

Complete response to romidepsin as monotherapy in treatment-resistant subcutaneous panniculitis-like T-cell lymphoma



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INTRODUCTION

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare, indolent primary cutaneous T-cell lymphoma characterized by the infiltration of neoplastic T-cells confined to the subcutaneous fat in a pattern of lobular panniculitis. The World Health Organization restricted this diagnosis to the alfa/beta phenotype and excluded the more aggressive gamma/delta phenotype.¹ The 5-year survival of SPTCL is 82% in patients without hemophagocytic syndrome (HPS) versus 11% in patients with primary cutaneous gamma/delta T-cell lymphoma.² Currently, there are no standardized treatment protocols for the disease; however, patients are often initially treated with prednisone, methotrexate, cyclosporine, or bexarotene.^{2,3} Treatment-resistant SPTCL is often treated with multiagent cytotoxic chemotherapy including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like therapies, with reports of complete remission in 3 of 8 cases in one study.² Even when CHOP or CHOP-like therapies were used as initial treatment, only 19 of 31 patients achieved complete remission, 2 of which relapsed at a median follow-up of 34 months. Of the remaining patients, 8 had ongoing disease and 4 patients died, including 3 with HPS and 1 from the side effects of treatment.² Thus, there is a need to develop more effective alternative treatment options for patients with refractory SPTCL.

Romidepsin is a histone deacetylase inhibitor that has been approved by the US Food and Drug Administration for the treatment of both peripheral and cutaneous T-cell lymphomas.⁴ However, most

Abbreviations used:

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone
HPS: hemophagocytic syndrome
SPTCL: subcutaneous panniculitis-like T-cell lymphoma

studies have focused on its use in mycosis fungoides and there are few reports of its use in SPTCL. Here, we report the case of a 49-year-old woman with SPTCL refractory to commonly prescribed treatments who achieved complete remission with romidepsin.

CASE REPORT

A 49-year-old woman with a history of SPTCL for 2 decades presented with numerous erythematous subcutaneous nodules of 2-9 cm on the face, trunk, and extremities, involving about 60% of her body surface area. These nodules had waxed and waned over the last 20 years and there was evidence of diffuse, cosmetically deforming lipoatrophy in the areas of resolved lesions. She had no associated lymphadenopathy or hepatosplenomegaly. She had previously been treated with prednisone, methotrexate, hydroxychloroquine, bexarotene, and acitretin with minimal response. She developed anemia and leukopenia and elevated ferritin along with B symptoms, which are concerning for HPS, but the skin and bone marrow biopsies were negative. Lactate dehydrogenase was elevated at 1153 IU/L. Histopathologic examination of an incisional biopsy of a nodule showed an atypical lymphoid infiltrate in the subcutaneous tissue, with characteristic rimming

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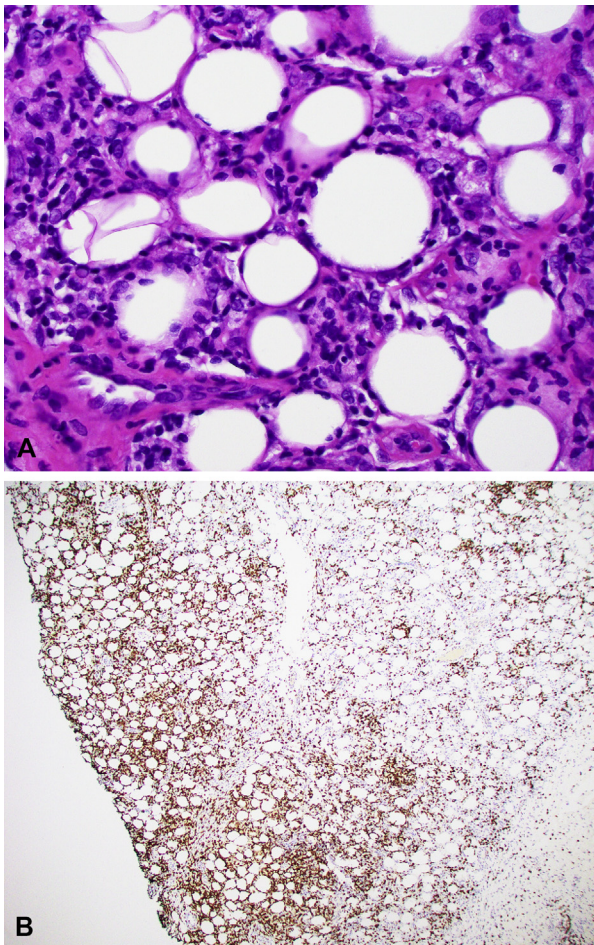


Fig 1. Histopathologic evaluation of the skin incisional biopsy. **A**, The hematoxylin-eosin stained section shows atypical lymphocytes that are small to medium sized and distributed along the fat globules. (Hematoxylin-eosin stain; original magnification: $\times 100$.) **B**, The atypical infiltrate $CD8^+$.

of adipocytes by small-to-medium-sized atypical lymphocytes (Fig 1, A). The infiltrate was $CD3^+$ and $CD8^+$ (Fig 1, B), $\beta F1^+$, $TIA-1^+$, $granzyme B^+$, and $perforin^+$ and $CD4^-$. Clinical, histologic, and immunohistochemistry features confirmed a diagnosis of SPTCL.

Owing to her lack of response to the standard recommendations for the treatment of SPTCL, she was started on 14 mg/m^2 romidepsin. She experienced a dramatic response after the first infusion with a 50% reduction in her subcutaneous nodules. After the second infusion on day 8, the dose was decreased to 12 mg/m^2 every 2 weeks instead of the standard infusion schedule at days 1, 8, and 15 in a 28-day cycle due to the significant side effects of fatigue, thrombocytopenia, and nausea, the latter of which not satisfactorily controlled with antiemetic agents. Subsequently, she tolerated the new dose

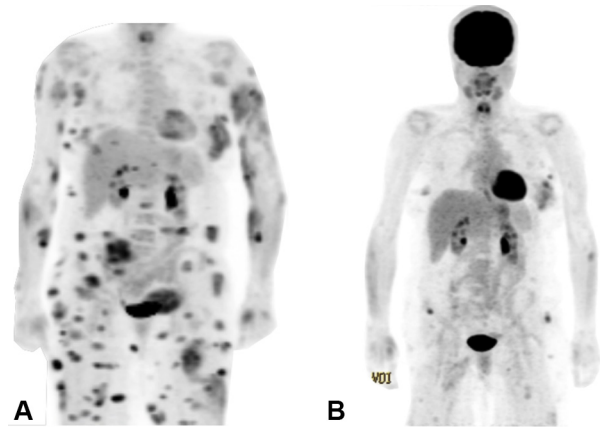


Fig 2. **A**, Positron emission tomography/computed tomography before romidepsin treatment shows diffuse nodules with increased uptake of fluorodeoxyglucose along the torso and extremities in the subcutaneous tissue. **B**, After 6 months of treatment with romidepsin, repeat positron emission tomography/computed tomography demonstrates a drastic reduction in fluorodeoxyglucose uptake with few residual nodules on extremities.

and schedule. Positron emission tomography/computed tomography at 6 months showed a dramatic reduction in the hypermetabolic activity in the subcutaneous tissue compared with the imaging performed prior to initiating treatment (Fig 2). Our patient achieved complete remission at 12 months; treatment was discontinued at 18 months, with no evidence of relapse for 4 months.

DISCUSSION

Few additional case reports exist on the use of romidepsin in SPTCL with mixed results. A case report showed its effectiveness in 2 patients with SPTCL and possible HPS, resulting in complete resolution of the disease at the 2- and 3-month follow-ups.⁵ The effectiveness of romidepsin was also seen in a sample of 3 patients in a trial with relapsed SPTCL.⁶ These patients had disease that was refractory to other treatments but had stable disease for 4 months while on romidepsin. Our case shows sustained response at the 22-month follow-up and along with the other reports highlights that romidepsin is a reasonable option to treat SPTCL especially given that romidepsin alone has a better side-effect profile than polychemotherapy that may be used to treat this disease. This case also demonstrates the safety of prolonged use of romidepsin in a patient with SPTCL, which should only be considered if the patient achieves at least stable disease while on treatment.⁶

Romidepsin is a histone deacetylase inhibitor that mediates its anticancer effects through multiple

mechanisms, including cell-cycle arrest and apoptosis.⁷ It is also known to target the PI3K/AKT/mTOR and the Jak/STAT pathways.⁸ A study of the genome-wide mutational landscape of SPTCL showed that there were epigenetic mutations in the PI3K/AKT/mTOR cascade and JAK-STAT pathway in patients with SPTCL. In the same study, the SPTCL cells were treated in vitro with romidepsin and revealed decreased cell viability at 72 hours.⁹ More recently, the gene coding for TIM-3, a transmembrane protein that is a negative immune checkpoint protein, was discovered to be mutated in SPTCL.¹⁰ This loss-of-function mutation leads to a revved-up immune system as seen in HPS. This may explain the role of immunosuppressive agents in the treatment of SPTCL.^{10,11} In this context, romidepsin may also act as an immunosuppressive agent through the upregulation of cell-dependent kinase inhibitors, downregulation of cyclin D1, and disruption of DNA repair through acetylation, leading to the downregulation of proteins and eventual apoptosis.¹²

Similarly, CHOP chemotherapy, the current recommendation for the treatment of resistant SPTCL, also prevents tumor cell proliferation by interfering with DNA replication and suppressing leukocyte migration. However, this regimen tends to have more adverse events than romidepsin. Therefore, we recommend that the clinicians consider romidepsin for patients with recalcitrant, diffusely distributed SPTCL. Our patient's sustained response to romidepsin for her treatment-resistant SPTCL shows that romidepsin should be considered as an additional therapeutic tool in the treatment of recalcitrant SPTCL.

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