Case Reports in Oncology

Case Rep Oncol 2025;18:406–412
DOI: 10.1159/000544782
Received: October 12, 2024
Accepted: February 4, 2025
Published online: February 18, 2025

Case Report

Refractory Subcutaneous Panniculitis-Like T-Cell Lymphoma with Hemophagocytic Syndrome Treated with Romidepsin and Allogeneic Hematopoietic Cell Transplantation

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Keywords

Subcutaneous panniculitis-like T-cell lymphoma · Hemophagocytic syndrome · Allogeneic hematopoietic cell transplantation · Romidepsin

Abstract

Introduction: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare subtype of cutaneous T-cell lymphoma (CTCL) that when refractory or complicated by hemophagocytic syndrome (HPS) has a poor prognosis. Romidepsin is a histone deacetylase inhibitor, but its efficacy for SPTCL is unknown. The efficacy of allogeneic hematopoietic cell transplantation (allo-HCT) is also unclear. Herein, we report a case of refractory SPTCL with HPS that was successfully treated with romidepsin followed by consolidation with allo-HCT. ***Case Presentation:*** A 26-year-old female presented with fever, generalized painful erythema, pancytopenia, and hemophagocytosis. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET) showed diffuse PET-avid infiltration of the subcutaneous adipose tissue found to be SPTCL via skin biopsy. Her SPTCL was refractory to conventional chemotherapy but complete metabolic

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response was achieved after romidepsin. An allo-HCT was used for consolidation, and she remains in complete remission 3 years later. ***Conclusion:*** Romidepsin with allo-HCT consolidation may be an effective approach for refractory SPTCL.

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is caused by neoplastic CD8 positive αβ T cells that infiltrate the subcutaneous adipose tissue. It is a rare subtype of peripheral T-cell lymphoma (PTCL), which collectively amount to 0.6% of all cutaneous lymphomas. SPTCL is more common in patients under 40 years old [1] and typically presents with lower extremity erythema nodosum-like subcutaneous nodules [2, 3]. Approximately 15–20% of patients develop hemophagocytic syndrome (HPS) [1], an acquired severe inflammatory syndrome caused by dysregulated cytolytic pathways in lymphocytes. HPS portends a poor prognosis with a 5-year overall survival of 46% versus 91% for those without HPS [4]. The first-line treatment of SPTCL with or without HPS typically consists of immunosuppression or various chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone, respectively [1, 5]. However, the optimal treatment of relapsed or refractory (R/R) disease has not been established.

Histone deacetylase (HDAC) inhibitors, including romidepsin, are used for R/R PTCL [6]. The mechanism of action of HDAC inhibitors in PTCL is unique as they not only inhibit tumor growth but also dampen immune function by decreasing inflammatory cytokine production and promoting Treg accumulation and function [7]. Case reports for four patients [8–10] showed successful treatment of R/R SPTCL with suspected HPS using the HDAC inhibitor, romidepsin. Long-term remission with another HDAC inhibitor, chidamide, was also reported for a single refractory patient [11]. While these reports suggest HDAC inhibitors likely achieve responses in patients with R/R SPTCL, their use as a bridge to consolidative allogeneic hematopoietic cell transplantation (allo-HCT) has not been described. Due to their immunosuppressive effects, HDAC inhibitors are also being studied for graft-versus-host disease (GVHD) prophylaxis following allo-HCT [7]. Here, we report on the successful treatment of R/R SPTCL with romidepsin followed by consolidation with allo-HCT. Our patient tolerated romidepsin well and did not develop severe GVHD or any other major allo-HCT-related complication. She remains in complete metabolic remission (CMR) 3 years post allo-HCT. In addition to our case report, we also review and discuss the reported R/R SPTCL cases treated with HDAC inhibitors as well as the use of allo-HCT for SPTCL. Altogether, our case and these previous reported cases suggest romidepsin followed by allo-HCT may be an effective approach for R/R SPTCL with HPS.

Case Report

A 23-year-old woman with autosomal dominant polycystic kidney disease presented in December 2020 to a local physician with fever, dry cough, and painful erythema of the upper extremities and trunk. A skin biopsy revealed SPTCL for which she was referred to our dermatology department in February 2021. Prednisolone at a dose of 0.4 mg/kg/day was initiated; however, her high-grade fever continued, and she then developed anemia and thrombocytopenia. HPS was suspected prompting referral to our hematology department

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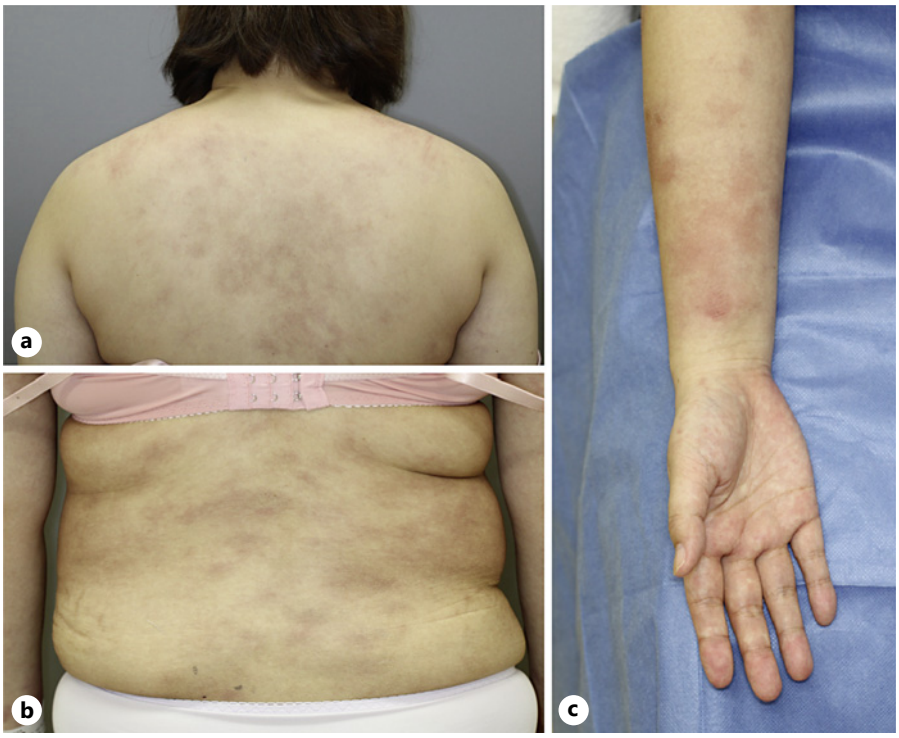

Fig. 1. Physical exam findings from our patient are shown. Multiple erythematous lesions were observed on her back (**a**), abdomen (**b**), and right forearm (**c**).

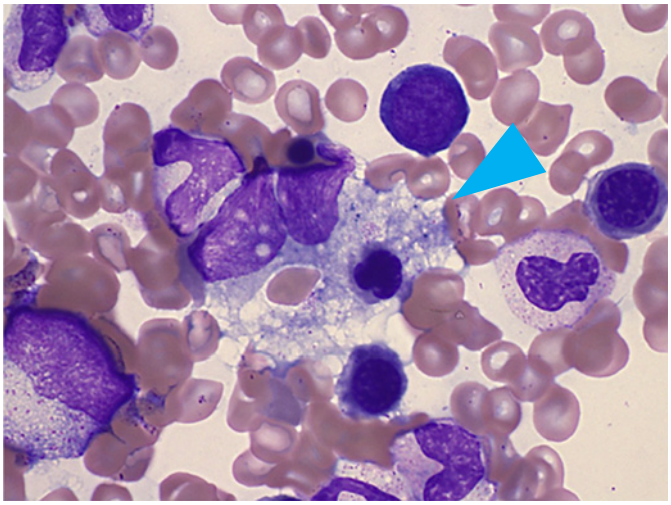

Fig. 2. A representative hemophagocytic macrophage (arrowhead) from our patient's bone marrow aspirate is shown.

where she presented with an ECOG performance status was of 1 and diffuse painful erythema but no hepatosplenomegaly (Fig. 1). Laboratory analysis revealed anemia (hemoglobin of 11.5 mg/dL), thrombocytopenia (platelet count of 14.0 × 10^4/μL), hyperferritinemia (5,662 mg/dL), elevated lactate dehydrogenase (1,109 U/L), an elevated soluble interleukin-2 receptor (4,985 U/mL), and hypofibrinogenemia (163.0 mg/dL). A bone marrow aspirate

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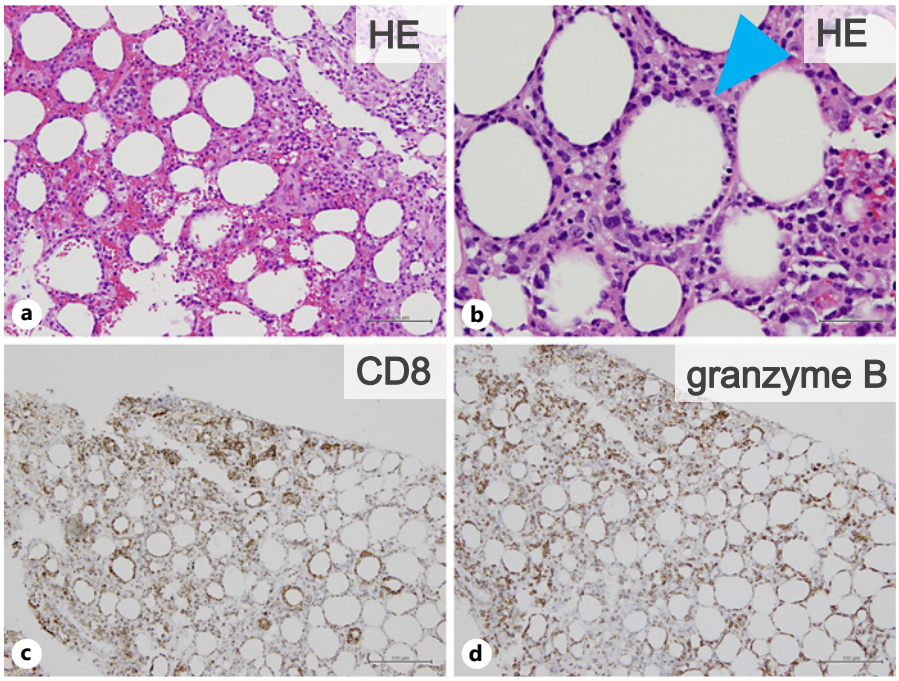

Fig. 3. Skin biopsy histopathology from our patient is shown. **a**, **b** Hematoxylin-eosin (HE) staining showed atypical lymphocytes infiltrating the subcutis and rimming adipocytes (arrowheads). **c**, **d** The atypical lymphocytes stained positive for CD8 (**c**) and granzyme B (**d**). **a**, **c**, **d** are at ×100 magnification. **b** is at ×200 magnification.

showed HPS (Fig. 2), and a repeat skin biopsy demonstrated atypical lymphocytes infiltrating the subcutis and rimming adipocytes. The atypical lymphocytes expressed CD3, CD4, CD8 (>CD4), and granzyme B; however, stains for CD56, perforin and βF-1 of the αβ T-cell receptor were negative (Fig. 3). ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (PET) revealed multiple PET-avid infiltrates in subcutaneous adipose tissue (Fig. 4). Based on these results, although βF-1 negativity is atypical, we clinically diagnosed SPTCL with HPS.

We initially treated her with cyclophosphamide, doxorubicin, vincristine, and prednisone, but her disease was refractory. Brentuximab vedotin (BV) as well as combinatorial chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (EPOCH) were also trialed but did not achieve a CR. Because of the inflammatory nature of her disease, we next administered romidepsin (14 mg/m^2 on day days 1, 8, and 15 of 28 day cycles), which has both antitumor and anti-inflammatory effects. After six cycles, a CMR (Fig. 4) was achieved and her inflammation subsided. There were no serious adverse events during treatment with romidepsin. To consolidate her response, she received an allogenic peripheral blood stem cell transplantation (allo-PBSCT) from a 7/8 human leukocyte antigen (HLA) matched (HLA-C locus mismatched) unrelated donor (CD34 positive cells were 2.87 × 10^6/kg) using cyclophosphamide (60 mg/kg) and total body irradiation (TBI, 12 Gy) conditioning. GVHD prophylaxis consisted of tacrolimus, short-term methotrexate, and rabbit anti-thymocyte globulin. Neutrophils and platelets engrafted on days 12 and 17 post allo-HCT, respectively. No severe complications during allo-HCT occurred, and her disease remains in CMR 3 years after allo-HCT (Fig. 4). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000544782).

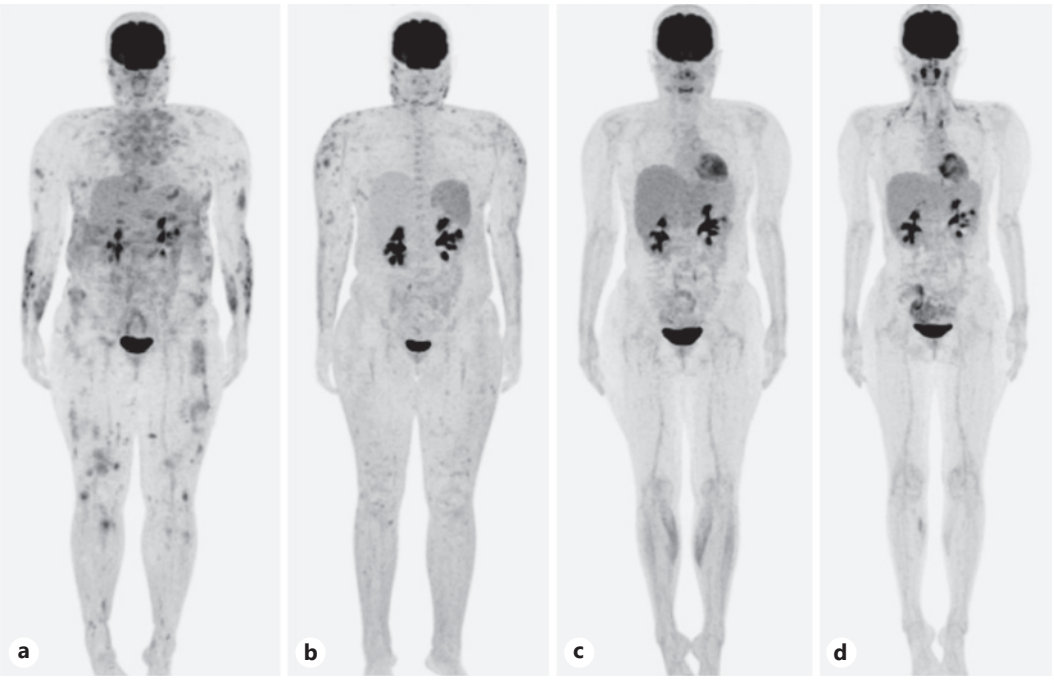

Fig. 4. Our patient's PET/CT response to each treatment modality is shown. Her pretreatment PET-CT is shown in (**a**) followed by that after CHOP, BV, and EPOCH chemotherapy in (**b**); after six cycles of romidepsin in (**c**); and 6 months after allo-HCT in (**d**). PET/CT before treatment (**a**) and after chemotherapy (**b**) showed diffuse abnormal accumulation in subcutaneous adipose tissue. After romidepsin, the accumulation disappeared (**c**), and a CMR was maintained after allo-HCT (**d**). PET-CT, positron emission tomography/computed tomography.

Table 1. Summary of patients using romidepsin for SPTCL

Patient number	Age/sex	HPS	Disease course	Response to initial treatment	Outcome (survival)	Ref.
1	49/F	Suspected	Worsening diagnosis at 20 years ago	Minimal response	CR, alive (1 years 10 months)	[8]
2	39/F	Suspected	Primary refractory	Persistent systemic symptom	CR, alive	[9]
3	32/F	Suspected	Primary refractory	Poor response	CR, alive	[9]
4	42/F	–	Primary refractory	Poor response	CR, alive (1 years)	[10]

CR, complete response; HPS, hemophagocytic syndrome.

Discussion

SPTCL is a rare subtype of CTCL that progresses relatively slowly. Its prognosis is usually good except for cases complicated by HPS. The first-line therapy often consists of immunosuppressive or combination chemotherapy especially for cases with HPS. The treatment of R/R SPTCL with HPS has not been established. Here, we report the successful treatment of refractory SPTCL with HPS using the HDAC inhibitor, romidepsin, followed by allo-HCT consolidation. We chose romidepsin based on its efficacy in four reported refractory SPTCL cases, of which 3 cases also had HPS (Table 1) [8–10]. In all 4 cases, a complete response was

achieved, and in at least 1 case, maintained for nearly 2 years of follow-up [8]. Romidepsin also produced a CMR in our patient after six cycles and was well tolerated.

The long-term prognosis and duration of response for refractory SPTCL with HPS treated with romidepsin is not known and will need careful study in future clinical trials. Due to this uncertainty and because our patient's autosomal dominant polycystic kidney disease put her at high risk for renal impairment that would potentially complicate high-dose chemotherapy used for relapsed disease, we consolidated her with allo-HCT. As with the prognosis following romidepsin, the effectiveness of allo-HCT for SPTCL is not clear. A phase III trial comparing autologous versus allogenic transplantation in young patients with poor-risk PTCL, including just one SPTCL patient treated with an autologous HCT, showed no significant difference in OS, EFS, or PFS [12]. However, a partial response to salvage chemotherapy has been reported in R/R SPTCL after conventional chemotherapy [6], and one report from Taiwan described several cases where up-front allo-HCT for refractory SPTCL with or without HPS resulted in durable responses [13]. Therefore, we reasoned that allo-HCT consolidation after romidepsin may be more effective than conventional chemotherapy, HDAC inhibitors, auto-HCT, or allo-HCT either individually or any of the other possible combinations thereof. Consistent with this, romidepsin achieved a CR in our patient that has been maintained for the past 3 years following consolidation with allo-HCT. Interestingly, HDAC inhibitors may be useful for GVHD prevention following allo-HCT. In our patient's case, it is not clear how prior romidepsin therapy influenced allo-HCT, but our patient did not experience any severe transplant-related complications.

Altogether, our case further supports the efficacy of romidepsin in R/R SPTCL, but its durability remains unknown. One possible alternative to romidepsin is allo-HCT, which can produce durable responses [13], but allo-HCT outcomes are often poor in the setting of uncontrolled inflammation associated with HPS [14, 15]. Thus, our combinatorial approaches using romidepsin to achieve a CR and abate inflammation prior to consolidation with allo-HCT may improve outcomes for R/R SPTCL complicated by HPS. However, this novel approach will need to be confirmed in future prospective clinical trials.

Conclusion

Bridging to allo-HCT with romidepsin is a potentially effective strategy for refractory SPTCL complicated by HPS.

Statement of Ethics

Written informed consent for publication of the clinical course and any accompanying images was obtained from the patient. This case report was reviewed and approved by the Ethical Review Committee of Yamagata University Faculty of Medicine, Approval No. 2024-S-73.

Conflict of Interest Statement

The authors have no conflict of interest.

Funding Sources

This work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (C) Grant No. JP23K07850 (T.T), the Japanese Society of Hematology Research Grant (T.T). National Institutes of Health grant K08 HL157619 (D.P.), an Amy Strelzer Manasevit Research Program

grant which is funded through the Be the Match Foundation® (D.P.), and start-up funds from the Indiana University School of Medicine and Melvin and Bren Simon Comprehensive Cancer Center (D.P.).

Author Contributions

Y.I., T.I., M.H., and T.T. diagnosed and treated the patient and wrote the article. D.P., R.Y., and K.I. provided instructions for writing this article. M.K., Y.N., R.T., M.H., Y.H., A.Y., T.S., K.A., and S.I. treated the patient.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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