Clinical and Pathological Features of Posttransplantation Lymphoproliferative Disorders Presenting With Skin Involvement in 4 Patients

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Background: Posttransplantation lymphoproliferative disorders (PTLDs) are lymphoid proliferations that can develop in recipients of solid organ or allogeneic bone marrow transplants. They are clinically and pathologically heterogeneous and range from polyclonal hyperplastic lesions to malignant lymphomas. Although extranodal involvement in PTLD is common, cutaneous presentation is rare, with only 19 cases reported previously.

Observations: We describe 4 patients with cutaneous presentations of PTLD. All patients had relatively late-onset PTLD (>1 year after transplantation) with a median of 8 years from organ allograft to tumor diagnosis. The extent, number, and anatomic location of skin lesions varied from a localized patch to widespread nodules. None of the patients exhibited systemic symptoms at the time of PTLD diagnosis. Pathological findings ranged from plasmacytic hyperplasia to monomorphic PTLD. In situ hybridization detected Epstein-Barr virus messenger RNA in all 3 cases with evaluable tissue. All patients underwent reduction in immunosuppressive therapy and received other individualized treatments. Median follow-up was 2.5 years. At the most recent follow-up, 3 patients were in complete remission and 1 had residual disease.

Conclusions: In this study, PTLD lesions presenting in the skin responded to therapy. Despite their relatively late occurrence after transplantation, most of these cases were positive for Epstein-Barr virus. As observed with other cutaneous lymphomas, the PTLDs with predominant skin involvement had a relatively favorable outcome.

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POSTTRANSPLANTATION LYMPHOPROLIFERATIVE DISORDERS (PTLDs) are a known complication of solid organ and bone marrow transplantation. The overall incidence of PTLD in allograft recipients is approximately 2%, with survival rates of approximately 50% to 80%. Most commonly, they represent an Epstein-Barr virus (EBV)–driven proliferation of B lymphocytes, which range in histological appearance from hyperplasia to malignant lymphoma. Although most PTLDs result from an abnormal growth of EBV-transformed B cells, EBV-negative PTLDs do occur, particularly in PTLDs that develop more than 1 year after transplantation. The incidence of PTLD varies because of several factors, including the EBV status of recipients, the type of organ transplanted, the type and amount of immunosuppressive therapy, and the age of the patient. The mainstay of treatment is reduction in immunosuppressive therapy, with approximately 25% responding to such measures alone. Anti-CD20 antibody therapy, chemotherapy, surgical resection, and radiation therapy are also used.

Posttransplantation lymphoproliferative disorders often present in extranodal sites, including the gastrointestinal tract, lungs, central nervous system, and transplanted organ. Although organ allograft recipients undergoing immunosuppression have an increased risk for development of certain cutaneous malignancies such as squamous cell carcinomas of the skin and Kaposi sarcoma, PTLD involvement limited to the skin is rare. We found 19 cases reported in the literature. We herein describe the clinical presentations, pathological features, and therapeutic responses of 4 patients with PTLD presenting in the skin, 3 of whom had disease limited to skin at the time of staging.

METHODS

All 4 patients in this study were identified within the Stanford University Hospital system, Stanford, Calif, from October 1, 1997, through May 30, 2001. Specifics regarding their presentations, treatments, and outcomes were obtained by review of patient records. Staging studies in-
cluded complete history and physical examination, comprehensive laboratory studies (lactate dehydrogenase [LDH] level was not measured in patient 1), bone marrow biopsy (not performed in patient 3), and axial computed tomography (CT) of the body and/or full-body positron emission tomography (PET) to determine the extent of disease. Patients underwent staging according to terminology derived from the Ann Arbor Staging System for Hodgkin disease and classification according to the International Prognostic Index for non-Hodgkin lymphoma.

All surgical biopsy specimens were fixed in formalin, processed, embedded in paraffin, and stained with hematoxylin-eosin for conventional histological examination. Specimens were classified into morphologic subtypes according to criteria originally reported by Harris and Swerdlow and now referred to in the World Health Organization classification scheme for PTLDs. Immunophenotyping of atypical lymphocytes was performed in each biopsy specimen with a standard peroxidase-antiperoxidase method that used primary antibodies at the minimum against CD20, CD3, and CD43. In situ hybridization studies for EBV RNA were performed using a 30-base oligonucleotide probe complementary to a portion of the EBV gene encoding RNA-1 (EBER1) as previously described by van de Rijn et al.

**RESULTS**

**PATIENT 1**

A 60-year-old man received his first cadaveric renal transplant in 1974 for end-stage renal disease secondary to ingestion of nephrotoxic mushrooms. The transplanted kidney underwent acute rejection with loss of the graft. After long-term maintenance hemodialysis for 16 years, he received a second cadaveric kidney transplant in June 1991. Posttransplantation immunosuppressive therapy consisted of prednisone (40 mg/d), cyclosporine (200 mg twice daily [bid]), and azathioprine (25 mg every other day). Ten years after his second renal transplant, the patient noted a 2-cm, nontender, firm nodule on his left dorsal wrist. During the next 5 months, similar nodules grew diffusely on his trunk and extremities. The patient reported no associated fevers, chills, weight loss, or malaise. Results of skin examination showed approximately 30 nontender, firm, mobile 1- to 8-cm subcutaneous nodules asymmetrically distributed on his trunk and extremities (Figure 1). Some nodules had overlying erythema. Results of lymph node examination showed a 1-cm lymph node in the left axilla and another 1-cm node in the right posterior cervical chain. The remainder of the examination findings were unremarkable. A fine-needle aspirate of the right posterior cervical lymph node showed no atypical cells. A bone marrow biopsy specimen exhibited no evidence of malignancy. Computed tomography of the chest, abdomen, and pelvis was unremarkable. Whole-body PET scan showed increased uptake limited to the subcutaneous nodules. A biopsy specimen from a right thigh nodule showed a deep dermal and subcutaneous infiltrate of monomorphic-appearing atypical lymphocytes with centroblastic large-cell morphology (Figure 2). Immunohistochemical analysis showed these cells to be CD20+ B cells. In situ hybridization detected EBV RNA. These findings represent a large cell–type B-cell lymphoma or monomorphic PTLD, clinical stage IVD+A. Treatment included reduction of immunosuppressive therapy (azathioprine therapy was discontinued and the cyclosporine dosage was decreased to 100 mg bid) and addition of acyclovir (800 mg 3 times daily). Rituximab therapy (375 mg/wk for 4 weeks) was started 1 week after immunosuppressive therapy was decreased. All lesions resolved by 4 weeks. At the 1.5-year follow-up, the patient remained alive with no evidence of PTLD recurrence.

**PATIENT 2**

A 49-year-old woman received a combined heart-lung transplant in November 1998 secondary to late repair of an atrial septal defect and Eisenmenger syndrome. The transplant was complicated by 1 episode of acute rejection that resolved with increased immunosuppressive therapy. Posttransplantation immunosuppressive therapy consisted of prednisone (8 mg bid), cyclosporine (125 mg bid), and azathioprine (125 mg/d). Nineteen months after transplantation, she presented with a slowly growing erythematous patch on her right thigh (Figure 3). She denied systemic symptoms. Results of skin examination showed an 11.5 × 9-cm, slightly tender, erythematous, reticular, focally indurated plaque with irregular borders on her right thigh. The remainder of the examination was unremarkable. The CT scan findings of the chest, abdomen, and pelvis were unremarkable. Whole-body PET scan showed faintly increased uptake limited to the right thigh patch. A biopsy specimen showed a polymorphous an-
giocentric and angiodestructive lymphoid infiltrate with a small subset of atypical lymphocytes (Figure 4). Immunophenotyping demonstrated a mixed population of CD20+ B cells, CD3+ and CD8+ T cells, and CD68+ histiocytes without evidence of monotypia. Results of IgH rearrangement studies performed by means of polymerase chain reaction analysis, however, showed a monoclonal B-cell population. In situ hybridization for EBV RNA was attempted, but the amount of tissue left in the block was insufficient. Quantitive polymerase chain reaction analysis of blood demonstrated no EBV DNA. The LDH value was within the reference range. On the basis of the clinical setting of posttransplantation immunosuppression and biopsy results, she was diagnosed as having polymorphic PTLD, clinical stage IEA. Accordingly, her immunosuppressive regimen was decreased (azathioprine dosage was tapered, cyclosporine dosage remained unchanged, and prednisone dosage was increased to 10 mg bid to prevent allograft rejection). After a 4-month interval with the new immunosuppressive regimen, the patient's thigh lesion did not regress. She then underwent involved field radiation therapy (total dose, 3000 rad [30 Gy]). Results of 3 subsequent skin biopsies showed no evidence of PTLD. At the 2-year follow-up, she remained without evidence of recurrent disease.

PATIENT 3

A 71-year-old man underwent cadaveric cardiac and renal transplantations in 1989 and 1993, respectively. He experienced a total of 4 mild episodes of rejection. His posttransplantation immunosuppressive therapy consisted of prednisone (10 mg/d), cyclosporine (100 mg bid), and azathioprine sodium (75 mg/d). In October 1997, he noted a rapidly enlarging, nontender, firm nodule on his left chest wall. The nodule grew to 1 cm in 1 week. The patient reported no other nodules or symptoms. Bone marrow biopsy findings and CT scans of the chest, abdomen, and pelvis were unremarkable. Results of an excisional skin biopsy showed a nodular infiltrate centered in the reticular dermis, composed of polymorphous lymphocytes, including irregular and angulated small cells, immunoblasts, and plasmacytoid cells. Most of the cells were CD20+ B cells. Light chain staining failed to reveal...
monotypia of κ or λ light chains. Results of in situ hybridization detected EBV RNA. The LDH value was within the reference range. The clinical setting and biopsy results were consistent with polymorphic PTLD, clinical stage IVA. Azathioprine therapy was discontinued, and the cyclosporine and prednisone dosages were decreased (75 mg bid and 5 mg/d, respectively). Antiviral therapy with acyclovir (800 mg 3 times daily) was given. Five years later, the patient remained free of recurrent disease.

PATIENT 4

A 13-year-old girl received a cadaveric renal transplant in 1993 secondary to membranous glomerulonephritis. The posttransplantation immunosuppressive regimen included prednisone (3 mg/d), cyclosporine (150 mg bid), and azathioprine (50 mg/d). In May 2001, she was hospitalized for a varicella-zoster virus infection, at which time a distinct, enlarging skin lesion was noted on her right cheek. The lesion was a 2 × 1.5-cm nontender, indurated, erythematous, triangular plaque with telangiectasia bordering her right nasolabial fold. There was associated diffuse swelling. A second lesion, a nontender, rubbery nodule of approximately 1 cm, was noted on her right arm. The remainder of the examination findings were unremarkable. The CT scan showed subcutaneous tissue thickening in the right cheek and multiple pulmonary nodules bilaterally. Results of a bone marrow biopsy were normal. A biopsy specimen of the right cheek showed aggregates of mature plasma cells in the dermis and subcutis. Immunophenotyping demonstrated no evidence of monotypia for κ or λ light chains. Results of in situ hybridization for EBV RNA were negative. A subcutaneous biopsy specimen from the arm showed a monomorphic population of immature-appearing plasma cells set in a background of amyloid. This proliferation was κ restricted by immunohistochemistry. In situ hybridization showed numerous cells containing EBV RNA. Fine-needle aspiration of a pulmonary nodule showed a monomorphic population of atypical lymphocytes, a subset of which stained positive for the B-cell markers CD20 and CD79a. Other immunohistochemical and in situ hybridization studies were noncontributory owing to the small amount of tissue. The LDH value was elevated. The clinical setting and biopsy results led to a diagnosis of monomorphic PTLD, clinical stage IVA with skin and lung involvement. Her skin lesions resolved with a reduction in immunosuppressive therapy (prednisone, 1 mg/d; cyclosporine, 75 mg bid; and discontinuation of azathioprine therapy) and the addition of antiviral (ganciclovir, 150 mg bid) and rituximab (400 mg/wk for 3 weeks) therapy. At the 2-year follow-up, no recurrent skin lesions were seen. At the most recent follow-up, the patient had minimal pulmonary disease.

COMMENT

Posttransplantation lymphoproliferative disorders are lymphoid proliferations or lymphomas that develop as a result of immunosuppression in recipients of solid organ or bone marrow allografts. Posttransplantation lymphoproliferative disorders complicate approximately 2% of solid organ transplants, with renal allografts having the lowest risk (<1%) and heart/lung allografts having the highest risk (5%),8,24 Most PTLDs are of B-cell origin and are positive for EBV, although T-cell lesions and EBV-negative lesions are reported.3 Although the pathogenesis of EBV-positive PTLD is not well understood, the decrease in EBV-specific T cells resulting from immunosuppression is thought to allow for the growth of EBV-infected monoclonal proliferations of B cells. One or more of these proliferations may become a dominant monoclonal proliferation and progress to an autonomous malignant lymphoma.25,26

Risk factors for the development of PTLD include primary EBV infection after transplantation, cytomegalovirus disease, and T-cell–specific immunosuppressive therapy such as OKT3 antibody therapy.7,27 The type of organ transplanted and age at transplantation also play important roles. Renal allograft recipients have the lowest risk and HLA-mismatched or T-cell–depleted bone marrow allograft recipients have the highest risk.28 A younger age of the patient at the time of transplantation also confers a higher risk for PTLD development, probably because of the increased risk of primary EBV infection.29

Posttransplantation lymphoproliferative disorders exhibit a broad spectrum of clinical behaviors that range from an infectious mononucleosis–like picture to that of an aggressive non-Hodgkin lymphoma, often with extranodal involvement. At present, no standardized approach to the evaluation and treatment of PTLD exists, although general guidelines for diagnosis and treatment have been pub-
The classification scheme used in this report was outlined by Harris et al., who placed PTLD lesions into the following 3 major categories: early lesions or plasmacytic hyperplasia, polymorphic PTLD, and monomorphic PTLD. Plasmacytic hyperplasia lesions are nearly always polyclonal and with rare exceptions regress in response to mild reduction in immunosuppressive therapy. Polymorphic PTLD lesions may be polyclonal, but are more often monoclonal and show evidence of clonal EBV infection. Monomorphic PTLDs are also monoclonal with morphologic characteristics consistent with lymphoma. They often contain alterations of oncogenes and/or tumor suppressor genes. Two of our patients had lesions classified as polymorphic PTLD and 2 had tumors classified as monomorphic PTLD. All lesions expressed B-cell markers and all 3 patients with sufficient tissue for analysis had EBV-positive PTLD. (Table 1 and Table 2 describe these and other clinical and pathological characteristics of our patients.)

Time from transplantation to PTLD diagnosis varies with some immunosuppressive regimens (eg, OKT3 antibody therapy results in earlier lesions), EBV presence in the lesion (EBV-positive lesions occur earlier), and PTLD subtype (most polymorphic and monomorphic PTLDs occur within the first year after transplantation). Of renal transplant recipients who developed PTLD within the first 6 years after transplantation, greater than 60% developed PTLD within the first year. In all 4 of our patients, relatively late-onset PTLD (>1 year after transplantation) developed, with time between organ allograft and tumor diagnosis ranging from 1.5 to 10 years (median, 8 years). Of our 3 patients with renal transplants, none developed cutaneous PTLD within the first 6 years after transplantation.

The mainstay of treatment for PTLD has been reduction in immunosuppressive therapy, which can result in a cure rate of approximately 25% to 50%. If reduction in immunosuppressive therapy is unsuccessful, other treatment modalities such as monoclonal antibodies against B cells, cytotoxic chemotherapy, radiation therapy, donor lymphocyte transfusion, interferon therapy, antiviral medications, and intravenous immunoglobulin therapy can be tried. These have shown promise in preliminary studies. In our study, treatment included reduction in immunosuppressive therapy for all patients, with the addition of anti-CD20 antibody therapy and antiviral therapy for patients 1 and 4 and radiation therapy for patient 2. Only 1 patient in our series underwent an initial trial of decreased immunosuppressive therapy alone, and this patient did not respond. Clinical outcome in our patients was excellent, with complete remission in 3 patients and asymptomatic, mild residual pulmonary disease in 1. To date, with
a median follow-up time of 2.5 years, no patient has experienced progression or recurrence.

The most commonly reported sites of PTLD include the gastrointestinal tract, lungs, central nervous system, and allografted organ. Skin involvement in PTLD is rare. On review of the literature, we found only 19 cases of PTLD presenting with cutaneous involvement. Only 1 patient was reported to have extracutaneous involvement at the time of diagnosis; however, staging studies were not performed in all patients (including, at the minimum, CT of the chest, abdomen, and pelvis). Gross morphology of these reported skin lesions include ulcers, nodules, and erythematous plaques. Anatomic sites included the face, trunk, and extremities. Consistent with previously reported lesions, our patients exhibited nodules and erythematous plaques on the face, trunk, and extremities. Seventeen of the previously reported cases had B-cell lesions, whereas 2 had T-cell lesions. Of the cases that underwent testing for EBV (15 of the 17 B-cell cases), all findings were positive for EBV. In our study, all lesions expressed B-cell markers, and most of the lesions analyzed were positive for EBV. Fourteen of the 17 previously reported B-cell PTLD cases went into remission after the reduction of immunosuppressive therapy with or without other adjuvants such as surgical excision, radiation therapy, and/or antiviral therapy. Three patients had progressive disease despite treatment efforts. All patients in our study had a favorable response to therapy. Although most previously reported cases show PTLD development within the first 5 years after transplantation, disease did not develop in 3 of our 4 patients until 8 or more years after transplantation.

The 4 cases presented herein are largely consistent with clinical and pathological characteristics previously reported for PTLD with initial skin presentation. Although the number of reported cases is small, PTLD lesions primarily involving the skin have consistently shown more favorable responses to therapy than other forms of PTLD. Cutaneous PTLDs also differ in clinical presentation from other

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Abbreviations: IPI, International Prognostic Index for non-Hodgkin lymphoma; LDH, lactate dehydrogenase; PTLD, posttransplantation lymphoproliferative disorder.

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Abbreviations: EBV, Epstein-Barr virus; PH, plasmacytic hyperplasia; PTLD, posttransplantation lymphoproliferative disorder; minus sign, negative; plus sign, positive.
common presentations of PTLD, as patients usually present later and rarely exhibit systemic symptoms at the time of diagnosis. As observed in cutaneous T-, B-, and natural killer/T-cell lymphomas, we found that cases of PTLD with primary skin presentation had a favorable outcome relative to the more general experience in PTLD, where presentation with extranodal disease involving the lungs, gastrointestinal tract, transplanted organ, and other sites is commonly seen. It is still unclear whether the seemingly more favorable outcome with primary cutaneous presentation reflects a fundamental biological difference in the pathogenesis of PTLD or whether it is a reflection of early diagnosis or a unique feature of the skin.

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REFERENCES