# Treatment of Sezary syndrome with combination romidepsin and tofacitinib: A case report

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***Key words:*** case report; CTCL; cutaneous T-cell lymphoma; HDAC; histone deacetylase inhibitor; JAK; Janus kinase inhibitor; romidepsin; Sézary syndrome; tofacitinib.

## INTRODUCTION

Treatment of Sézary syndrome varies by stage and individual patient factors. Romidepsin is a commonly used histone deacetylase (HDAC) inhibitor, preferred for its efficacy and reduced toxicity compared to traditional chemotherapies.[1] Tofacitinib, a Janus kinase (JAK) inhibitor Food and Drug Administration-approved for the treatment of arthritis and ulcerative colitis, has been increasingly used off-label for the treatment of dermatological conditions, including sarcoidosis.[2] While basic science studies of combined HDAC and JAK inhibition have proved promising, there is limited clinical literature on their combined use in patients with cutaneous T-cell lymphoma (CTCL). Here, we present the case of a 64-year-old woman with Sézary syndrome and sarcoidosis treated with combination romidepsin and tofacitinib.

*Abbreviations used:*

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|---|---|
| ACE: | angiotensin-converting enzyme |
| Akt: | protein kinase B |
| CTCL: | cutaneous T-cell lymphoma |
| ERK1/2: | extracellular signal-regulated kinase 1/2 |
| HDAC: | histone deacetylase |
| JAK: | Janus kinase |
| JNK: | c-Jun N-terminal kinases |
| PICC: | peripherally inserted central catheter |
| STAT3: | signal transducer and activator of transcription 3 |

## CASE REPORT

The patient is a 64-year-old female from South America with a past medical history of sarcoidosis, lifestyle-controlled type 2 diabetes mellitus, stroke without residual deficits, and provoked deep vein thrombosis and pulmonary embolism. In her late fifties, the patient began noticing a granulomatous "rash" on her axillary and inguinal regions and was diagnosed with sarcoidosis following positive skin and lymph node biopsies. At that time, she began experiencing skin fragility and sensitivity with easy ulceration in response to extreme temperatures. Her sarcoidosis was treated with daily prednisone 5 mg for several years. Over time, she developed progressive worsening of her skin pain and erythema. In the summer of 2023, at age 63, she presented to a dermatologist for several months of worsening skin fragility, hyperpigmentation, and a burning sensation. A skin biopsy of the ribcage was concerning for epidermotropic CTCL with an interstitial granulomatous dermal pattern seen in some variants of mycosis fungoides. That summer, the patient was also hospitalized for an infected lower extremity wound, with her course complicated by an upper extremity deep vein thrombosis and single subsegmental pulmonary embolism secondary to a malfunctioning peripherally inserted central catheter line.

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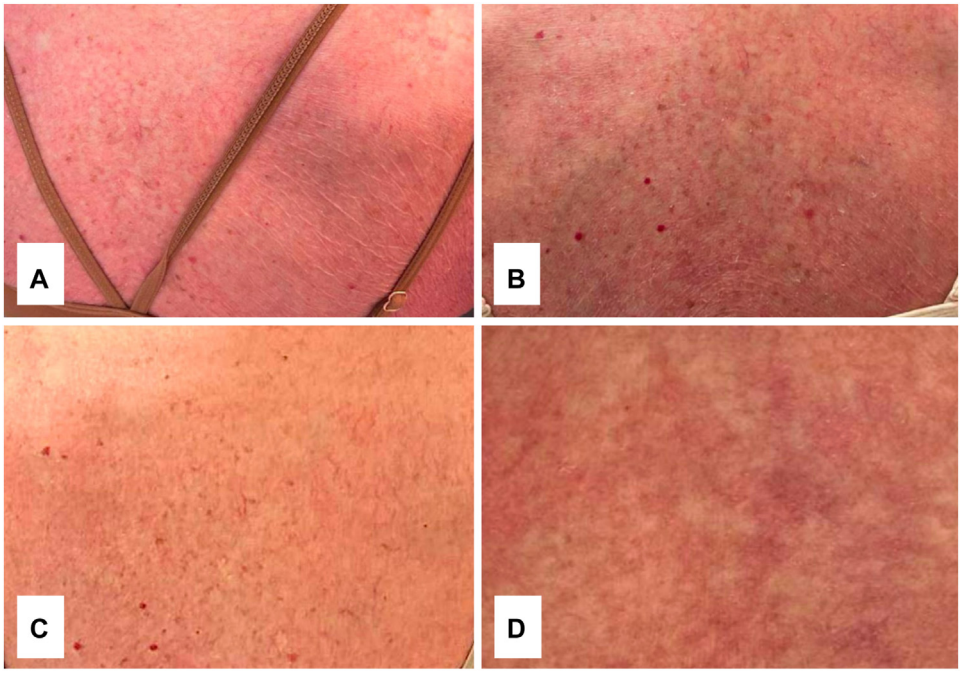


**Fig 1.** Posterior trunk of patient with Sézary syndrome before and after treatment. Clinical images of the back at initial presentation (**A**), after ~1 month of romidepsin monotherapy (**B**), and of the superior (**C**) and inferior (**D**) back after ~2 months of treatment with romidepsin and tofacitinib.

In the fall of 2023, at age 63, she presented to a cutaneous oncologist, with physical exam notable for generalized erythema, a wrinkled skin surface with overlying scale, and reticular violaceous purpuric patches on all extremities with a variegated reddish-brown appearance (Figs 1, *A* and 2, *A*). Her skin was diffusely tender to palpation, and she had tender bilateral axillary and inguinal lymphadenopathy. Repeat punch biopsies of the abdominal and posterior trunk skin confirmed CTCL. Peripheral blood flow cytometry was notable for a positive T-cell receptor gamma chain rearrangement, a positive FISH study for trisomy 7, and an atypical CD4-positive T-cell population with aberrant loss of CD7 and bright expression of CD2. Labs revealed an elevated ACE level of 149 units/L. Positron emission tomography - computed tomography revealed bilateral axillary and pelvic lymphadenopathy. A biopsy of the left inguinal lymph node showed partial involvement of a clonal T-cell population in addition to extensive non-necrotizing granuloma involvement. Given the patient's elevated ACE levels and lymph node biopsy results, a diagnosis of concurrent CTCL and sarcoidosis was favored over a single diagnosis of granulomatous CTCL.

The patient was staged as IVA, T4N2M0B2 Sézary Syndrome, and she began romidepsin in November 2023. In January 2024, she was found to have a partial response with significantly improved erythroderma that the patient felt had recently plateaued (Figs 1, *B* and 2, *B*). After the January visit, she began concurrent tofacitinib 5 mg daily for sarcoidosis. In March 2024, she was seen after completing her fourth romidepsin infusion. She was noted to have significant improvement since January, with a reduction of generalized erythema, minimal tenderness of the skin to palpation, and no cervical, axillary, or right inguinal lymphadenopathy. She continued to have diffuse reticular violaceous purpuric patches and erythematous scaly plaques occupying an estimated 2% to 3% total body surface area, but clear islands of normal skin appeared for the first time since her initial presentation (Figs 1, *C* and *D*, 2, *C*). Notably, throughout her course of combined treatment with romidepsin and tofacitinib, there was no hematologic toxicity observed beyond what is expected of treatment with single-agent romidepsin.

## DISCUSSION

This patient's disease continued to improve on a combined regimen of romidepsin and tofacitinib without evidence of any additional toxicity. The degree of improvement attributable to the addition of a JAK inhibitor, if any, cannot be quantified. However, the potential synergistic effects of combination therapy with HDAC and JAK inhibitors for

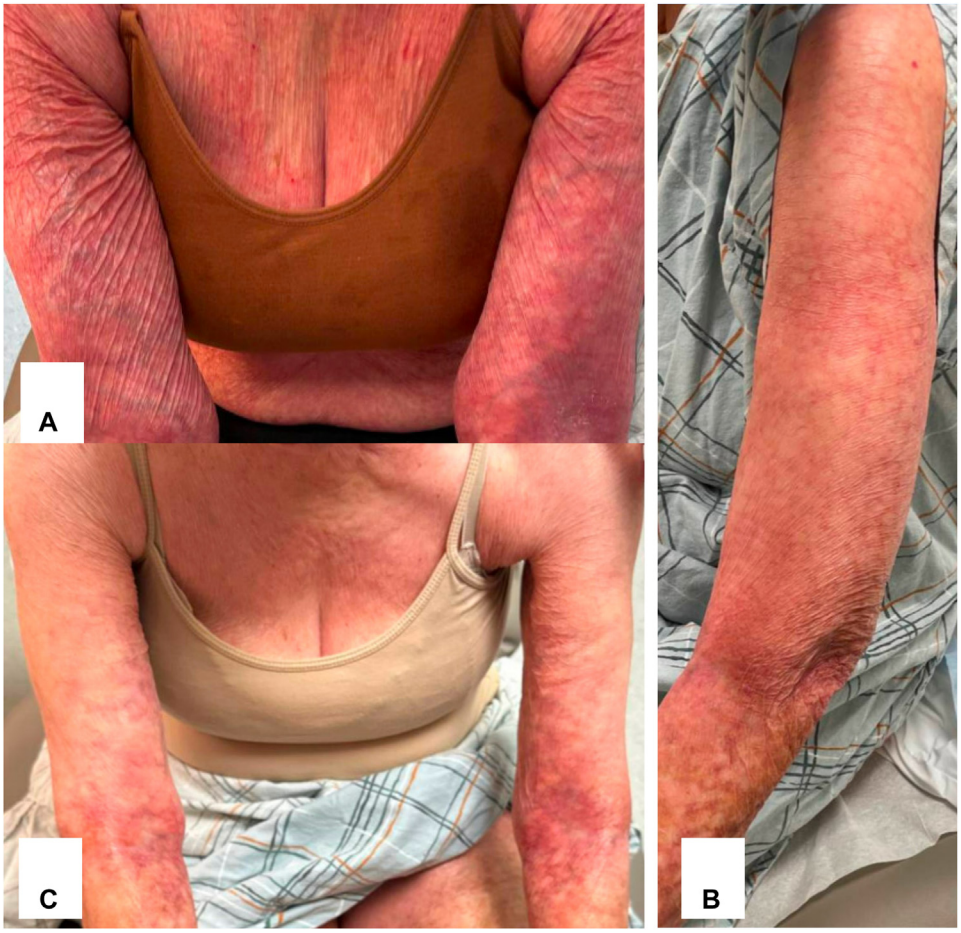


**Fig 2.** Upper extremities and chest of patient with Sézary syndrome before and after treatment. Clinical images of the chest and anterior arms at initial presentation (**A**), left arm after ~1 month of romidepsin monotherapy (**B**), and chest and anterior arms after ~2 months of treatment with romidepsin and tofacitinib (**C**).

hematologic malignancies, including CTCL, have been repeatedly discussed in the literature.[3] The 2024 study by Shih et al showed synergistic anti-tumor effects with romidepsin and afatinib attributed to Jak-signal transducer suppression in CTCL cell lines.[4] Similarly, a 2021 study by Karagianni et al reported a combinational effect of dual HDAC and JAK inhibitor therapy with ruxolitinib and resminostat. They found that combined HDAC/JAK inhibition was more effective in reducing cell proliferation and inducing apoptosis compared to either therapy individually, which was attributed to inhibited phosphorylation of protein kinase B, Signal Transducer and Activator of Transcription 3, extracellular signal-regulated kinase 1/2, and JNK.[5] A 2020 study by Yumeen et al found that JAK inhibition potentiated the cytotoxicity of malignant cells when combined with HDAC inhibitors.[6] The 2021 study by Cortes et al identified JAK inhibition as an important mediator of the anti-tumor effect of romidepsin and an alkylating agent using CTCL cell lines, primary samples, and in an in vivo mouse model of Sézary syndrome.[7]

In human studies of patients with T-cell lymphomas, romidepsin has been safely used in combination with several cytotoxic chemotherapies, including pralatrexate and the "CHOP" regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone.[8,9] Beneficial and well-tolerated use of combination therapy with romidepsin and other small-molecule inhibitors has also been reported in the literature. A phase I/II open-label multicenter study of patients with relapsed or refractory T-cell lymphoma found that the combined use of tenalisib and romidepsin was favorable in terms of both safety and efficacy.[10] Our case contributes to the literature by providing an example of continued clinical improvement of Sézary syndrome following the addition of a JAK inhibitor to HDAC therapy without evidence of additional hematologic toxicity. This

suggests the potential promise of combination HDAC/JAK inhibitor therapy in patients with advanced or refractory disease and prompts further investigation.

### Conflicts of interest

Dr Geskin has served as an investigator for Helsinn Group, J&J, Mallinckrodt, Kyowa Kirin, Soligenix, Innate, Merck, BMS, and Stratpharma; on the speakers' bureau for Helsinn Group and J&J; and on the scientific advisory board for Helsinn Group, J&J, Mallinckrodt, Sanofi, Regeneron, and Kyowa Kirin. Authors Suhl, Lapolla, and Kaminsky have no conflicts of interest to declare.

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