Posttransplant Cutaneous T-Cell Lymphoma

Case Reports and Review of the Association of Calcineurin Inhibitor Use With Posttransplant Lymphoproliferative Disease Risk

Rebecca G. Pomerantz, BA; Lauren S. Campbell, MD; Drazen M. Jukic, MD, PhD; Larisa J. Geskin, MD

**Background:** Cutaneous T-cell lymphoma occurring in the context of posttransplant immunosuppression is rare, with 27 cases documented to date.

**Observations:** We report 2 new cases of posttransplant cutaneous T-cell lymphoma in patients treated at our institution. Both were male recipients of renal transplants who had undergone transplantation a mean of 5.3 years previously and were taking various multidrug immunosuppressive regimens, including cyclosporine, tacrolimus, mycophenolate mofetil, and prednisone.

**Conclusions:** These cases underscore the association of posttransplant cutaneous T-cell lymphoma with renal transplantation, cyclosporine and tacrolimus therapy, male sex, and later onset compared with B-cell posttransplant lymphoproliferative disease. Relative to the general population, the incidence of cutaneous T-cell lymphoma seems increased among transplant recipients receiving immunosuppressive medications.

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POSTTRANSPLANT LYMPHOPROLIFERATIVE diseases (PTLDs) are well-known adverse sequelae of transplantation, occurring in 1% to 2% of solid-organ recipients. Most frequently, PTLDs are B-cell lymphomas, with T-cell lymphomas accounting for few cases. Posttransplant cutaneous T-cell lymphoma (PT-CTCL) is rarer still, with 27 cases reported in the literature.1-4 We report 2 new cases of PT-CTCL in renal transplant recipients. We then briefly review the reported cases to date and summarize clinical characteristics of PT-CTCL relative to other types of PTLDs, comment on the role of immunosuppression in the development of PTLDs, and evaluate the incidence of CTCL among transplant recipients compared with the general population.

REPORT OF CASES

CASE 1

A 29-year-old man who 3 years previously had received a cadaveric renal transplant for a hereditary nephritic syndrome was seen with a 5-week history of an intensely pruritic rash on the groin, scalp, and inguinal area. He reported hair loss on the left side of his scalp and a 9-kg (20-lb) weight loss over the past 4 to 5 months. His immunosuppressive regimen had included tacrolimus (FK 506), prednisone, and mycophenolate mofetil. Physical examination revealed erythematous well-circumscribed plaques with follicular prominence involving approximately 30% of the total body surface area (Figure, A). His examination also revealed alopecia on the left posterior scalp involving approximately 25% of the total scalp (Figure, B). In addition, he had bilateral axillary and inguinal firm nontender lymphadenopathy. A skin biopsy was performed, and the specimen was diagnostic for mycosis fungoides (Figure, C-E).

Staging, including computed tomography of the chest, abdomen, and pelvis with and without contrast, was performed and showed diffuse lymphadenopathy without evidence of visceral disease. An excisional lymph node biopsy specimen revealed basic retention of the nodal architecture, with prominent T-zone nodules; their pigment and foci included many atypical cerebriform-type lymphocytes consistent with mature T-cell lymphoma, graded as LN3 or World Health Organization grade 2 and associated with dermatopathic changes. Peripheral blood studies revealed normal flow cytometry, but polymerase chain reaction showed a T-cell receptor gene rearrangement. His Epstein-Barr virus (EBV) status was positive based on in situ hybridization of the lymph node biopsy specimen. The patient was diagnosed as having stage IIA mycosis fungoides.

His tacrolimus dosage was reduced, and oral bexarotene was started at the recommended dosage of 300 mg/m². His condi-

Author Affiliations:
Department of Dermatology,
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.
tion showed dramatic improvement initially, with complete clearance of skin lesions and regrowth of hair within 4 months. However, the patient died suddenly approximately 1 year after diagnosis. The specific cause of death was undetermined, and an autopsy was declined.

CASE 2

A 69-year-old man who had a long-standing history of Wegener granulomatosis and had undergone renal allograft transplantation 7½ years earlier was seen with a several-month history of a diffuse pruritic rash, increased skin thickness, and scaling with painful fissures on his palms and soles. His immunosuppressive regimen included cyclosporine, mycophenolate, and prednisone. On physical examination, the patient had erythroderma with palmar and plantar keratoderma and bilateral ectropion. He also had diffuse lymphadenopathy. A skin biopsy was performed, and the specimen was diagnostic for mycosis fungoides.

Epstein-Barr virus in situ hybridization was performed, and the findings were negative. Peripheral blood flow cytometry revealed a 37:1 ratio of CD4 cells to CD8 cells, with a loss of CD7 marker in 97% of CD4-positive cells, and polymerase chain reaction showed a clonal T-cell receptor gene rearrangement. A peripheral smear demonstrated small- to medium-sized atypical lymphoid cells with convoluted nuclei that were morphologically compatible with Sézary syndrome. Laboratory studies showed a white blood cell count of 47,000/μL, platelet count of 379 × 10^9/μL, and hematocrit of 37.6% (to convert white blood cell count to ×10^9/L, multiply by 0.001; to convert hematocrit to proportion of 1.0, multiply by 0.01). A diagnosis of Sézary syndrome was made.

Cyclosporine therapy was discontinued after consultation with the transplant team, and treatment with extracorporeal photopheresis, oral bexarotene at the dosage of 300 mg/m², and topical nitrogen mustard was initiated. The patient had a near-complete response to therapy, with resolution of erythroderma and keratoderma, abatement of pruritus with significant improvement in quality of life, and reduced white blood cell count to 13,000/μL. Throughout the treatment, he maintained normal renal function and had no evidence of kidney rejection. Eighteen months after diagnosis, the patient relapsed with symptomatic and more aggressive disease. Because of high CD25 counts (human T-cell lymphotropic virus type 1 negative), treatment with low-dose demileukin difitox was attempted, with partial improvement. However, his disease rapidly progressed, renal failure developed, and he died 23 months after diagnosis.

COMMENT

Posttransplant lymphoproliferative diseases occur in approximately 1% to 2% of transplant recipients.7 Traditionally, the term posttransplant lymphoproliferative disease has been applied to EBV-induced B-cell lymphomas that develop in patients taking immunosuppressants.6,7 Compared with lymphomas among the general population, non-Hodgkin lymphomas following transplantation are associated with extranodal involvement, a more

Figure. Case 1. A, Erythematous well-circumscribed plaque on the left antecubital fossa. B, Erythema and alopecia on the left posterior scalp. C, Atypical lymphocytes at the dermoepidermal junction and within the epidermis with characteristic perinuclear “halos” (hematoxylin-eosin, original magnification ×40). D, Strong CD4-positive staining among all cells in the infiltrate (original magnification ×20). E, Multiple hyperchromatic and atypical lymphocytes around eccrine ducts and within them with characteristic halos (hematoxylin-eosin, original magnification ×40).
Table 1. Comparison of Calcineurin Inhibitors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>11-α-amino acid cyclic peptide derived from the fungus <em>Tolypocladium inflatum</em></td>
<td>Macrolide antibiotic product from the soil fungus <em>Streptomyces tsukubaensis</em></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Binds to cyclophilin, drug-cyclophilin complex inhibits calcineurin phosphatase and T-cell activation</td>
<td>Binds to FKBP 12, drug-FKBP 12 complex inhibits calcineurin phosphatase and T-cell activation</td>
</tr>
<tr>
<td>Year of introduction</td>
<td>1976</td>
<td>1989</td>
</tr>
<tr>
<td>Association with PTLDs, %</td>
<td>1.2-1.4</td>
<td>1.2-18.9</td>
</tr>
</tbody>
</table>

Abbreviation: PTLDs, posttransplant lymphoproliferative diseases.

Table 2. Characteristics of Posttransplant Lymphoproliferative Diseases (PTLDs)

<table>
<thead>
<tr>
<th>Variable</th>
<th>B-Cell Lymphoma</th>
<th>T-Cell Lymphoma</th>
<th>PT-CTCL</th>
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</thead>
<tbody>
<tr>
<td>Association with PTLDs</td>
<td>86%-96%</td>
<td>3%-14%</td>
<td>29 Documented cases</td>
</tr>
<tr>
<td>Clonality</td>
<td>Oligoclonal or polyclonal</td>
<td>Monoclonal</td>
<td>Monoclonal</td>
</tr>
<tr>
<td>Association with Epstein-Barr virus</td>
<td>90% Positive</td>
<td>25% Positive</td>
<td>Usually negative</td>
</tr>
<tr>
<td>Time of development after transplantation, y</td>
<td>&lt;1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Response to reduced immunosuppression</td>
<td>Often</td>
<td>Infrequent</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>

Abbreviation: PT-CTCL, posttransplant cutaneous T-cell lymphoma.

aggressive course, and poorer response to conventional therapy.9-10

An increased incidence of posttransplant lymphomas was noted after the introduction of cyclosporine as an immunosuppressant for solid-organ transplantation (Table 1). The incidence was as high as 10% in some series.11-13 This phenomenon was later attributed to other concurrent risk factors14 such as the length and intensity of immunosuppression rather than the type or specific agent used.15 For example, lymphoma incidence is higher among heart-lung and lung transplant recipients, which is thought to be a result of more aggressive immunosuppression during the first year, although lymphomas pose a continuous long-term risk for these patients.16

More recently, tacrolimus was introduced as a primary immunosuppressive agent (Table 1), and less is known about its association with PTLDs. Because tacrolimus is 50 to 100 times more potent than cyclosporine as an immunosuppressant, one would speculate that PTLDs should be a more frequent occurrence with tacrolimus use. Although some evidence has shown an increased incidence of PTLDs with tacrolimus use after liver transplantation,17 other findings in patients receiving newer lower dosages of tacrolimus supported an increased risk of PTLDs among renal transplant recipients18 but not among liver transplant recipients.19 A 2006 review article19 revealed that PTLDs occur with similar incidence among liver transplant recipients taking cyclosporine and those taking tacrolimus, again suggesting that immunosuppression and not a particular agent favors the development of PTLDs. However, there may be an increased incidence of PTLDs among renal transplant recipients taking tacrolimus vs cyclosporine.16,18

Antimetabolite therapy (ie, mycophenolate and azathioprine sodium) has been associated with a lower risk of PTLDs compared with calcineurin inhibitor use.15 This is somewhat surprising because of the strong immunosuppressive effect of mycophenolate. One mechanism that could potentially explain the reduced incidence of PTLDs associated with mycophenolate use relative to other immunosuppressants is its demonstrated antineoplastic properties. Mycophenolate has been shown to inhibit the growth of various tumor cell lines in vivo, including melanoma,20 prostate cancer,21 and colon and pancreatic adenocarcinoma and various hematologic malignant neoplasms.22 Different molecular mechanisms, including induction of apoptosis,23 inhibition of angiogenesis,24 and depletion of cyclin-dependent kinases leading to cell cycle arrest,25 may explain the in vivo antitumor effects of mycophenolate. Whether the decreased risk of PTLDs with antimetabolites vs calcineurin inhibitors is in fact due to these antineoplastic properties remains undetermined.

In contrast to B-cell lymphomas, T-cell lymphomas following transplantation are rare (Table 2). Only 3% to 14% of PTLDs are classified as related to T cells.6,26-28 Although most commonly encountered in the setting of cadaveric renal transplantation,29,30 T-cell PTLDs have also been documented in pancreatic31 bone marrow,32 and heart33,34 transplant recipients. Most of these cases represent peripheral T-cell lymphomas. Compared with B-cell PTLDs, posttransplant T-cell lymphomas tend to develop later after transplantation and have poorer response to reduced immunosuppression.

Within the small subset of T-cell PTLDs, PT-CTCL seems rarer yet (Table 2). Including our 2 patients, only 29 cases have been reported in the literature. With so few documented cases, it has been difficult to draw any major conclusions regarding patient characteristics. A 2006 review article by Ravat et al1 found that most PT-CTCL occurs after renal transplantation, among patients taking cyclosporine and azathioprine, and in men. The mean time from transplantation to diagnosis was 6.4 years. A link between posttransplant lymphomas and EBV was less clear than for B-cell PTLDs, with no consistent viral association noted among cases.

Our 2 cases underscore the association of PT-CTCL with renal transplantation, cyclosporine or tacrolimus immunosuppressive therapy, later onset compared with B-
cell PTLDs (mean, 5.3 years after transplantation among the cases presented herein), and male sex, as well as its inconsistent association with EBV. Immune suppression as a predisposing factor for development of CTCL may also explain the increased incidence of second malignant neoplasms, particularly lung cancer and other lymphomas, among patients with this disease.33,36

In reviewing the reported cases of PT-CTCL, including the 2 reported herein, 14 cases occurred from 1996 to 2005 in renal transplant recipients; 3 of these were reported in the United States. All patients received cyclosporine, tacrolimus, or both. Within the same time frame, 136,488 patients received renal transplants in the United States,35 and most of these patients likely received systemic immunosuppression with a calcineurin inhibitor; therefore, one can estimate the incidence of PT-CTCL among immunosuppressed renal transplant recipients to be approximately 2.20 cases per 100,000. Even with so few reported cases and with potential underreporting, this incidence is still increased over that of 0.64 cases per 100,000, the incidence of CTCL among the general US population.36 While use of calcineurin inhibitors, specifically tacrolimus, seems to increase the risk of PTLDs, they may also have a role in the development of PT-CTCL.

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Correspondence: Larisa J. Geskin, MD, Department of Dermatology, University of Pittsburgh School of Medicine, Presby South Tower, Ste 3880, 200 Lothrop St, Pittsburgh, PA 15213 (geskinlj@upmc.edu).

Author Contributions: Dr Geskin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Pomerantz, Campbell, and Geskin. Acquisition of data: Jukic and Geskin. Analysis and interpretation of data: Pomerantz, Campbell, Jukic, and Geskin. Drafting of the manuscript: Pomerantz and Geskin. Critical revision of the manuscript for important intellectual content: Pomerantz, Jukic, and Geskin. Administrative, technical, and material support: Pomerantz. Financial Disclosure: Dr Geskin has served as a consultant to Eisai and Therakos.

REFERENCES