oncor, Gaithersburg, MD) were performed in selected cases. In situ hybridization for EBV-encoded RNA (EBER1) mRNA and immunohistochemical stain for EBV latent membrane protein (LMP) were performed on all antemortem biopsies and on selected postmortem samples. EBV serologies were used to classify infections as negative, primary, or reactivation.14 Primary infection was diagnosed if the immunoglobulin (Ig)
G antibody titer to EBV nuclear antigen was $\geq 1:2$, and IgG and/or IgM antibody to viral capsid antigen (VCA) and IgG antibody to EBV early antigen were elevated. In patients whose EBV nuclear antigen titer was $\geq 1:2$, EBV reactivation was defined as the presence of high titers of IgG antibody to VCA and early antigen. When making a final interpretation of positive EBV serologies, consideration was given to the possibility that patients might have received intravenous immunoglobulin, blood transfusions, or passively acquired maternal antibodies.

RESULTS

Autopsy was performed on 7 transplant patients who had PTLD. Five of the 7 autopsies were performed at CHOP in 4 different years. In those 4 years, a total of 20 autopsies were performed on patients who had transplants; the incidence of PTLD in this autopsy transplant population, therefore, was 25% (5/20 transplant patients).

Clinical characteristics of the 7 patients are presented in Table 1. PTLD was diagnosed in 5 patients (patients 1–5) at a mean interval of 3 months (range: 1.5–4 months) after transplant. PTLD was diagnosed in 2 patients (patients 6 and 7) at autopsy 2.5 and 4 months after transplant; antemortem, PTLD was suspected but not proven by biopsy in patient 6 and was not suspected in patient 7.

Patients presented with a variety of signs and symptoms, in most cases suggestive of viral illness. Adenopathy was diagnosed by physical examination or by imaging studies in 5 cases (patients 1–5). Four patients had fever (patients 1, 3, 4, and 6). One child (patient 2) presented with seizures. Three patients had respiratory compromise (patients 1, 3, and 6). The youngest patients (patients 4 and 6) had signs of sepsis (hypotension, tachycardia, respiratory acidosis). Patient 5 presented with gastrointestinal (GI) symptoms (diarrhea, weight loss, anorexia), and patient 4 had heme-positive stools.

PTLD Histology

The histologic classification of postmortem PTLD matched the classification of antemortem biopsies in all 5 cases (patients 1–5) who had antemortem samples. Six PTLD were lymphoma (Fig 1), 1 was hyperplasia. (Table 2) One lymphoma (patient 6) also had areas of hyperplasia. Six cases were B cell PTLD, and 1 (patient 2) was T cell polymorphous lymphoma. Extensive necrosis was found at autopsy in the PTLD of patient 5, who received chemotherapy, and of patient 4, who did not receive any treatment. There was extensive vascular invasion by PTLD in 3 cases (patients 1, 4, and 6).

Clonality studies of 3 PTLD were performed antemortem; 2 cases that seemed histologically to be B cell lymphoma (patients 1 and 5) had immunoglobulin gene rearrangements and did not have T cell receptor gene rearrangements; the third case was hyperplasia (patient 3) and did not have B or T cell gene rearrangements. In one case (patient 5), sequential samples of PTLD from 2 different sites (cervical lymph node and bowel) had monomorphous B cell PTLD histology and resembled large cell lymphoma. A homogeneous population of large terminal deoxynucleotidyl transferase-positive B cells was detected by flow cytometry of the bowel lesion, and Southern blot hybridization demonstrated immunoglobulin heavy chain gene rearrangements, confirming monoclonality; however, a monoclonal population was not detected by flow cytometry of the lymph node biopsy.

EBER1 messenger RNA (Fig 2) was detected by in situ hybridization in all PTLD except the T cell lymphoma and was detected in tissue from patients who did not have positive EBV serology. EBV LMP was detected by immunohistochemistry in 4 of 5 cases.

EBV serology was determined in 6 patients and was negative in 3 (Table 2). EBV antibodies detected in the serum of the youngest patient (3.5 months old, patient 4) may have been maternal in origin, and serology in this patient was, therefore, noncontributory. Patient 6 had only a borderline elevation of IgG to VCA and this was considered indeterminate for EBV infection. Pretransplant EBV serologic status was determined only for patient 3, who showed evidence of recent EBV infection before bone marrow transplant, and serology at the time of PTLD indicated past EBV infection. EBV serology of the donors was not determined.

Extent of PTLD

PTLD that had been clinically apparent was widely distributed at autopsy (patients 1–6; Table 3). PTLD was found in lymph nodes of all 7 patients. The kidney was infiltrated in all 5 cases that had clinically apparent disease and complete autopsies, and the GI tract and brain were infiltrated in 4 of

| TABLE 1. | Clinical Characteristics |
|---|---|---|---|---|---|
| Age (Years)/ Gender | Organ transplant = bone marrow | Immunosuppression | Interval to PTLD (Months) | Treatment | Survival (Days) |
| 1 | 3.5/M | Cy, Cs | 4 | RIS, Gan, TCI | 11 |
| 2 | 11/M | Cy, Cs | 3 | Acy | 29 |
| 3* | 3/F | Cy | 3.5 | Acy, IFN, IVIG | 8 |
| Organ transplant = liver | | | | | |
| 4 | 0.3/F | Cy, Cs, OKT3, Imuran | 1.5 | None | 8 |
| 5 | 12/M | FK506, Cs | 3.5 | RIS, Chem, Acy | 1 |
| 6† | 1.1/F | FK506, Cs | 4 | RIS | NA |
| 7† | 6/M | FK506, Cs | 2.5 | NA | NA |

Cy indicates cyclosporine; Cs, corticosteroids; RIS, reduced immunosuppression; Gan, gancyclovir; TCI, T-cell infusion; Acy, acyclovir; IFN, interferon; IVIG, intravenous immunoglobulin; chem, chemotherapy; NA, not applicable.

* Autopsy restricted to chest organs.
† PTLD diagnosed at autopsy.
these 5 cases. Uncommon sites of PTLD infiltration were skin, muscle, prostate, ovary, and adrenal glands. PTLD was widely disseminated in 1 case diagnosed at autopsy (patient 6) and was confined to abdominal lymph nodes in the other case discovered at autopsy (patient 7).

PTLD was found in allografts: PTLD was present in the bone marrow of all 3 patients who received marrow transplant but only 1 of 4 patients who had liver transplant. PTLD infiltrated 2 of 4 liver allografts. The pattern of hepatic infiltration by PTLD mimicked cellular rejection, including endothelialitis and bile duct damage; however, the atypicality of the cells, the predominance of B cells, and the presence of EBER1 were features that distinguished the infiltrate from rejection.

**Associated Pathology**

Conditions other than PTLD were frequently identified in these autopsies. (Table 4). Five of 7 patients had evidence of infection. Two bone marrow transplant patients had fungal infection, manifest as organisms consistent with *Candida* in the lung and *Candida albicans* in the GI tract (patients 1 and 3); *Candida* was recovered from a leukens culture 3 days antemortem and from postmortem blood culture of patient 1, but blood and lung cultures of patient 3 were negative. One marrow transplant patient had colonization of an esophageal ulcer by Gram-positive cocci (patient 2); postmortem lung culture was negative. One marrow and 2 liver transplant patients had acute bronchopneumonia (patients 2, 5, and 7). Patient 5 had massive GI bleeding before death and blood cultures at the onset of bleeding 2 days antemortem grew *Klebsiella*; Gram-positive cocci were found in postmortem blood smear but culture was negative. Postmortem blood and peritoneal fluid cultures for bacteria and liver culture for virus of patient 7 were negative. Postmortem blood cultures of patient 6 for virus, bacteria, and fungi were negative. Splenic infarcts were found in 3 patients (patients 4, 5, and 7) and a liver infarct in 1 patient (patient 1). Diffuse alveolar damage was present in 3 patients (patients 3, 4, and 6). Other pathologic lesions were thromboemboli (patients 4 and 7), nephrocalcinosis (patients 2 and 5), graft-versus-host disease (patient

**Table 2.** Histology, Serology, and Clonality

<table>
<thead>
<tr>
<th>Biopsy Site</th>
<th>Type</th>
<th>EBV Sero</th>
<th>EBER1</th>
<th>LMP</th>
<th>Clonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bone marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Adenoids</td>
<td>PBCL</td>
<td>ND</td>
<td>Pos</td>
<td>Pos</td>
<td>Yes</td>
</tr>
<tr>
<td>2 Brain</td>
<td>PTCL</td>
<td>Neg</td>
<td>Neg</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3 LN</td>
<td>PBCH</td>
<td>Past infection</td>
<td>Pos</td>
<td>Neg</td>
<td>No</td>
</tr>
<tr>
<td>Organ transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 LN</td>
<td>PBCL</td>
<td>?Maternal</td>
<td>Pos</td>
<td>Pos</td>
<td>ND</td>
</tr>
<tr>
<td>5 LN, bowel</td>
<td>MBCL</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>No/yes†</td>
</tr>
<tr>
<td>6† NA</td>
<td>PBCL</td>
<td>Neg</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7† NA</td>
<td>PBCL</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>ND</td>
</tr>
</tbody>
</table>

Sero indicates serology; PBCL, polymorphous B cell lymphoma; ND, not done; Pos, positive; PTCL, polymorphous T cell lymphoma; Neg, negative; LN, lymph node; PBCH, polymorphous B cell hyperplasia; MBCL, monomorphous B cell lymphoma; NA, not applicable.

* Autopsy restricted to chest organs.
† PTLD diagnosed at autopsy.
‡ PTLD in lymph node was not clonal; PTLD in bowel was clonal.
Fig 2. In situ hybridization demonstrates EBER1 messenger RNA in nuclei of this PTLD. Darkly staining nuclei contain EBER1 messenger RNA.

2), acute inflammation in the cecum (patient 2), esophageal ulceration (patient 2), and gastric erosions (patient 2).

**Cause of Death**

Autopsy findings elucidated the terminal courses of these patients. Patients 1, 3, 4, and 6 died with respiratory disease, and autopsy showed obstructing upper airway adenopathy and pneumonia (patient 1), diffuse alveolar damage (patients 3, 4, and 6), pulmonary PTLD (patients 3, 4, and 6), and walled-off abscesses containing fungi consistent with *Candida* (patient 3). PTLD in the lungs of patient 6 had an interstitial pneumonia-like pattern.

Acute renal failure occurred terminally in patients 1 and 6. Antemortem imaging studies of patient 1 showed normal-sized kidneys without evidence of obstruction. However, at autopsy the weight of the kidneys was twice normal and renal parenchyma and blood vessels were massively infiltrated by PTLD resulting in widespread necrosis that accounted for organ dysfunction (Fig 3). The kidneys of patient 6 showed evidence of poor renal perfusion and were diffusely mildly infiltrated by PTLD.

Patient 5 died from massive GI bleeding after chemotherapy for PTLD; at autopsy hemorrhagic foci of PTLD were found throughout the GI tract consistent with tumor lysis syndrome (Fig 4). *Giardia* infection had complicated the differential diagnosis for this patient’s GI symptoms; the infection was treated and *Giardia* was not found at autopsy. Patient 4 had heme-positive stools, and at autopsy, the GI tract was markedly infiltrated by PTLD.

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**TABLE 3.** Distribution of PTLD at Autopsy

<table>
<thead>
<tr>
<th>Organ transplant = bone marrow</th>
<th>Lymph Node</th>
<th>Bone Marrow</th>
<th>Spleen</th>
<th>Thymus</th>
<th>GI</th>
<th>Liver</th>
<th>Kidney</th>
<th>Heart</th>
<th>Lung</th>
<th>Brain</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>NA*</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3†</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Organ transplant = liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5†</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6‡</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>7‡</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA indicates not assessed.

* Splenectomy performed before transplant.
† Autopsy restricted to chest organs.
‡ PTLD diagnosed at autopsy.

**TABLE 4.** Associated Pathology

<table>
<thead>
<tr>
<th>Organ transplant = bone marrow</th>
<th>Infection</th>
<th>Infarct</th>
<th>Diffuse Alveolar Damage</th>
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<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3*</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Organ transplant = liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5†</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6‡</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7‡</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Autopsy restricted to chest organs.
† PTLD diagnosed at autopsy.
Patient 7 died from intracranial hemorrhage after second liver transplant. The brain was not examined microscopically at autopsy. This patient had Alagille syndrome and intracranial hemorrhage occurs infrequently in patients who have Alagille syndrome.

**DISCUSSION**

In this study, autopsy uncovered PTLD that was clinically silent, documented wide PTLD dissemination in children who died with clinically apparent disease, and clarified causes of organ dysfunction. There are many reasons to perform autopsies on children who die with malignancy.9 In a series of 40 such autopsies, new information was obtained in 20% and important additional information was provided in 55%.10 Autopsy is especially critical to our understanding of the natural history and response to treatment of diseases such as PTLD that affect only certain populations but that inflict significant morbidity and mortality.

Unfortunately, despite a high overall mortality rate, there are few previous descriptions of PTLD at autopsy (Table 5), consisting of reports of 3 children, 3 adults, and 1 patient whose age is not given.11–15 Nevertheless, these studies suggest that disseminated PTLD is more common in children than in adults: 5 of 6 children who had complete autopsy in this series and 3 children reported by others11,12 had disseminated PTLD, compared with only 1 of 3 adults.13–15 Children who die with lymphoproliferative disorders other than PTLD also have widely disseminated disease at autopsy.16,17

Autopsy findings refine the differential diagnosis of PTLD. PTLD in its disseminated or localized forms can clinically and histologically mimic other diseases, such as infections. Sudan et al11 reported an infant who, like the youngest patients in this series, had a sepsis-like illness after liver transplant; liver biopsy showed rejection that was treated with increased immunosuppression, but when the child...
died 1 month later with persistent fever and multiorgan failure, autopsy revealed PTLD in multiple organs. The distinction between graft rejection and PTLD is critical because the treatment is different: PTLD may regress with reduced immunosuppression, but rejection requires increased immunosuppression. To distinguish PTLD from rejection may be very difficult in small biopsies. The presence of atypical/malignant cells and the demonstration of EBV in the lesion are very helpful to identify an infiltrate as PTLD.

In addition to mimicking infection and rejection, PTLD may form space-occupying lesions. Ulrich et al.14 reported a 59-year-old female who had fever and abdominal pain 3 months after renal transplant and died from pulmonary emboli 6 months after transplant; autopsy showed a renal T cell lymphoma that had been diagnosed as a perirenal hematoma antemortem.

**PTLD Histology**

The histologic classification of PTLD given at autopsy was the same as the classification of the antemortem biopsies in the 5 cases in this series that had both antemortem and postmortem samples. PTLD histology may change over time. Recurrent PTLD may have histology different from the original lesion. This series does not include any cases of recurrent PTLD, and the time interval from PTLD clinical diagnosis to death of most of these patients was extremely short.

PTLD clonality also may change over time, or even may differ contemporaneously between anatomic sites: both monoclonal and polyclonal samples of PTLD have been obtained from different anatomic sites of the same patient, as in one of our cases. Sampling a single site of PTLD for clonality, therefore, may be misleading and may reveal only a polyclonal population.

EBV latent membrane protein was detected by immunohistochemistry in 4 of 5 antemortem biopsies in this series. EBV LMP transforms cells and LMP gene deletions have been detected in 4 of 4 aggressive PTLD. However, in a larger series of 32 PTLD cases, deletion of the LMP gene did not correlate with PTLD clonality, morphology, or outcome. LMP deletion was found in all cases of PTLD having EBV B strain that transforms cells less efficiently than EBV A strain, larger studies are needed to determine whether LMP deletion is necessary for PTLD to develop after infection with B strain of EBV.

**Extent of PTLD**

Kidney was infiltrated by PTLD in all clinically apparent cases in this study and is often infiltrated in myeloproliferative and lymphoproliferative disorders, particularly acute lymphocytic leukemia and low-grade non-Hodgkin’s lymphoma. Uncommonly, lymphoma arises in the kidney. Kidney could be a diagnostic biopsy site for PTLD in patients who do not have more readily accessible sites of disease, especially if imaging studies show renal megaly. An expansile infiltrate that contains atypical cells and exhibits serpiginous necrosis are features that distinguish PTLD from renal cellular rejection.

In our series, PTLD commonly infiltrated the brain. PTLD has been found in the brains of 2% to 7% of patients with hematologic malignancies than were diagnosed postmortem than were diagnosed antemortem. GI tract may be infiltrated in cases of disseminated PTLD and is the predominant site of involvement in ~17% of PTLD patients. GI PTLD tends to be multifocal and to involve the distal small bowel, which normally contains the greatest concentration of lymphoid tissue in the GI tract. Surgical resection may be helpful for patients with predominantly GI PTLD.

The liver and heart each were infiltrated in 2 cases in this series. The liver is frequently involved in patients who die with myeloproliferative syndrome (80%–100%), acute leukemia (60%–70%), and non-Hodgkin’s lymphoma (50%–60%). Primary hepatic and cardiac lymphomas are rare.

Vascular infiltration by PTLD was found in several of our cases. EBV-driven lymphoid proliferations may invade blood vessels of patients who have PTLD, X-linked lymphoproliferative syndrome, or acquired immunodeficiency syndrome. EBV infects endothelial cells in vitro. Vascular invasion by PTLD may have contributed to hepatic and splenic infarcts in our cases.

**Associated Pathology**

Infection other than EBV should be anticipated in the autopsy of transplant patients who have PTLD. Invasive fungal infections, especially *Candida* and *Aspergillus*, are more common in autopsies of patients who die with hematologic malignancies than in autopsies of other patients; also, more infections are diagnosed postmortem than were diagnosed ant-

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### Table 5. Previous Reports of PTLD at Autopsy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Gender</th>
<th>Organ</th>
<th>Interval</th>
<th>EBV Status</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>1.5 y/F</td>
<td>Liver</td>
<td>24 mo</td>
<td>NS</td>
<td>DNA ISH negative</td>
</tr>
<tr>
<td>16</td>
<td>11 mo/M</td>
<td>Liver</td>
<td>19 mo</td>
<td>DNA ISH negative</td>
<td>Liver</td>
</tr>
<tr>
<td>17</td>
<td>7.8 y/M</td>
<td>Liver</td>
<td>7 mo</td>
<td>Serology negative</td>
<td>Liver</td>
</tr>
<tr>
<td>17</td>
<td>NS</td>
<td>Liver</td>
<td>NS</td>
<td>NS</td>
<td>Liver</td>
</tr>
<tr>
<td>18</td>
<td>60 y/M</td>
<td>Heart</td>
<td>5 mo</td>
<td>DNA ISH, PCR positive</td>
<td>LN, spleen, liver, kidney</td>
</tr>
<tr>
<td>19</td>
<td>59 y/F</td>
<td>Kidney</td>
<td>6 mo</td>
<td>NS</td>
<td>Kidney</td>
</tr>
<tr>
<td>20</td>
<td>42 y/M</td>
<td>Liver</td>
<td>2 mo</td>
<td>DNA ISH positive</td>
<td>Liver</td>
</tr>
</tbody>
</table>

Interval indicates time from transplant to autopsy; NS, not stated; ISH, in situ hybridization; LN, lymph node; RCA, right coronary artery.
temortem in patients who had malignancy. Respiratory insufficiency attributable to infection with cytomegalovirus or fungus is the most common cause of death of adults with T cell leukemia/lymphoma. Infection may be associated with diffuse alveolar damage in bone marrow transplant recipients, and pulmonary infection, mostly fungal, is identified at autopsy in 29% of patients who die with so-called idiopathic pneumonia syndrome after bone marrow transplantation, performed mostly to treat leukemia.

Cause of Death
In this series, most patients died from multiorgan dysfunction caused by widely infiltrative PTLD. Causes of death in the other reported cases of PTLD (Table 5) were multiorgan failure in 2 young children, attributed to disseminated PTLD in 1 of them, bowel obstruction possibly attributable to PTLD, diffuse alveolar damage and acute renal failure in an adult with disseminated PTLD, graft (liver) failure caused by PTLD that was present in the graft only, and pulmonary thromboembolus.

EBV Surveillance
Serology for EBV may be uninformative or negative in patients who have biopsy-proven PTLD in which EBV gene expression is detected by in situ hybridization, as we have documented in this report. Polymerase chain reaction (PCR) is a sensitive means to detect EBV and has been used for EBV detection in the peripheral blood of patients who have had transplants. Detection of EBV by PCR in peripheral blood seems to identify pediatric patients at risk to develop PTLD. Modulating immunosuppression based on quantitative PCR for EBV in peripheral blood may diminish the incidence of PTLD. Antiviral agents used preemptively may also reduce the incidence of PTLD.

CONCLUSION
Autopsy should be performed on all children who die after organ transplant. In this series, unsuspected PTLD was diagnosed at autopsy, more extensive disease was documented than had been suspected clinically, reasons for organ dysfunction were clarified, and other infections were detected. Autopsy will determine the efficacy of strategies to treat and prevent PTLD, such as immunomodulation based on PCR and preemptive use of antiviral agents.

ACKNOWLEDGMENT
This work was supported in part by Grant IRG-135N from the American Cancer Society (to K.T.M.).

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