Cutaneous Manifestations of Unspecified Peripheral T-Cell Lymphoma May Be Indicative of Disease Activity and Predict Response to Therapy

Introduction

Cutaneous manifestations of internal malignancy encompass both direct extension of tumor to the skin and indirect involvement (the so-called paraneoplastic syndromes). Direct cutaneous manifestations parallel systemic disease in progression, remission, and response to treatment. Peripheral T-cell lymphoma (PTCL) comprises a group of mature T-cell malignancies that together make up less than 15% of all non-Hodgkin's lymphoma; PTCL has been reported to directly involve the skin in a minority of cases.¹ Unspecified PTCL (PTCL-u) makes up the majority of these lymphomas (60% to 70%).² We report a patient with PTCL-u with secondary cutaneous involvement who was treated with a new histone deacetylase inhibitor, romidepsin (Istodax; Celgene, Summit, NJ). Because skin manifestations correlate with systemic disease activity, cutaneous manifestations can aid in monitoring of the systemic responses to therapy and can be a first warning sign of relapse.

Case Report

A 68-year-old man was referred to the Cutaneous Lymphoma Clinic at the University of Pittsburgh Medical Center for evaluation of a so-called skin eruption. Eight months before, he was diagnosed with PTCL-u with CNS involvement. A magnetic resonance imaging scan of the brain showed multiple left meningeal and cervical lesions as well as intradural and extradural spinal lesions. A computed tomography scan revealed bilateral axillary and inguinal lymphadenopathy and a splenic mass. CSF and bone marrow biopsies were negative for malignant cells. Flow cytometric analysis of the axillary lymph node revealed a predominance of CD4+ and CD8-, and a diagnosis of PTCL-u was given. Additional cell surface receptor characterization of the tumor cells showed CD3+, CD4+, CD20-, CD8-, with a partial loss of CD7. Immunohistochemical staining for Ki-67 expression revealed a low proliferative index. Subsequent molecular study showed clonal rearrangement of the T-cell receptor gene. Records from the time of initial diagnosis of PTCL-u also mentioned a history of rash that later resolved.

The patient was treated with radiation therapy to the brain and spine and intrathecal methotrexate. The therapy was complicated by renal failure, which prompted discontinuation of methotrexate after three doses despite a partial response. This therapy was followed by 6 months of temozolomide with a complete clinical response for 2 months.

The patient presented to us with concern about a rash that was similar to his initial eruption at the time of PTCL-u diagnosis. On skin examination, he had numerous firm purple papules on his abdomen and knees bilaterally (Fig 1A). His lesions were intensely pruritic. Shave biopsies of the left knee and mid-lower abdomen revealed

Fig 1.

numerous medium to large lymphocytes with irregular nuclear contours and moderate amounts of pale cytoplasm (Fig 2). Immunohistochemistry highlighted strong positivity of CD3, CD4, CD5, and beta-F1, with diminished expression of CD2, CD7, CD8, TIA-1, and granzyme B. CD30, CD56, and CXCL2 highlighted only a few scattered cells. Anaplastic lymphoma kinase-1 and epithelial membrane antigen were negative on the larger cells. Programmed death-1 stained a moderate number of mostly smaller cells. Ki-67 showed a low proliferative index. Reports were compared with previous biopsies of the right axillary lymph node that were taken at the time of the initial PTCL-u diagnosis and were found to be similar. Positron emission tomography/computed tomography revealed hypermetabolic lymphadenopathy, including an index right axillary node that measured 12 × 8 mm with a standardized uptake value (SUV) of 1.4, an index left axillary node that measured 11 × 6 mm with an SUV of 1.5, and a right hilar node that measured 4 mm in the short axis with an SUV of 2.4. Soft tissue hypermetabolic activity was noted in subcarinal soft tissue with an SUV of 2.5 (Fig 1A). A diagnosis of PTCL-u relapse and secondary cutaneous involvement was made.

Fig 2.

After discussing all treatment options with the patient, he opted to be treated with romidepsin, to be infused at a dose of 14 mg/kg per day on days 1, 8, and 15 of a 28-day cycle. After six infusions, 90% of the patient's skin lesions cleared. After a subsequent four cycles, the lesions cleared completely and there was resolution of [^{18}F]fluorodeoxyglucose-avid mediastinal and axillary lymph nodes (Fig 1B). The adverse effects that were experienced by this patient were generally mild and included nausea, fatigue, and weight loss. The patient's disease status has been classified as complete clinical response for the last year.

Discussion

PTCL-u is the most common subtype of a rare and heterogeneous group of non-Hodgkin's lymphomas. These lymphomas demonstrate poor response to conventional therapies such as cyclophosphamide, doxorubicin, vincristine, and prednisone, although this regimen anachronistically remains first-line therapy despite never having been established as the preferred or most effective treatment for ALK-negative PTCL.^{3,4} Five-year survival rates for T-cell lymphoma that is treated with regimens like cyclophosphamide, doxorubicin, vincristine, and prednisone remains in the 20% to 35% range, and are below reported response rates in similarly aggressive B-cell lymphoma counterparts.⁵ Recent clinical practice has expanded the use of new and experimental treatments in clinical trials. Evidence-based recommendations in fact advocate the use of experimental agents in controlled settings.⁴

Romidepsin belongs to an epigenetic regulator class of drugs known as histone deacetylase inhibitors. The response of PTCL to romidepsin was documented in a case report in 2001.⁶ On the basis of the results of two phase II trials, the US Food and Drug Administration approved romidepsin for patients who have received at least one previous treatment.⁷ These phase II trials reported overall response rates of 26% to 38%, with complete response rates of 13% to 18%.^{8,9}

Skin involvement is a rare occurrence in PTCL-u, with reports of cutaneous lesions in 10% to 18% of patients.^{1,10} Unlike primary cutaneous T-cell counterparts, cutaneous involvement in PTCL-u has been described as a poor prognostic factor, with 5 year survival rates of 12% despite treatment.¹¹

Cutaneous response to romidepsin therapy in our patient allowed us to predict corresponding systemic response. In those rare

patients with PTCL and cutaneous involvement, skin lesions and their responses to therapy may offer a window into systemic responses to romidepsin and may guide further investigation as necessary.

We observed cutaneous manifestations of PTCL-u to fully correlate with the state of the systemic disease. This allowed us to diagnose a relapse of the disease and to predict response to the therapy. Because PTCL with cutaneous manifestations is rare, it is unlikely that our observations can be tested in future clinical trials. However, we wanted to alert the hematology-oncology community that cutaneous manifestations may be useful in monitoring the disease activity and response to therapy in patients with PTCL and cutaneous manifestations.

Michael K. Schowalter, Oleg E. Akilov, and Sara K. Story
University of Pittsburgh, Pittsburgh, PA

Larisa J. Geskin

University of Pittsburgh; and University of Pittsburgh Cancer Institute, Pittsburgh, PA

ACKNOWLEDGMENT

Supported by National Institutes of Health Specialized Programs of Research Excellence Grant No. 5P50CA121973-03 Project 5 (L.G.) and the Doris Duke Charitable Foundation (M.S.).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Larisa J. Geskin, Celgene (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

- Rodriguez-Abreu D, Filho VB, Zucca E: Peripheral T-cell lymphomas, unspecified (or not otherwise specified): A review. *Hematol Oncol* 26:8-20, 2008

2. Rodríguez J, Gutiérrez A, Martínez-Delgado B, et al: Current and future aggressive peripheral T-cell lymphoma treatment paradigms, biological features and therapeutic molecular targets. *Crit Rev Oncol Hematol* 71:181-198, 2009
3. Gisselbrecht C, Gaulard P, Lepage E, et al: Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas: Group d'Etudes des Lymphomes de l'Adulte (GELA). *Blood* 92:76-82, 1998
4. Dearden CE, Johnson R, Pettengell R, et al: Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). *Br J Haematol* 153:451-485, 2011
5. Armitage JO, Vose JM, Weisenburger DD: Towards understanding the peripheral T-cell lymphomas. *Ann Oncol* 15:1447-1449, 2004
6. Piekarz RL, Robey R, Sandor V, et al: Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: A case report. *Blood* 98:2865-2868, 2001
7. Celgene: Istodax (romidepsin) for injection: US prescribing information. http://www.istodax.com/pdfs/ISTODAX_PackageInsert.pdf
8. Piekarz RL, Frye R, Prince HM, et al: Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood* 117:5827-5834, 2011
9. Coiffier B, Pro B, Prince HM, et al: Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic. 53rd Annual Meeting and Exposition of the American Society of Hematology, Orlando, FL, Dec 4-7, 2010 (abstr 114)
10. Armitage JO, Cavalli F, Zucca E, et al (eds): *Text Atlas of Lymphomas* (ed revised). London, United Kingdom, Martin Dunitz, 2002, pp 30-43
11. Bekkenk MW, Vermeer MH, Jansen PM, et al: Peripheral T-cell lymphomas unspecified presenting in the skin: Analysis of prognostic factors in a group of 82 patients. *Blood* 102:2213-2219, 2003

DOI: 10.1200/JCO.2012.41.6644; published online ahead of print at www.jco.org on August 6, 2012