Posttransplant T-Cell Lymphoproliferative Disorders—An Aggressive, Late Complication of Solid-Organ Transplantation

By Michelle N. Hanson, Vicki A. Morrison, Bruce A. Peterson, Kevin T. Stiegibauer, Virginia L. Kubic, Stanley R. McCormick, Ronald C. McGlennen, J. Carlos Manivel, Richard D. Brunning, and Craig E. Litz

T-cell non-Hodgkin’s lymphomas are an uncommon occurrence after solid-organ transplantation. We describe a morphologically and immunophenotypically distinct group of T-cell lymphoproliferative disorders that occurred late in the course of six patients with solid-organ transplants. The patients ranged in age from 31 to 56 years (median, 43). Three were male; all were splenectomized. The interval from transplant to the diagnosis of lymphoma ranged from 4 to 26 years (median, 15). Symptoms at presentation were related to sites of involvement. Pulmonary, marrow, and CNS involvement were present in five, four, and one case, respectively. No patient had lymphadenopathy. Five patients had an elevated lactate dehydrogenase level (range, 226 to 4,880 IU/L; median, 1,220 IU/L). Five of six patients had a leukoerythroblastic reaction. All cases had large-cell histology and frequently contained cytoplasmic granules. Those cases tested expressed CD2, CD3, and CD8 and were negative for B-cell antigens. T-cell receptor β- and γ-chain genes were clonally rearranged in three of three and one of three cases, respectively. All T-cell posttransplant lymphoproliferative disorders (T-PTLDS) studied were negative for Epstein-Barr virus (EBV), human T-cell leukemia/lymphoma virus type 1 (HTLV-1), human T-cell leukemia/lymphoma virus type 2 (HTLV-2), and human herpes virus type 8 (HHV-8) genomes. Treatment with acyclovir (three patients) or chemotherapy (three patients) resulted in two responses. All patients had an aggressive course, with a median survival duration of 5 weeks. In conclusion, a clinically aggressive T-PTLD may be a late complication of solid-organ transplantation and does not appear to be related to EBV, HTLV-1, HTLV-2, or HHV-8 infection.

POSTTRANSPLANT lymphoproliferative disorders (PTLDS) are recognized as a significant and morbid complication of solid-organ transplantation. The majority of these disorders are of B-cell phenotype and are associated with Epstein-Barr virus (EBV) infection. In contrast, T-cell non-Hodgkin’s lymphomas have uncommonly been reported in the posttransplant setting. Like their B-cell counterparts, these disorders are often extranodal at presentation, with occasional cases involving primarily the blood and bone marrow (BM).

We report six cases of a distinct T-cell posttransplant lymphoproliferative disorder (T-PTLD) with unusual clinical, morphologic, ultrastructural, and immunophenotypic characteristics. These disorders appear to be distinct from B-PTLD and represent a new potential complication in the posttransplant setting.

MATERIALS AND METHODS

Patients and Clinical Evaluation

Six patients who had undergone solid-organ transplantation and were diagnosed with T-PTLD between 1985 and 1995 at the University of Minnesota Hospital, United Hospital, or Hennepin County Medical Center in the Minneapolis/St Paul metropolitan area were included for study. A baseline evaluation was completed at diagnosis. A complete blood count and a screening battery of chemistry tests, including the serum lactic dehydrogenase level, were obtained. Computed tomographic (CT) scans of the head, chest, and abdomen were obtained for staging, as were BM aspiration and bilateral biopsy specimens. Lumbar puncture with CSF cytology was obtained in most patients. Disease stage at diagnosis was classified by the Ann Arbor staging criteria.

Treatment and Outcome

At lymphoma diagnosis, all patients were receiving and had received immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, antilymphocyte globulin, and cyclosporine. None of the patients received OKT3.

Several therapeutic modalities were used for treatment of the lymphoproliferative disorder. On diagnosis of the lymphoproliferative disorder, the first step in the majority of patients was to decrease or discontinue immunosuppressive therapy. In patients with extensive disease, standard combination chemotherapy regimens were used, including cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP), etoposide-doxorubicin-cyclophosphamide-vincristine-prednisone (VACOP-B), methotrexate-doxorubicin-cyclophosphamide-vincristine-prednisone-bleomycin (MACOP-B), and etoposide-cyclophosphamide-doxorubicin-vincristine-prednisone (EPOCH). High-dose parenteral acyclovir (5 to 15 mg/kg intravenously up to three times daily) was used both as a single agent or followed by chemotherapy in some patients. Outcome was assessed by response to therapy, remission duration, and survival. Complete remission (CR) was defined as no evidence of disease by standard laboratory, radiographic, or histopathologic parameters; partial remission (PR) was defined as a ≤50% decrease in the sum of the products of the perpendicular diameters of all measurable disease sites, without the appearance of new lesions. Remission duration is the interval from documentation of a response to the first evidence of relapse or death. Survival was defined as the time from diagnosis of the lymphoproliferative disorder to death.

Tissue Specimens

Peripheral blood, BM aspirate, and biopsy specimens were available on all patients. In addition, involved lung tissue was available from two patients and involved spinal and peritoneal fluid from one
Table 1. Primer Sequences for Genotyping/Viral Studies

<table>
<thead>
<tr>
<th>Primer (pairs)</th>
<th>Sequence</th>
<th>Target</th>
<th>Product Size</th>
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<tr>
<td>JH-S</td>
<td>5'-CTG-TCG-ACA-CGG-CGG-TGT-ATT-CTG-3'</td>
<td>Ig heavy chain (Framework 3A)</td>
<td>See text</td>
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<td>JH-A</td>
<td>5'-AAC-TGC-AGA-GGA-GAC-GGT-GAC-C-3'</td>
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<tr>
<td>JH2-S</td>
<td>5'-TGG-(AG)TCG(CA)-CAG-(GC)TGC CTCC(C)-CNG-3'</td>
<td>(Framework 2A)</td>
<td></td>
</tr>
<tr>
<td>Tg-V</td>
<td>5'-TGT-AGTC-TGT-GCA-CGA-G-3'</td>
<td>Tβ T-cell receptor gene</td>
<td>See text</td>
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<td>Tg-D1</td>
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<tr>
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<td>Jg11</td>
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<td>Ty T-cell receptor gene</td>
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<td>VH-L (ex/la)</td>
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<td>HTLV-1 pol reg</td>
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<td>KS330 minor capsid</td>
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<td>VH-L (int/lt)</td>
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</table>

Abbreviations: ext, external primers; int, internal primers.

Patient. All tissue specimens were processed by routine methods.

Cytotoxic staining for myeloperoxidase and alpha naphthyl butyrate esterase were available on three and two cases, respectively.

Ultrasound Analysis

Material was obtained for electron microscopy in three cases. Lung, BM, and blood, respectively, were processed for routine ultrasound analysis.\(^{19}\) In addition, the blood specimen was reacted for localization of ultrastuctural peroxidase.\(^{20}\) Thin sections were stained with uranyl acetate and/or lead citrate and examined in a Phillips 201 electron microscope (Phillips Electronic Instrument, Inc, Schaumburg, IL).

Immunophenotyping

Flow cytometric analysis on BM lymphoma cells (cases 1 through 3, and 5) or frozen-section immunohistochemistry (case 6) was performed on five cases. Only immunohistochemical staining for CD20 (L26; Dako, Carpinteria, CA) and CD45RO (UCHL-1; Dako) was available on formalin-fixed, paraffin-embedded section material from case 4.\(^{21}\) Cases were assessed positive if greater than 20% of the lymphoma cells expressed the given antigen.

Genotyping and Viral Detection

Fresh tissue was available on patients no. 1, 3, and 4, from whom genomic DNA specimens could be obtained. Genomic DNA was isolated by standard methods. T-cell receptor β- and γ-chain genes, as well as immunoglobulin Jh heavy-chain genes were examined for clonal rearrangement by polymerase chain reaction (PCR) and Southern blot methods. Amplification of the B-cell and T-cell receptor gene rearrangements by PCR was achieved using a modification of the method reported by McCarthy et al.\(^{22-24}\) For immunoglobulin heavy-chain gene rearrangements, two sets of oligonucleotide primers were used: JH-A+JH-S, and JH-A+JH2-S (Table 1). For T β rearrangements, four sets of oligonucleotide primers were used for each sample: T β-V+I β-J1, T β-V+I β-J2, T β-D1+I β-J2, T β-D2+I β-J2 (Table 1). Samples were routinely amplified for 35 cycles. Internal positive and negative controls were run with each PCR setup. Amplification products were electrophoresed and visualized on 5% nondenaturing, polyacrylamide gels (Novex, San Diego, CA). A positive result is based on the presence of a sharp band in the specified size ranges for each of the primer pairs.\(^{22-24}\)

Single-round PCR was used for the detection of human T-cell leukemia virus type 2 (HTLV-2), while nested PCRs were used for the detection of human T-cell leukemia virus type 1 (HTLV-1) and human herpesvirus type 8 (HHV-8) sequences. The primer pairs are indicated in Table 1; the sequences were derived from previously published data.\(^{25-28}\) Briefly, each PCR reaction used approximately 0.06 μg of genomic DNA or appropriate control template, 2.5 U of Taq polymerase (AmpliTaq; Perkin-Elmer Cetus, Norwalk, CT), 100 μmol/L of each dNTP, 3.5 mmol/L MgCl₂, 20 pmol of each primer, and 0.01% gelatin in a final volume of 100 μL. PCR amplification were performed using a Perkin-Elmer 480 Thermocycler. The following parameters were used for all reactions: initial denaturing at 94°C for 3 minutes, followed by 35 to 40 cycles of 94°C for 1 minute, 63°C for 1 minute, and 72°C for 1 minute, followed by a final extension step at 72°C for 10 minutes. Ramp times of 1 second were used between steps. For the nested reactions, the same parameters and reaction mixtures were used, except that the internal primer pairs as indicated in Table 1 were used with 1 μL of the internal PCR mixture as the template material. The initial PCR for HTLV-1 was performed in a “hot” start fashion.

Amplification products were visualized using nondenaturing polyacrylamide gels (Novex) stained with ethidium bromide, and were evaluated for the presence or absence of the appropriate amplified DNA fragment as compared with the control template and the predicted size for the given reaction (see Table 1). Control template titration experiments showed that these PCR conditions allowed the detection of less than 100 copies of viral sequence per reaction. In all instances, sensitivity controls and negative controls were run and gave the appropriate positive and negative result, respectively.

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In situ hybridization for the detection of Epstein-Barr-encoded RNA (EBER) using commercially available reagents (Dako) was performed on involved paraffin-embedded tissues from three cases according to the manufacturer's recommendation.

RESULTS

Clinical Characteristics and Outcome

Clinical data from these six cases are summarized in Table 2. All patients received at least one kidney transplant; three (no. 1, 2, and 5) received a second kidney transplant 18, 13, and 14 years after the initial transplant, respectively. In addition, patient no. 2 underwent a pancreas transplant 2 years before the diagnosis of T-PTLD. The primary disease diagnoses for patients no. 1 through 6 were poststreptococcal, diabetic, immunoglobulin A, lupus, diabetic, and postinfectious nephropathy, respectively. All patients received immunosuppressive therapy for periods of 7 to 26 years (median, 15), consisting of azathioprine and prednisone alone (patient no. 3), or with antilymphocyte globulin (no. 4 through 6), or cyclosporine (no. 1 and 2).

The patients ranged in age from 31 to 56 years (median, 43); three were male; all were splenectomized as part of the transplant protocol of the time. Presenting symptoms were fever and cough (patients no. 1 through 3, and 6), fever with lymphadenopathy (no. 4 and 5), or chemotherapy (no. 2, 4, and 6) resulted in only two responses; these occurred in patients no. 4 and 6, who had stage III disease and lower initial lactate dehydrogenase values. Both responders lived longer than the other patients. Patient no. 6 received 12 cycles of MACOP-B and achieved a CR for 150 days; the patient subsequently relapsed and died of disease 30 days later. Patient no. 4 achieved a PR with five cycles of CHOP (following initial acyclovir therapy, which resulted in no response); this patient died of progressive disease 180 days after diagnosis. Survival times ranged from 7 to 180 days (median, 35) after diagnosis, with all patients dying of progressive disease.

Morphologic Features

Medullary findings. The lymphoma cells were large, measuring up to 40 to 50 μm in diameter, although some variability in cell size was noted in any given case. The cells resembled monoblasts, with moderate to abundant lightly basophilic cytoplasm, fine to coarse azurophilic cytoplasmic granules, irregular nuclear contours, and one or more prominent nucleoli (Figs 1A, 2, and 3). Cytochemical stains for myeloperoxidase and nonspecific esterase were negative in three of three and two of two cases, respectively. Typically, the BM was hypercellular and extensively involved by the T-cell PTLD in an interstitial pattern (Fig 1B and C).

Extramedullary findings. Lung biopsies from patients no. 4 and 6 showed focal effacement of the pulmonary architecture by a lymphomatous process, with areas of necrosis and peripheral lymphatic tracking. The cytology was similar to that noted in the marrow specimens. Infiltration of the small pulmonary vessels by lymphoma cells was frequently noted, while the airways were relatively spared.

Ultrastructural findings. The malignant lymphoid cells from the three cases examined showed similar ultrastructural morphology (Fig 4). They were characterized by round to slightly indented nuclei, with prominent, often multiple nucleoli. The chromatin was peripherally condensed. The abundant cytoplasm contained short profiles of rough endoplasmic reticulum, scattered polyribosomes, and prominent granulation. The granules were variable in size, moderately electron-dense, and often showed central condensation. Parallel tubular arrays were not identified. The granules were peroxidase-negative. In two of the three cases, abnormalities in the myeloid cell lines were noted. Granulocytes showed granule abnormalities, including pseudo-Chediak Higashi inclusions. Monocytes contained large, complex, electron-
Fig 1. Photomicrographs of BM aspirate and low- and high-power view of the marrow section involved by lymphoma from patient no. 1. The lymphoma cells show variation in size and chromatin condensation on the aspirate material; nucleoli are conspicuous (A). Low-power view of the sections shows an interstitial pattern of involvement by lymphoma (B). High-power view illustrates the overall histology of the lymphoma cells (C). Abundant cytoplasm and variably present nucleoli are noted. (A: Wright-Giemsa, original magnification x 400; B and C: hematoxylin and eosin, original magnifications x 40 and 256, respectively.)

Fig 2. Photomicrographs of blood (A) and BM aspirate (B) from patient no. 2 show lymphoma cells. The cells are large with moderate amounts of lightly basophilic cytoplasm and fine azurophilic granules. The nuclei are oval to irregular in outline with occasionally prominent nucleoli. The cells resemble monoblasts. (Wright-Giemsa, original magnification x 400.)

Fig 3. Photomicrograph of the BM aspirate from patient no. 3. In addition to the features noted in the previous figures, the lymphoma cells in this case had prominent, coarse, azurophilic granules in the cytoplasm. (Wright-Giemsa, original magnification x 400.)
Fig 4. Electron micrograph of a granulated lymphoma cell from patient no. 3. Note the electron-dense granules. Parallel tubular arrays noted in the cells of typical large granular lymphocytosis of the T-cell type were not noted in these cells. (Uranyl acetate and lead citrate, original magnification × 10,000.)

dense lysosomal inclusions of uncertain origin. In one case, micromegakaryocytes were present in the blood.

Immunophenotyping

The results of immunophenotypic analysis of the lymphoma cells are summarized in Table 3. The malignant cells expressed the T-cell antigens CD2, CD3, and CD8 in all studied cases. Three of three cases and two of four cases were positive for CD5 and CD7, respectively. CD30 was expressed in the one case examined. There was variable expression of CD4, CD16, and CD56. Three of three cases were negative for CD57. B-cell antigens, including CD19, CD20, CD22, CD23, CD24, CD25, and Slg, were negative in all cases tested. CD14 was expressed in one patient. Other myeloid antigens and terminal deoxynucleotidyltransferase (Tdt) were also negative.

Immunohistochemical stains on paraffin-embedded material were only available from patient no. 4. The lymphoma cells were CD45RO (UCHL-1, T-cell)-positive and CD20 (L26, B-cell)-negative.

Genotyping

Three of the six lymphoproliferative disorders were tested for both B-cell and T-cell gene rearrangements (Table 4). All three cases showed clonal rearrangement of the T-cell receptor β-chain gene by Southern blot or PCR analysis. One of three cases had clonal rearrangement of the T-cell receptor γ-chain gene. There were no clonal rearrangements of the Jh region of the immunoglobulin heavy-chain gene in the three cases.

Viral Studies

These results are summarized in Table 4. Two patients were analyzed for evidence of HTLV-1 and -2 and HHV-8 proviral DNA by PCR and were negative. The three cases examined for EBV infection by EBER analysis were all negative.

DISCUSSION

With the advent of solid-organ transplantation, posttransplant complications related primarily to chronic immunosuppression have been well recognized and include neoplastic disorders such as carcinoma and lymphoma. PTLDs are most frequently 'polymorphous lymphomas' of B-cell type and are related to EBV infection. T-PTLDs have only occasionally been described; most of these reports have included a wide clinical and morphologic spectrum of le-
POSTTRANSPLANT T-CELL LYMPHOMAS

Table 3. Immunophenotyping Data Posttransplant T-Cell Lymphoproliferative Disorders

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<th>Pt</th>
<th>CD1a</th>
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Table 4. Viral Status and Genotyping Data Posttransplant T-Cell Lymphoproliferative Disorders

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<th>T/7</th>
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The current study describes six cases of a distinct, aggressive T-PTLD characterized by an acute leukemia-like presentation with fever, anemia, leukoerythroblastic reaction, and an elevated lactate dehydrogenase level.

Certain features of these T-PTLD contrast with those of B-PTLD. The T-cell processes occurred in splenectomized patients with prolonged immunosuppression. For the T-PTLDs, the median time from transplant to diagnosis was 15 years, as compared with 7 years for B-PTLD. Extensive disease was common at presentation; blood and BM involvement by lymphoma were frequently diagnostic findings not often noted in the B-PTLD. A leukoerythroblastic blood picture, cytopenias, and a markedly elevated lactate dehydrogenase level were present in our patients. Unlike most B-PTLDs, evidence of EBV infection could not be detected in our cases. Findings similar to B-PTLD noted in our cases included extranodal disease and absent lymphadenopathy at presentation.

Clinical, morphologic, and immunophenotypic findings indicate these lesions represent a distinct subset of peripheral T-cell lymphomas. Our cases frequently resembled acute leukemia with blood and BM involvement, cytopenias, and absent lymphadenopathy. These features are not typical of peripheral T-cell lymphomas at presentation, although an occasional case may show circulating lymphoma cells late in the course of disease. The lymphoma cells of the posttransplant cases showed an infiltrative pattern of marrow involvement leaving the fatty marrow architecture relatively intact even when the degree of involvement was pronounced. Although this pattern of involvement has been described, most peripheral T-cell lymphomas show focal or diffuse ablation of the fatty architecture. In addition to the lymphoma cells, abnormalities in myeloid maturation were occasionally noted that superficially resembled an acute myeloid leukemia; these unexplainable findings are only rarely described in association with peripheral T-cell lymphomas. Immunophenotypically, the lymphoma cells uniformly expressed CD8. One case coexpressed CD4 and an occasional case was positive for CD16 and/or CD56. The primary class of peripheral T-cell lymphomas that share this phenotype are the T-cell large granular lymphocytic leukemias (LGL); however, the large-cell morphology, lack of the parallel tubular arrays on ultrastructural analysis, and clinical aggressiveness of the posttransplant lesions are distinct from typical LGL. An aggressive variant of LGL and a hepatosplenic γδ T-cell lymphoma have both been recently described that share many features of the currently described lesions.

The currently described malignancies also share many clinical, morphologic, and immunophenotypic features of some of the natural killer–like T-cell lymphomas described recently by Macon et al. All six patients in that series presented with fever and disseminated disease at diagnosis; blood and BM involvement were frequently noted. Four of their six patients studied had received immunosuppression, although the duration of immunosuppression ranged from 0.5 to 4 years and was less than in the currently described cases. The malignant cells were large, with abundant cytoplasm, involved the marrow in an interstitial pattern, and uniformly expressed CD8 and CD56. The malignancies were aggressive, with a median survival duration of 2 months. These similarities suggest that at least some of the lymphomas described by the Vanderbilt group represent a similar if not the same pathologic entity described in the current report. Although CD56 expression is noted in the lymphoma cells from both studies, convincing evidence for natural killer cell differentiation is lacking. The T-cell receptor is clonally rearranged in these lesions and cytotoxicity assays were not performed. Because of this, we prefer to designate the current series as a subset of T-cell lymphomas without reference to natural killer cell activity.

The occurrence of these lesions in splenectomized patients with a history of prolonged immunosuppression strongly suggests an infectious etiology; however, attempts to elucidate a pathologic viral agent in the current study were unsuccessful. EBV has been previously implicated in an occasional posttransplant and extranodal T-cell lymphoma. In contrast to the lymphomas described by Macon et al, we could not detect evidence of EBV infection. HTLV-1 and HTLV-2 are other transforming viruses that have an etiologic role in the pathogenesis of the T-cell lymphoproliferative disorders; however, we were also unable to demonstrate these viral agents in the cases studied. HHV-8 has recently been associated with Kaposi's sarcoma and an unusual form of body-cavity–based lymphomas in AIDS patients; however, we did not find an association with this virus either.

In conclusion, this form of aggressive T-cell lymphoproliferative disorder should be considered in chronically immunosuppressed, solid-organ transplant patients who present with a disseminated hematologic malignancy. The process frequently resembles an acute myeloid leukemia and may
have accompanying cytopenias and abnormalities in myeloid maturation; clinical history and immunophenotyping are critical in recognizing this entity. Although studies for infectious agents have not yielded a possible etiologic pathogen in these cases thus far, studies using general methodologies in cloning differences between the genomes of the lymphoma cells and normal cells may reveal DNA segments of a responsible infectious agent.49

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