Donor-Derived Lymphomatoid Papulosis in a Stem-Cell Transplantation Recipient

Case Report

The patient was a 60-year-old woman with a history of Langerhans cell histiocytosis who completely responded to a 5-month course of cladribine in 2001 to 2002. Seven years later, she presented with a rash on her thighs, fever, and leukocytosis of $180 \times 10^3/\mu\text{L}$. Bone marrow biopsy showed acute myelogenous leukemia with a marked increase in blasts. Skin biopsy demonstrated leukemia cutis. The acute myelogenous leukemia was attributed to prior treatment with cladribine. She underwent induction chemotherapy with cytarabine, daunorubicin, and etoposide followed by T cell–depleted allogeneic stem-cell transplantation (SCT) from an 8/10 matched unrelated male donor with busulfan, melphalan, and fludarabine conditioning chemotherapy, with two doses of antithymocyte globulin (ATG). She received four doses of ATG for marrow failure 2 months post transplantation. Patient and donor were cytomegalovirus seropositive.

One month post transplantation, the patient was seen by dermatology for a rash of 2 days duration. Examination revealed two non-tender, nonpruritic erythematous papules on the left forearm and axilla. Biopsies showed a dermal infiltrate of small and large mononuclear cells, lymphocytes, and eosinophils, which were further characterized by immunohistochemistry. Two months later, she presented to dermatology with a 1-week history of tender, erythematous, papulonecrotic lesions on the tongue, periorally, and on the trunk, groin, and fingers (Figs 1, 2). Biopsies from tongue and chest lesions showed a wedge-shaped infiltrate of large atypical mononuclear cells, small lymphocytes, and eosinophils (Figs 3, 4). Immunohistochemical studies showed that the large atypical mononuclear cells stained strongly for CD30 (Fig 5). They were negative for additional markers relevant

Fig 2.

for the differential diagnosis, including CD1a and S100 protein to exclude recurrent Langerhans cell histiocytosis. Recurrent leukemia was ruled out by comparing the cutaneous infiltrate with the prior bone marrow infiltrate. Although the leukemic infiltrate in the bone marrow was positive for CD34, CD117, and myeloperoxidase, the cutaneous mononuclear cell infiltrate was not. Studies for Epstein-Barr virus (EBV) were negative. In the absence of nodal and extracutaneous disease, a diagnosis of a CD30+ infiltrate consistent with lymphomatoid papulosis was rendered.

Given the close post-transplantation succession of our patient's new onset lymphomatoid papulosis and the absence of the usual

Fig 1.

Fig 3.

Fig 4.

potential contributory immunosuppressive medications, engraftment studies were performed to assess the genetic origin of lesional lymphocytes. Fluorescence in situ hybridization XY analysis performed on sections from the left forearm biopsy showed that 192 (96%) of 200 cells were XY, or of donor origin, with X and Y chromosomes staining red and green, respectively (Fig 6). Polymorphism analysis using short tandem repeats showed that only 30% of cells were of host origin (Fig 7). As depicted, the donor is homozygous with a single peak, and the recipient heterozygous; lesional skin contains both types of cells, although the diminution in height of the recipient-specific peak (Fig 7, arrow) suggests a predominance of donor cells. In concert, the molecular and cytogenetic results confirmed that the lesional cells were primarily donor derived. The patient's skin lesions were treated with bexarotene 1% gel and gradually improved. The patient died as a result of sepsis 7 months after transplantation.

Discussion

Post-transplantation lymphoproliferative disorders (PTLDs) are lymphoid proliferations or lymphomas that develop in a recipient of a

Fig 5.

Fig 6.

solid-organ or bone marrow allograft.¹ The incidence of PTLDs in patients undergoing allogeneic hematopoietic SCT is approximately 1%.² The incidence can increase to 8% with additional risk factors, such as human leukocyte antigen (HLA) mismatch, T-cell depletion, and therapies used to treat graft-versus-host disease.³

Data from the Cincinnati Transplant Tumor Registry show that 86% of PTLD lymphomas are of B-cell origin, 14% of T-cell origin, and less than 1% of null origin.⁴ Post-transplantation B-cell lymphomas are typically associated with EBV. Immunosuppression used to prevent graft rejection leads to relaxation of T-cell control over EBV infection, viral reactivation, and proliferation of EBV-infected B lymphocytes.⁵ No pathogenic equivalent to EBV has been implicated in cases of post-transplantation cutaneous T-cell lymphoma (CTCL).⁶ One explanation for such lymphomas is that they are derived from donor lymphocytes. Most cases of PTLD in solid-organ transplantation recipients are of host origin, indicating the evasion of EBV-positive host cells from immune surveillance; most PTLDs in recipients of marrow allografts are of donor origin, reflecting that allografting results in an immune system of donor origin.⁷

Primary CTCL (PCTCL) represents a small fraction of post-transplantation lymphomas of T-cell origin. A 2006 review of PCTCL occurring after organ transplantation reported 23 cases.⁶ The most commonly reported subtypes included primary cutaneous anaplastic large-cell lymphoma (eight cases), peripheral T-cell lymphoma (six cases), and erythroderma (five cases). One case of lymphomatoid papulosis was included.⁸ Most of the reported cases occurred in the setting of post-transplantation immunosuppressive therapy, namely cyclosporine, prednisolone, and methotrexate.

Primary cutaneous CD30+ lymphoproliferative disorders are the second most common group of CTCLs after mycosis fungoides. The spectrum of CD30+ cutaneous lymphoproliferative disorders includes lymphomatoid papulosis, primary cutaneous anaplastic large T-cell lymphoma, and borderline CD30+ lesions. Lymphomatoid papulosis is characterized by chronic, recurrent, erythematous dome-shaped papules or nodules that spontaneously regress over weeks with scaling, crusting, and ulceration.⁹ Current classification schemes regard lymphomatoid papulosis as an indolent cutaneous lymphoma.¹⁰ There are three well-established histopathologic subtypes: types A (histiocytic type), B (lymphocytic type), and C (borderline lymphomatoid papulosis–anaplastic large T-cell lymphoma).^{10–12}

Fig 7.

Histologically, our patient's skin lesions were characteristic of type A lymphomatoid papulosis, which is described as a wedge-shaped, inflammatory cell infiltrate with scattered large atypical CD30+ lymphocytes in a background of small lymphocytes, often with neutrophils, eosinophils, or both.⁹ That the lesions stained positively for T-cell markers, and the large atypical mononuclear cells were CD30+, provided conclusive evidence for a diagnosis of lymphomatoid papulosis.

The skin lesions occurred on the patient's trunk, limbs, tongue, and periorally. Although oral lymphomatoid papulosis is rare, there are at least six reported cases involving the tongue or oral commissure.¹³⁻¹⁷ It is thought that oral involvement does not have prognostic significance in lymphomatoid papulosis.¹⁵ These lesions were treated with bexarotene 1% gel three times a day and showed gradual improvement. Topical bexarotene gel for lymphomatoid papulosis has reportedly demonstrated faster resolution, less necrosis, and fewer new lesions.¹⁸

A review of the literature revealed five previously reported cases of post-transplantation lymphomatoid papulosis,^{8,19-22} one of which

occurred after allogeneic SCT,²¹ and the others after solid-organ transplantation. Three patients were male. Ages ranged from 15 to 64 years. The latency period from transplantation to appearance of lesions was between 6 months and 9 years. All patients were receiving immunosuppressive therapy (ie, cyclosporine, prednisone, azathioprine) when the lesions developed. The eruption showed clinical improvement after dose reduction or discontinuation of such agents, suggesting that the development of post-transplantation lymphomatoid papulosis was the result of iatrogenic immunosuppression.

Our patient did not receive these post-transplantation immunosuppressive therapies, because she underwent T cell-depleted transplantation. She did receive ATG with the conditioning regimen before transplantation and for marrow failure after the initial development of the skin lesions. The more widespread progression of the cutaneous lesions occurred 1 month later. It remains unclear whether the administration of ATG contributed to the development and/or progression of lymphomatoid papulosis.

Previously, a case of donor-derived post-transplantation PCTCL after allogeneic SCT was described.⁷ A 56-year-old man underwent transplantation for treatment of mantle-cell lymphoma from an HLA-matched sister and developed an eczematous eruption 6 years later. The lesions demonstrated a dense lichenoid infiltrate of CD4+ lymphocytes consistent with mycosis fungoides. Fluorescence in situ hybridization XY analysis and microsatellite genotyping were used to demonstrate that cells within the skin lesions were of donor origin. Additionally, transmission of subcutaneous panniculitic T-cell lymphoma by allogeneic bone marrow transplantation has been reported.²³

Hypotheses to explain donor-derived PTLs include the presence of occult leukemia in the donor, transfer of oncogenic material from host to donor cells, impaired immune surveillance, drug therapy, and a host environment that promotes transformation.²⁴ In our case, we considered the possible contributions of aberrant immune stimulation from antigenic differences related to HLA and donor sex mismatch. In addition, impaired immune surveillance related to ATG, pretransplantation chemotherapy, or the immune-compromised state after T cell-depleted transplantation may have played a role.

Although to our knowledge this is the first reported case of donor-derived lymphomatoid papulosis after SCT, it is possible that other cases exist that have not been identified, because the chimerism of skin lesions has not been assessed.²⁵ None of the previously reported cases of post-transplantation lymphomatoid papulosis studied the genetic composition of skin lesions.

Although our studies shed light on the pathogenesis of this patient's disease, the clinical role for such assays has yet to be determined. In rare reported cases of donor-derived lymphomas, a history of lymphoproliferative disease within the donor was identified, which could serve as confirmation of the source.^{23,26} In our case, there was no history of lymphoma in the donor database, but that does not exclude the possibility that a subclinical lymphoma may have once been present in the donor as an unevaluated rash. This may have implications for the screening of donor populations in the future, although at this point, additional studies are needed.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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