Hepatosplenic gamma/delta T-Cell Lymphoma in Immunocompromised Patients

Report of Two Cases and Review of Literature

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Key Words: Lymphoma; gamma/delta T-cell receptor; Hepatosplenitic; Extranodal; Posttransplant; Epstein-Barr virus; Isochromosome 7q

Abstract

We describe 2 male patients in whom hepatosplenic gamma/delta T-cell lymphoma (HSTL) developed 6 and 10 years after renal transplantation. The onset was abrupt with systemic symptoms, cytopenia, and hepatosplenomegaly. The histologic examination of the spleen (case 1), liver, and bone marrow revealed sinusoidal infiltrates of markedly abnormal lymphocytes. The neoplastic cells in these cases were CD2+, CD3+, CD4−, CD5−, CD7+, CD8+, CD16+, CD56+, betaF1-negative, and TIA-1-negative. Both cases displayed clonal rearrangement of the T-cell receptor (TCR) delta gene and the TCR beta gene. The spleen in case 1 was positive for Epstein-Barr virus genome and showed TCR-gamma gene rearrangement by polymerase chain reaction. Isochromosome 7[i(7)(q10)] was found in each case. Both patients died within 4 months of diagnosis. HSTL has been reported in only 5 renal transplant recipients. HSTL may be relatively more frequent in immunocompromised patients compared with the general population.

There are 2 mutually exclusive subtypes of CD3-associated T-cell receptor (TCR) molecules expressed on normal T cells, namely alpha/beta and gamma/delta. In contrast with the alpha/beta T cells, which are mostly CD4+ or CD8+, the gamma/delta T cells are primarily CD4− and CD8−. These cells frequently express natural killer (NK) cell–associated antigens (CD16, CD56) and have cytotoxic activity. Although the exact pathophysiologic role of gamma/delta T cells is unknown, reports suggest that these cells may have a role in the immune reaction during infection and in the regulation of pathophysiologic autoimmune responses.1 Like their normal counterparts in the peripheral blood (PB), most of the peripheral (postthymic) T-cell lymphomas (PTCLs) are also of alpha/beta T-cell derivation,2 characterized as CD2+, CD3+, and CD4+ or CD8+. They commonly have prominent bone marrow (BM) involvement. PTCLs originating from gamma/delta T cells are rare. Most occur as extranodal tumors. The tumor cells show a homing pattern reminiscent of normal gamma/delta T cells, which preferentially occupy the sinusoidal areas of the spleen, intestinal mucosa, and skin.3 Their phenotype is typically CD2+, CD3+, CD4−, and CD8−.

Among the gamma/delta postthymic PTCLs, 2 distinct groups were described initially: a predominant hepatosplenic form (hepatosplenic gammata delta T-cell lymphoma [HSTL])4-19 and a cutaneous form.20-22 However, a growing number of such neoplasms have been reported in many other organs, including small intestine,20,23 nasal cavity,20 lymph nodes,24 larynx,20,22 and lung.20 Many neoplasms that arise from this T-cell subpopulation belong to the hepatosplenic form. To our knowledge, 42 well-documented cases of HSTL have been reported in the literature, mostly in immunocompetent patients. We describe 2 cases of this rare form of PTCL encountered at William Beaumont Hospital, Royal...
Oak, MI, in 2 renal transplant recipients receiving immunosuppressive therapy. Only 8 cases of HSTL have been previously reported in patients immunocompromised by therapy.\textsuperscript{5-11}  This includes 5 renal transplant recipients,\textsuperscript{5-9} as are our 2 present cases. The first case presented is unusual because the tumor cells were positive for Epstein-Barr virus (EBV). Our cases confirm that HSTL is a distinct clinicopathologic entity with aggressive clinical behavior that may occur more frequently in the setting of therapeutic immunosuppression and commonly has the nonrandom chromosomal abnormality isochromosome 7. A comprehensive overview of the cases reported in the literature also is presented.

Case Reports

Case 1

A 41-year-old man who had end-stage renal disease from IgA nephropathy received a cadaveric renal transplant in 1987 and thereafter was treated with low-dose immunosuppressive therapy with cyclosporine and prednisone. Mycophenolate mofetil was added to the immunosuppressive regimen in October 1996. In May 1997, he sought care because of anorexia, fever, profound weakness, weight loss, night sweats, dyspnea, and thrombocytopenia. His platelet count had been normal 2 months earlier.

The CBC count results were as follows: WBC count, 16,000/µL (16.0 × 10\(^9\)/L); neutrophils, 12,000/µL (12 × 10\(^9\)/L); lymphocytes, 1,080/µL (1.08 × 10\(^9\)/L); RBC count, 4.4 × 10\(^12\)/L (4.4 × 10\(^12\)/L); hemoglobin, 11.9 g/dL (119 g/L); hematocrit, 34.3% (0.34); mean corpuscular volume, 80.3 µm\(^3\) (80.3 fL); and platelet count, 50 × 10\(^9\)/L (50 × 10\(^9\)/L). The physical examination revealed a temperature of 38°C, no lymphadenopathy, and soft abdomen with no palpable organomegaly. Initially, the patient was treated with plasmapheresis for a presumed diagnosis of thrombotic thrombocytopenic purpura with no response. During the next 3 months, the patient experienced chronic rejection, graft dysfunction, and unremitting thrombocytopenia with bleeding. Because platelet-associated antibodies were demonstrated, he was treated with gamma globulin and corticosteroids with limited success. During this time, 2 BM examinations were performed to exclude the possibility of infection or a lymphoproliferative disorder, and results of both were negative. Similarly, the results of flow cytometric (FCM) studies on BM and PB samples were normal. By September 1997, severe anemia had developed (RBC count, 1.7 × 10\(^12\)/L; hemoglobin, 5.1 g/dL [51 g/L]) that was associated with reticulocytosis and erythroblastosis. Severe thrombocytopenia (8 × 10\(^9\)/µL [8 × 10\(^9\)/L]) persisted. There was no PB lymphocytosis. At this time, the patient had hepatosplenomegaly. A computed tomography scan in October 1997 revealed a 7-cm spleen, which by November 1997 had enlarged to 22 cm in greatest dimension.

Splenectomy and liver biopsies were performed. Histologic examination revealed diffuse large cell lymphoma, which also involved the liver and an accessory spleen. Immunophenotyping by FCM studies indicated an abnormal T-cell population suggestive of HSTL that was confirmed on molecular studies. A staging BM biopsy again failed to show an infiltrate on routinely stained sections, but a slight increase in blast-like cells was identified by BM differential, and scattered large cells with NK cell phenotype were identified in the BM biopsy specimen by immunohistochemical analysis. Pneumonia with bilateral malignant pleural effusion and massive ascites developed. The patient was not given any chemotherapy. Terminally, abnormal lymphocytes were seen in the PB. His renal function deteriorated further, and he died of septicemia in February 1998, 4 months after the diagnosis of gamma/delta T-cell lymphoma was made. No autopsy was performed.

Case 2

A 62-year-old man with essential hypertension who had end-stage renal disease from focal segmental glomerulosclerosis received a cadaveric renal transplant in 1991 and was treated with immunosuppressive therapy with cyclosporine and prednisone thereafter. In late April 1998, he had a 2-week history of anorexia, increasing fatigue, and low-grade fever (37.5°C).

Laboratory tests showed renal insufficiency (blood urea nitrogen, 37 mg/dL [13.2 mmol/L]; and creatinine, 2.4 mg/dL [212 µmol/L]) and pancytopenia with evidence of direct antiglobulin–negative hemolytic anemia. The CBC count results were as follows: WBC count, 2,000/µL (2 × 10\(^9\)/L); neutrophils, 700/µL (0.7 × 10\(^9\)/L); lymphocytes, 630/µL (0.63 × 10\(^9\)/L); RBC count, 3.8 × 10\(^12\)/L (3.8 × 10\(^12\)/L); hemoglobin, 12.3 g/dL (123 g/L); hematocrit, 35.4% (0.35); mean corpuscular volume, 94 µm\(^3\) (94 fL); and platelet count, 121 × 10\(^9\)/µL (121 × 10\(^9\)/L). Marked abnormalities of liver function (aspartate aminotransferase, 319 U/L [319 U/L]; alanine aminotransferase, 635 U/L [635 U/L]; and total bilirubin, 3.5 mg/dL [60 µmol/L]) also were noted. All laboratory values except the renal function tests (blood urea nitrogen, 21 mg/dL [7.5 mmol/L]; and creatinine, 1.7 mg/dL [150 µmol/L]) had been normal in March 1998. Prothrombin time and partial thromboplastin time values were within the normal ranges, and a disseminated intravascular coagulation screen was negative at diagnosis. Results of serologic studies, blood cultures, and polymerase chain reaction (PCR) for cytomegalovirus detection were negative.

The physical examination revealed no lymphadenopathy or palpable hepatosplenomegaly. However, ultrasonography
showed splenomegaly. A computed tomography scan of the abdomen did not show evidence of retroperitoneal or pelvic adenopathy. BM and liver biopsies were performed to evaluate pancytopenia and persistent elevated liver enzyme levels. Both procedures revealed non-Hodgkin lymphoma that was characterized as gamma/delta T-cell lymphoma by immunohistochemical analysis, FCM studies, and molecular studies. A splenectomy was not done. He was weaned off cyclosporine, and 1 cycle of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy was given.

The patient had a progressive downhill course, and multiple episodes of septicemia developed. His other laboratory values also deteriorated markedly (hemoglobin, 6.9 g/dL [69 g/L]; RBC count, 3.0 × 10⁹/µL [3.0 × 10¹²/L]; platelet count, 20 × 10⁹/µL [20 × 10⁹/L]; bilirubin, 40 mg/dL [684 µmol/L]; lactate dehydrogenase, 1,939 U/L [1,939 U/L]). Terminally, leukocytosis developed (WBC count, 45,000/µL [45 × 10⁹/L]; lymphocytes, 3,900/µL [3.9 × 10⁹/L]), and, as in case 1, an increased number of abnormal lymphocytes were seen in the PB. Multiorgan failure developed secondary to sepsis, and the patient died in June 1998, 5 weeks after the initial diagnosis. An autopsy was not performed.

### Materials and Methods

#### Morphologic Studies and Immunophenotyping

PB and BM smears were stained with Wright-Giemsa. The BM clot and core biopsy specimens were fixed in B-5, sectioned after decalcification when appropriate, and stained with H&E by standard methods. Specimens from the spleen and liver were fixed in formalin and processed according to standard methods. Paraffin sections were stained with H&E for histologic examination. Portions of the specimens were snap frozen for immunohistochemical analysis and molecular studies.

Three-color FCM studies were performed on an Ortho Cytoron (Ortho Diagnostic Systems, Raritan, NJ) using CD3, CD20, and CD45 gating. The FCM antibody panel comprised the following antibody-fluorescent conjugates: CD3-PC5, CD8-EC, CD19-EC, CD25-fluorescein isothiocyanate (FITC), CD45-FITC, and CD56-RD1 (Coultier, Miami, FL); and CD1a-FITC, CD2-phycoerythrin (PE), CD4-PE, CD5-FITC, CD7-FITC, CD10-FITC, CD11b-PE, CD11c-PE, CD16-FITC, CD20-PE, CD22-PE, CD23-PE, CD38-PE, CD57-FITC, and surface light chains (Becton-Dickinson, San Jose, CA). Antigen density, as interpreted from fluorescence intensity relative to a normal comparative cell type, was expressed as not detectable, subnormal, normal, or increased.

FCM immunophenotyping was done on BM (cases 1 and 2), spleen (case 1), and liver (case 2). No FCM studies were performed on the liver specimen in case 1. An immunohistochemical analysis panel (CD3, CD43, CD45RO, CD45RA, CD20, CD56, and CD57) was performed on paraffin or frozen sections of the spleen (case 1) and liver (both cases), using the peroxidase-antiperoxidase and avidin-biotin complex method.

Paraffin sections of spleen (case 1) were used for the detection of T-cell restricted intracellular antigen (TIA-1) and granzyme, and BM sections from case 2 were used for the detection of TIA-1 and betaF1. The BM specimens in case 1 (post-splenectomy specimen only) and case 2 also were studied by immunohistochemical analysis using a limited panel of CD3, CD20, CD56, and CD57. Appropriate positive and negative controls were performed.

### Southern Blot, In Situ Hybridization, and Polymerase Chain Reaction Analysis

DNA was extracted from frozen aliquots of the spleen (case 1) and fresh BM aspirates (both cases) according to standard technique. Extracted DNA was digested using restriction endonuclease enzymes (BamHI, EcoRI, and HindIII for case 1 and EcoRI, HindIII, and BglII for case 2). The digested DNA was size-fractionated by agarose gel electrophoresis, transferred to a membrane by the method of Southern, and analyzed by hybridization with complementary DNA probes using a chemiluminescent detection system. Probes for the immunoglobulin (IgH and IgK) TCR gamma genes, including the N region, was carried out on DNA extracted from BM aspirate and spleen (case 1), with analysis by acrylamide gel electrophoresis.

#### Cytogenetics

In both cases, cytogenetic analysis was performed on cell suspensions from BM samples. BM aspirates were prepared by a direct method or after a short-term culture (16-24 hours) according to standard procedures. Chromosome analysis was done on GTG banded spreads. No less than 20 cells were analyzed, and 5 to 8 were karyotyped. Karyotypes...
are described according to the International System for Human Cytogenetic Nomenclature.28

Results

Gross and Histopathologic Features

In case 1, the spleen weighed 1,600 g and measured 26 × 15 × 7.5 cm. The cross-section showed a diffuse, firm white surface. The smaller, accessory spleen measured 1.5 × 1.2 × 1 cm. A spleen specimen was not available for case 2. Histologic examination of the spleen in case 1 showed a dense, monotonous population of lymphoid cells diffusely infiltrating the red pulp and almost totally obliterating the preexisting splenic architecture. The lymphoma also involved an accessory spleen. Tumor cells were medium sized and had fine chromatin and small nucleoli. The nuclei tended to be oval, although a few folded and elongated forms also were noted. Many cells also showed clear cytoplasm. Mitoses were noted frequently. Similar lymphocytes were present in the hepatic sinusoids with sparing of the hepatic portal triads in case 1. Liver involvement in case 2 was characterized by a striking infiltration of abnormal medium to large lymphocytes in the sinusoids and around the portal triads. Central lobular necrosis of hepatocytes also was observed in case 2. There was no evidence of hemophagocytosis in either case.

Both cases showed normocellular BM. In case 1, no definite infiltrate diagnostic of a lymphoproliferative disorder was identified in the initial clot or core biopsy sections on 2 occasions. However, postsplenectomy BM smears showed a subtle infiltrate of abnormal blast-like cells scattered throughout the hematopoietic marrow. These constituted about 8% of the nucleated marrow elements. Erythropoiesis and granulopoiesis were adequate. In case 2, a significant population of abnormal lymphocytes representing 22% of the total marrow elements was observed. These abnormal cells were scattered as single immature cells throughout the marrow and also formed subtle, ill-defined interstitial aggregates. The morphologic features of the tumor cells in the BM were similar in both cases. These abnormal cells were intermediate to large with minimal to moderate amounts of basophilic cytoplasm. Occasional cells contained fine cytoplasmic granules. The nuclei were round to highly irregular with prominent nucleoli. Numerous pigment-laden histiocytes were noted in the BM in case 2, which also showed increased erythropoiesis and markedly decreased granulopoiesis with delayed maturation.

In both cases, no abnormal lymphocytes were seen in the PB at the initial examination. However, during the terminal stages (last 1 month) of the disease, abnormal lymphocytes were noticed in the PB, accounting for approximately 15% of the total PB lymphocytes (3,400/µL [3.4 × 10^9/L] in case 1; 990/µL [0.99 × 10^9/L] in case 2). The morphologic features of these cells in the PB were similar to that noted in the BM in both cases.

Immunophenotyping

The immunophenotype of the neoplastic cells in these 2 cases is shown in Table 1. In both cases, the abnormal cells

Image 11 (Case 1) Histologic features of spleen showing the neoplastic cells of hepatosplenic gamma/delta T-cell lymphoma infiltrating the splenic red pulp (H&E, original magnification ×1,000).

Image 21 (Case 2) Histologic features of liver in hepatosplenic gamma/delta T-cell lymphoma showing the neoplastic cells (arrows) infiltrating the hepatic sinusoids (H&E, original magnification ×1,000).
demonstrated a T-cell lineage with an NK-like cell phenotype, were negative for B-cell markers (CD19, CD20, CD22, CD23, and FMC7), and lacked light chain expression. This was suggestive of either HSTL or NK-like T-cell lymphoma.

FCM studies of the postsplenectomy BM specimen showed an increased number of similar abnormal NK-like T cells estimated as approximately 55% of the lymphoid population, constituting 15% of the total leukocytes. Their phenotype was similar but not identical to that obtained with the splenic lymphoma, differing in CD3, CD5, and CD8 expression. The pleural fluid also showed similar abnormal lymphoid cells by FCM studies, constituting approximately 75% of the lymphocytes. In case 2, FCM studies revealed that the abnormal lymphocytes from the BM constituted 80% of the lymphoid population. The sample from liver was paucicellular and had reduced cell viability, thus limiting the completeness of the immunophenotyping. Paraffin sections for immunohistochemical analysis of the spleen (case 1) and liver (both cases) showed the tumor cells to be positive for T cell markers (CD3, CD43, CD45RO) and an NK-cell marker (CD56+, but CD57−) and negative for CD20 and CD45RA. Immunohistochemical analysis for TIA-1 and granzyme was negative for the splenic specimen in case 1. A more limited panel on BM identified CD56+/CD57− (both cases), and CD3+, betaF1-negative, TIA-1-negative (case 2) tumor cells. Studies for betaF1 were not performed in case 1.

Molecular Analysis

Southern blot analysis on the BM (both cases) and spleen (case 1) showed a clonal rearrangement of the TCR-delta gene and TCR-beta gene rearrangement. In case 1, 1 rearranged band was seen in each of the 3 restriction enzyme digests using the C_{theta} probe and 1 rearranged band in 2 of the 3 restriction enzyme digests using the J_{theta} probe. A probe for the TCR-delta chain gene showed 1 rearranged band in the BglII digest and 2 rearranged bands in the EcoRI and HindIII digests. In case 2, 1 rearranged band was observed with probes for the beta chain of the TCR (C_{theta} and J_{theta}) in enzyme digests using EcoRI and BglII. Rearranged bands also were seen in case 2 in the EcoRI and HindIII digests using the T-delta probe. No rearranged bands were visualized using probes for the immunoglobulin genes in case 1. Similarly, no rearranged bands were visualized by Southern blot analysis using probes for TCR-gamma gene in either case. However, PCR analysis on the spleen in case 1 showed TCR-gamma rearrangement, representing a clonal T-cell population; this rearrangement was not detected in the BM specimen. ISH on the splenic specimen showed scattered

Table 1
Immunophenotyping of Abnormal Lymphoid Cells by Flow Cytometry and Immunohistochemical Analysis in Two Cases of Hepatosplenic gamma/delta T-Cell Lymphoma*

<table>
<thead>
<tr>
<th>Antigen Expression</th>
<th>Case No./ Sample</th>
<th>CD2</th>
<th>CD3</th>
<th>CD4</th>
<th>CD5</th>
<th>CD7</th>
<th>CD8</th>
<th>CD16</th>
<th>CD38</th>
<th>CD56</th>
<th>CD57</th>
<th>TIA-1</th>
<th>betaF1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1 Spleen</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(dim)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>‡</td>
<td>–‡</td>
</tr>
<tr>
<td></td>
<td>Bone marrow‡</td>
<td>+</td>
<td>–</td>
<td>–</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></td>
<td>Liver‡</td>
<td>ND</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>+</td>
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<td>–</td>
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<td>–</td>
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<tr>
<td></td>
<td>Pleural fluid</td>
<td>ND</td>
<td>+</td>
<td>–</td>
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<td>–</td>
<td>–</td>
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<td>+</td>
<td>–</td>
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<td>–</td>
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<tr>
<td>2 Bone marrow‡</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+ (dim)</td>
<td>+ (dim)</td>
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<td>+</td>
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<tr>
<td>Liver‡</td>
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<td>+</td>
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<td>ND</td>
<td>+ (dim)</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>–</td>
<td>–‡</td>
<td>–‡</td>
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</tbody>
</table>

ND, not done; NE, not evaluable; TIA-1, T-cell restricted intracellular antigen; +, positive; −, negative; a, few cells positive.

‡ Pan B-cell markers were negative for all samples.

‡ Postsplenectomy sample.

‡ Studied by immunohistochemical analysis only.
EBV-positive tumor cells in case 1 that was confirmed by PCR results. However, the BM sections from case 2 were not interpretable for EBV owing to high background staining.

Cytogenetics

In case 1, an isochromosome for the entire long arm of chromosome 7, i.e., i(7)(q10), was present in 19 of 20 cells analyzed. In addition, trisomy 21 and monosomy 17 were found in 8 of 20 cells; tetrasomy 21, monosomy 17, and a marker chromosome were found in 8 of 20; the remaining 3 cells contained only trisomy 21 as an additional abnormality. An apparently normal male karyotype, 46.XY, was present in 1 of 20 cells examined. Thus, the karyotype designation for case 1 is 47.XY,i(7)(q10),+21[3]/46,idem,–17[8]/48,idem,–17,+21,+mar[8]/46.XY[1]. In case 2, an i(7)(q10) and a loss of the Y chromosome were observed in 14 of 20 cells analyzed. The remaining 6 cells had an apparently normal male karyotype. The karyotype designation for case 2, therefore, is 45,X,–Y,i(7)(q10)[14]/46,XY[6].

Discussion

Most of the clinicopathologic features of our 2 cases are characteristic of HSTL, a relatively rare lymphoid neoplasm that belongs to the clinically heterogeneous group of PTCLs. Because of its unique clinical manifestations, histologic pattern of infiltration, and immunophenotypic features, it has been recognized as a distinct entity in the World Health Organization Classification of Lymphoid Malignancies.29 Since its first description as a distinct entity among PTCLs in 1990,4 42 well-documented cases of HSTL have been reported in the literature. It is an unusual lymphoma that primarily involves liver and spleen. Characteristic features include occurrence in young males (median age, 32 years) with marked hepatosplenomegalgy, the absence of appreciable lymphadenopathy, expression of gamma/delta-TCR, and the presence of gamma/delta-TCR gene rearrangements in the neoplastic lymphocytes. The striking male predominance (M/F ratio, 5:1) is yet to be explained. Data regarding the incidence in different races is incomplete, but the disease seems to affect all racial groups. The clinical course is aggressive with a poor response to combination chemotherapy, and the median survival is less than 1 year.

As in the present 2 cases, the majority of patients have systemic signs and symptoms attributed to cytopenias and hepatic involvement. Severe neutropenia previously has been noted in only 4 cases described in the literature.7-14

Table 2

T-Cell Receptor Genotyping by Southern Hybridization in Two Cases of Hepatosplenic gamma/delta T-Cell Lymphoma

<table>
<thead>
<tr>
<th>Probe</th>
<th>Restriction Enzyme</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Jp</td>
<td>BamIII</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G†</td>
<td>ND</td>
</tr>
<tr>
<td>Jp</td>
<td>EcoRI</td>
<td>G</td>
<td>ND</td>
<td>G</td>
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<td>ND</td>
<td>G</td>
<td>ND</td>
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<tr>
<td>Jp</td>
<td>HindIII</td>
<td>G</td>
<td>ND</td>
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<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
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<tr>
<td>Jp</td>
<td>BglII</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
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<tr>
<td>Jp</td>
<td>R</td>
<td>ND</td>
<td>ND</td>
<td>G</td>
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</tr>
<tr>
<td>Jp</td>
<td>G/R‡</td>
<td>ND</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
<td>G</td>
<td>ND</td>
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</table>

G, germline configuration; ND, not done; R, 1 gene rearrangement band detected; RR, 2 gene rearrangement bands detected.
† Case 1, spleen and bone marrow; case 2, bone marrow.
‡ Not done on spleen; germline in bone marrow.

Image 41 (Case 2) Cytogenetic analysis showing isochromosome 7q (arrow) and loss of Y chromosome in hepatosplenic gamma/delta T-cell lymphoma (GTG banding; original magnification x2,500).
was seen in our case 2. The neutropenia may be related to hypersplenism or suppression of the myeloid/monocyte colony forming units by the lymphokines produced by the tumor cells. A similar suppressive effect of the high serum levels of gamma-interferon, elaborated by gamma/delta T-cell lymphoma, has been described by Burg et al. A variable number of abnormal lymphocytes can be detected in the PB in most patients (up to 60%) at some stage of the disease. However, this is more frequently seen after splenectomy or during the late stages of this disease, as was observed in our 2 cases.

The diagnosis of HSTL can be difficult and can be easily missed initially. Like our case 1, many previous cases were diagnosed initially as idiopathic thrombocytopenic purpura. The majority of cases are diagnosed at splenectomy. In the absence of splenectomy, however, a liver biopsy may provide a specific diagnosis of HSTL if sufficient material can be obtained for specialized panels containing the betaF1 and/or delta1TCR antibodies and molecular studies, as demonstrated by our case 2.

The typical histologic pattern of intrasinusoidal infiltration of abnormal lymphocytes in the organs involved was seen in our 2 cases. This peculiar tropism for the hepatic sinusoids and splenic red pulp with sparing of portal triads and splenic white pulp, respectively, is proposed to be due to an interaction between neoplastic gamma/delta T cells and endothelial cells of these organs. Splenic red pulp involvement usually is diffuse without nodule formation, except in 1 report. Mild white pulp infiltration has been reported rarely. The white pulp most often is atrophic. Mild portal infiltration, portal fibrosis, and hepatocellular necrosis/atrophy were reported in 4 previous cases. Our portal infiltration, portal fibrosis, and hepatocellular carcinoma were observed in 4 previous cases. The white pulp most often is atrophic. Mild portal infiltration, portal fibrosis, and hepatocellular necrosis/atrophy were reported in 4 previous cases. Our portal infiltration, portal fibrosis, and hepatocellular carcinoma were observed in 4 previous cases. The white pulp most often is atrophic.

In reported cases, BM involvement ranged from subtle infiltrates that were detected only by immunostains to up to 70% marrow involvement. The majority of cases are diagnosed at splenectomy. In the absence of splenectomy, however, a liver biopsy may provide a specific diagnosis of HSTL if sufficient material can be obtained for specialized panels containing the betaF1 and/or delta1TCR antibodies and molecular studies, as demonstrated by our case 2.

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The diagnosis of HSTL can be difficult and can be easily missed initially. Like our case 1, many previous cases were diagnosed initially as idiopathic thrombocytopenic purpura. The majority of cases are diagnosed at splenectomy. In the absence of splenectomy, however, a liver biopsy may provide a specific diagnosis of HSTL if sufficient material can be obtained for specialized panels containing the betaF1 and/or delta1TCR antibodies and molecular studies, as demonstrated by our case 2.

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localization of TCR-beta and TCR-gamma genes to the long and short arms of chromosome 7, respectively, may have some etiologic implications. One possibility is the loss of a putative suppressor gene resulting from i(7)(q10). At least 2 oncogenes, MET and TIM, and several kinases, including cyclin-dependent kinase 5, are located on the long arm of chromosome 7. Their amplification in i(7)(q10) may have a role in tumor genesis. Another chromosomal abnormality reported with high frequency is trisomy 8, observed in 45% of cases (10/22). Neither of our cases, however, showed this abnormality. Trisomy 8 often is classified as a secondary event associated with disease progression. It should be noted that trisomy 8 and, to a lesser degree, i(7)(q10) have been reported in a large variety of other hematolymphoid neoplasms, as well as in many solid organ malignant neoplasms. Our first case demonstrated multiple other structural and numerical chromosomal abnormalities. These less commonly reported chromosomal abnormalities have been described in many previous reports, are not consistent, and have no correlation with HSTL. Interestingly, about one third of the cases (7/22) also showed loss of the Y chromosome (–Y). Although the loss of the Y chromosome observed in our case 2 might be age related, 4 of the 6 previously reported cases with this abnormality were quite young (mean age, 30 years).

In general, immunocompromised patients, especially those who receive long-term immunosuppressive therapy for organ transplantation, are at high risk of developing secondary lymphoproliferative disorders. These usually are EBV-related B-cell lymphoproliferative disorders and often are polyclonal. Although exceedingly rare, T-cell lymphoproliferative disorders have been reported after heart, renal, and bone marrow transplantation. While most HSTL cases occur in immunocompetent patients, about one fourth have been associated with immunosuppressive therapy for various reasons, including organ transplants (6 cases), ulcerative colitis (1 case), and Hodgkin disease (1 case). The median duration of immunosuppression was 5 years (range, 6 months to 10 years) compared with 7 years for B-cell posttransplant lymphoproliferative disorders. Clinicopathologic and survival data on these cases and for our 2 cases are summarized in Table 3. Seven cases arose subsequent to therapeutic

### Table 3

<table>
<thead>
<tr>
<th>Reference/Case No./Sex/Age (y)</th>
<th>Clinical Features</th>
<th>Immunophenotyping (Cluster Designation)</th>
<th>TCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis (y)</td>
<td>Organ Involved*</td>
<td>2 3 5 7 16 56 57</td>
</tr>
<tr>
<td>Francois et al5/1/M/34</td>
<td>HD (0.5)</td>
<td>LN</td>
<td>+ + − − − − − ND +</td>
</tr>
<tr>
<td>2/M/44</td>
<td>KD (4)</td>
<td>PB</td>
<td>+ + − ND − − + ND +</td>
</tr>
<tr>
<td>Garvin et al6/3/3/M/32</td>
<td>KD (10)</td>
<td>PB, LN, O</td>
<td>+ + ND ND − − ND ND</td>
</tr>
<tr>
<td>Jonveaux et al7/4/M/19</td>
<td>KD (3)</td>
<td>+ + + − − − − ND ND</td>
<td>− +</td>
</tr>
<tr>
<td>Ross et al5/5/M/31</td>
<td>KD (3)</td>
<td>PB</td>
<td>+ + − ± − − − + +</td>
</tr>
<tr>
<td>Hanson et al5/6/M/56</td>
<td>KD (7)</td>
<td>PB, O</td>
<td>+ + ND + − + ND +</td>
</tr>
<tr>
<td>Kraus et al87/7/F/5</td>
<td>HR (5)</td>
<td>PB</td>
<td>+ + − ± − − ND + ND</td>
</tr>
<tr>
<td>Macon et al10/UC (?)</td>
<td>UC (?)</td>
<td>PB</td>
<td>+ + + + − + ND + −</td>
</tr>
<tr>
<td>Present cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M/41</td>
<td>KD (10)</td>
<td>KB (+)</td>
<td>+ + + ± + − + + + − +</td>
</tr>
<tr>
<td>2/M/62</td>
<td>KD (6)</td>
<td>KB (+)</td>
<td>+ + + + − + + + + − +</td>
</tr>
</tbody>
</table>

**ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; asp, asparaginase; CHOP, HOP, cyclophosphamide; cye, cyclophosphamide; cty, cytarabine; cytaBOM-proMACE, CHOP, methotrexate, bleomycin, etoposide, cytarabine, leucovorin; dau, daunorubicin; dex, dexamethasone; et, etoposide; G, gremlin; HD, Hodgkin disease; HOP, doxorubicin, vincristine, prednisone; HR, heart transplant; i(7)(q10), isochromosome 7; ifn, interferon; KD, kidney transplant; LN, lymph nodes; mit, mitoxantrone; mtx, methotrexate; ND, not done; NE, not evaluable; O, other organs; PB, peripheral blood; pred, prednisone; R, rearranged; TCR, T-cell receptor; UC, ulcerative colitis; VAD, doxorubicin, vincristine, dexamethasone; vin, vincristine; x, equivocal; −, negative; ?, uncertain; +, positive.

* In addition to the involvement listed, the spleen and liver were involved in all cases except case 6; in case 8, liver involvement was uncertain; the bone marrow was involved in all cases.

† All patients died of disease, except in case 8, in which the patient died with no evidence of disease.

‡ 45,X is constitutional karyotype.
immunosuppressive therapy in renal transplant recipients. Although the overall frequency of HSTL may be underestimated, inherent in its difficult recognition by morphologic features alone, which requires extensive immunophenotyping and molecular studies, it seems that this rare type of lymphoma is relatively more frequent in immunocompromised patients than in the general population. Based on the available data, however, there are no significant clinical or pathologic differences between the HSTL arising in the immunocompromised patients and the general population.

Although studies on many previous cases of HSTL using ISH, Southern blot analysis, and PCR have failed to identify EBV DNA within the tumor cells,\textsuperscript{5,8-11,18} suggesting no direct role for EBV in the pathogenesis of HSTL, our case 1 was positive for EBV by ISH (confirmed with PCR analysis). One reported case of HSTL\textsuperscript{10} developed in a pediatric patient with a history of an EBV-positive B-cell lymphoproliferative disorder. Also, some cases of non-HSTLs\textsuperscript{22,24} have been related to EBV infection. It remains to be determined whether EBV infection has a role in the development of HSTL or whether infection of the tumor cells occurs after clonal expansion. Recent studies\textsuperscript{35} suggest that the gamma/delta T cells may have an important role in the immune response to human renal allografts and in renal graft rejection. It has been proposed that the long-term antigenic stimulation may selectively stimulate and unmask T-cell clones. In addition, immunosuppressive therapy may also have a role in the emergence of a clonal T-cell lymphoproliferative disorder.

HSTL is highly aggressive with an inexorable clinical course and a short survival. The majority of the patients described in the literature (86\%) were treated with multiagent chemotherapy and most (75\%) underwent splenectomy. In addition, 4 patients also underwent bone marrow transplantation.\textsuperscript{7,18} Apart from its role in establishing diagnosis, splenectomy may have a potential therapeutic effect on the course of this disease. The average and median survival figures for patients with splenectomy were 15 and 11 months, respectively, compared with 6 and 5 months, respectively, for patients without splenectomy (Student t test; \( P < .05 \)). Of the 38 patients described who received chemotherapy, only 10 were described to have achieved remission that was transient or incomplete. Overall, the median survival is 9.5 months.

The distinctive clinical, histopathologic, immunophenotypic, molecular, and cytogenetic features of HSTL reflect a specific biologic entity. The relatively more frequent occurrence in renal transplant recipients is unusual. Additional reports, including additional molecular and cytogenetic data, will not only contribute to the general understanding of this lymphoma, but also will help improve diagnosis and management of this peculiar neoplasm.

<table>
<thead>
<tr>
<th>EBV Karyotype</th>
<th>Therapy</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47,XY(i7)(q10),+8</td>
<td>ACVB/cyt, dex</td>
<td>3</td>
</tr>
<tr>
<td>45,X,Y,del(1)p21p22, i(7)(q10),add(19)(q21)</td>
<td>Dau, cyt, cyc, vin, predVAD</td>
<td>10</td>
</tr>
<tr>
<td>ND</td>
<td>CHOP, et, mtx/cyt, asp/fn</td>
<td>12</td>
</tr>
<tr>
<td>ND 47,XY(i7)(q10),+8</td>
<td>CHOP</td>
<td>11</td>
</tr>
<tr>
<td>45,XY,i(7;9)(p15;q13), t(13q;14q)</td>
<td>HOP, asp/cyt, mit</td>
<td>5</td>
</tr>
<tr>
<td>ND</td>
<td>No chemotherapy</td>
<td>0.5</td>
</tr>
<tr>
<td>45,X,i(7)(q10),t(8;10)</td>
<td>CHOP, cytaltimore proMACE</td>
<td>1.5</td>
</tr>
<tr>
<td>46,XY,i(7)(q10),t(8;14)</td>
<td>Multiagent chemotherapy</td>
<td>2</td>
</tr>
<tr>
<td>+ 47,XY,i(7)(q10),+21</td>
<td>No chemotherapy</td>
<td>4</td>
</tr>
<tr>
<td>NE 45,X,Y,i(7)(q10)(14)/46,XY[1]</td>
<td>CHOP</td>
<td>1</td>
</tr>
</tbody>
</table>

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Acknowledgments: We thank Amy Chadburn, MD, and Ethel Cesaran, MD, New York Hospital–Cornell Medical Center, NY, for performing immunohistochemical, in situ hybridization, and polymerase chain reaction studies; the molecular diagnostics laboratory of Karen Kaul, MD, Evanston Hospital, Evanston, IL, for performing acrylamide gel electrophoresis; and Saima Kokikheil for secretarial assistance and editing of the manuscript.

References


