# Romidepsin-induced neutrophilic urticaria

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## INTRODUCTION

Romidepsin is a histone-deacetylase inhibitor administered for treatment-refractory mycosis fungoides. Common side effects include fatigue, weakness, nausea, and cytopenia. We report a patient with Sézary syndrome treated with romidepsin who developed a reproducible neutrophil-rich urticarial eruption.

## CASE REPORT

A 72-year-old Caucasian woman with Sézary syndrome was treated for 3 years with interferon alfa-2b and extracorporeal photopheresis. In a span of 8 weeks between clinic visits, she developed 2.4-cm lymphadenopathy and worsening erythroderma. Histology of the surgically excised node revealed Dutch grade III changes with proliferation of atypical lymphocytes and partial architectural effacement. T-cell gene rearrangement studies of the lymph node revealed the same clone as was present in the leukemic cells. Her Sézary cell count abruptly increased in the same time frame from 8.2% to 50% of the total lymphocytes, and counts increased from 410 to 4410 cells/$\mu$L. Positron emission tomography fluorodeoxyglucose scan showed avid uptake in axillary, inguinal, and pelvic lymph nodes, the largest measuring 1.7 cm and 1.8 cm in the left axillae and right inguinal area, respectively.

Because of disease progression, interferon and extracorporeal photopheresis were discontinued and treatment was initiated with romidepsin (14 mg/m$^2$) on days 1, 8, and 15, along with bexarotene (150 mg) twice daily. Clinically, she responded well to romidepsin with resolution of the erythroderma after the first infusion. However, within 5 hours after second infusion, she developed bright, hot, salmon-pink, nonscaly edematous nummular patches and plaques in body folds and on the face, upper aspect of the chest, and back (Figs 1 and 2). She reported that her skin felt like a heat rash with minimal pruritus. She had no fevers, skin pain, lymphadenopathy, mucositis, arthralgia, transaminitis, neutrophilia, or eosinophilia.

The eruption was treated with desonide 0.05% ointment applied to the face and triamcinolone 0.1% ointment applied to the body. Punch biopsy specimen demonstrated a neutrophilic infiltrate in the papillary and superficial reticular dermis with mild spongiosis and no epidermal necrosis (Fig 3). The eruption began to subside on day 3 postinfusion and was completely resolved before the next infusion 1 week later (Fig 4). This reaction recurred in the same distribution with every subsequent romidepsin infusion, consistent with an urticarial fixed drug eruption. Trials of preinfusion and postinfusion diphenhydramine, dexamethasone, methylprednisolone, cooling packs, doxycycline, and dapsone on the day before and day of infusion failed to modify the development or character of the reaction. Romidepsin treatment was continued but gabapentin was added to the regimen with moderate relief of pruritus. After a period of 4 months, the eruption was still present and reproducible but was significantly milder in severity.

## DISCUSSION

Romidepsin is a novel treatment for mycosis fungoides that works primarily by binding a zinc ion needed for histone deacetylase function. Loss of histone deacetylase promotes apoptosis in rapidly dividing lymphocyte populations, with a response

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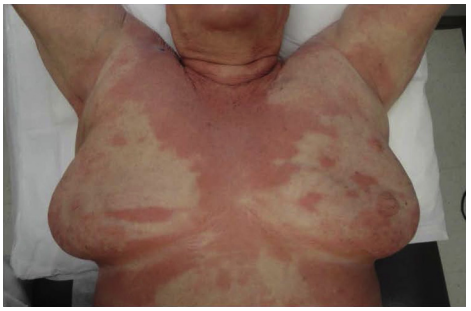

**Fig 1.** Drug eruption on the chest of patient 1 day after romidepsin infusion.

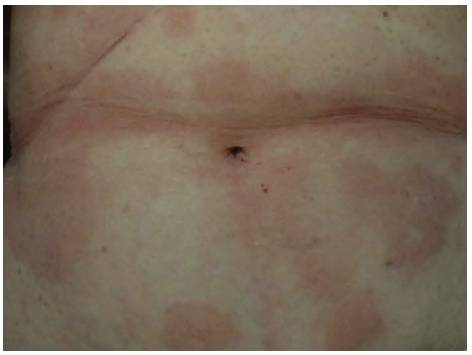

**Fig 2.** Drug eruption on the abdomen of patient 1 day after romidepsin infusion.

rate of 34% in refractory cutaneous T-cell lymphoma. Median time to response is 8 weeks and the median duration of response is between 13 and 15 months. Mild side effects of nausea and fatigue occur in about half of patients, and asymptomatic T-wave flattening occurs in about 80% of patients. Approximately one quarter of patients can experience cytopenias.[1,2] Although 1 patient was noted to develop dermatitis medicamentosa during phase-II trials, no details regarding the nature of the eruption were provided.[2]

Drug-induced urticaria is the second most common pattern of cutaneous drug eruption, second only to morbilliform lesions.[3] Lesions are typically pruritic, edematous, and erythematous wheals. Histologically, there is dermal edema with perivascular and interstitial infiltrates of lymphocytes, eosinophils, and neutrophils.[4] "Neutrophilic urticaria" is a term used to describe the 5% to 9%[5,6] of urticarial lesions that show a predominantly neutrophilic infiltrate on histologic examination. In contrast to conventional urticaria, neutrophilic urticaria has a shorter duration, is less pruritic, and responds poorly to antihistamines, which suggests a pathway that may be less reliant on mast-cell degranulation relative to conventional urticaria.[6,7]

The differential diagnosis for a drug eruption with a predominantly neutrophilic infiltrate includes

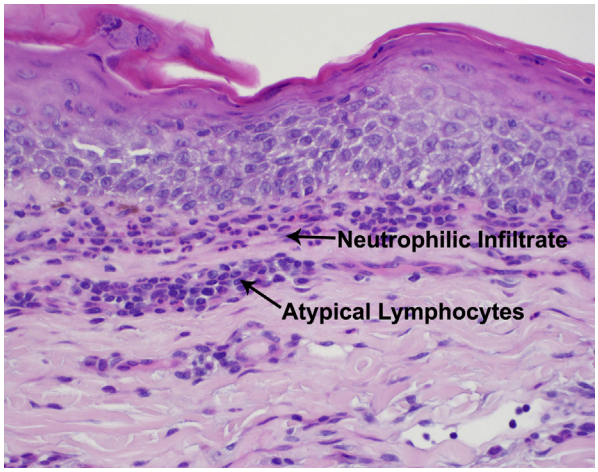


**Fig 3.** Eruption skin biopsy specimen demonstrating a neutrophilic infiltration with admixed atypical Sézary cells. (Hematoxylin-eosin stain; original magnification: ×40.)

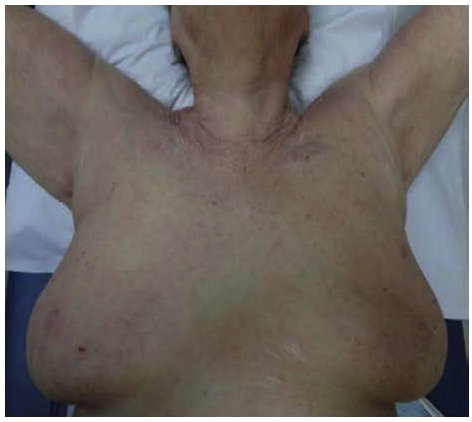

**Fig 4.** Chest of patient 6 days after romidepsin infusion showing near complete resolution of prior erythematous rash.

neutrophilic urticaria with systemic inflammation and drug-induced Sweet syndrome. Neutrophilic urticaria with systemic inflammation is a recently described entity composed of erythematous macules clinically and a neutrophilic infiltrate histologically. However, neutrophilic urticaria with systemic inflammation can be differentiated from neutrophilic urticaria by minimal dermal edema, neutrophil infiltration into the more reticular dermis, leukocytoclasia, and presence of systemic inflammation or a collagen vascular disease, none of which were found in our patient.[8] In drug-induced Sweet syndrome, erythematous plaques are typically painful or tender along with a dense neutrophilic infiltrate and fever, which our patient lacked.[3]

Our patient developed reproducible urticarial lesions within 5 hours of each romidepsin infusion, which would self-resolve over the subsequent

3 days. The papillary dermal neutrophilic infiltrate on biopsy specimen and lack of response to antihistamines suggest a neutrophilic urticarial drug eruption. Although this adverse effect has not necessitated discontinuation of romidepsin treatment, the pruritus and cosmesis of the rash negatively impact the patient's quality of life. Clinicians and patients should be aware of this potential adverse effect that does not require discontinuation of the drug unless deemed intolerable by the patient.

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