Treatment of cutaneous lupus with topical ruxolitinib cream

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Key words: CLE; cutaneous lupus; discoid lupus; DLE; JAK; lupus; ruxolitinib; SLE; topical.

INTRODUCTION

Cutaneous lupus erythematosus (CLE) is an autoimmune disease that can present in the setting of multiorgan system involvement such as systemic lupus erythematosus (SLE) or as isolated skin disease.[1] To date, no medication has been specifically approved for the treatment of CLE, and existing guidelines focus on topical agents, antimalarials, corticosteroids, and immunosuppressive drugs.[2] However, recent advances in understanding the molecular pathogenesis of CLE have opened the possibility of new treatment modalities.[1] Skin lesions in patients with CLE are characterized by cytotoxic immune responses targeting keratinocytes after a primary trigger such as UV light, followed by the release of cell debris and activation of the innate immune response, leading to a self-amplifying, proinflammatory cycle.[3] A key molecular hallmark for CLE is the activation of type I interferon-driven pathways, including the expression of CXCL10. CXCL10 expression in the lower epidermis of inflamed skin drives the recruitment of $CXCR3^{+}$ effector cells and the development of the characteristic interface dermatitis.[4] Given that the JAK-STAT pathway plays an important role in the autocrine loop for type I interferons, the JAK1/2 inhibitor ruxolitinib is a promising therapeutic candidate for CLE.[3,4] Ruxolitinib has been shown to control skin lesions in a case of chilblain lupus erythematosus[5] and topical tofacitinib was effective in treating a case of periorbital discoid lupus erythematosus (DLE)[6]; however, there have not been reports of the use of topical JAK inhibitors for scalp lesions of CLE. Here, we present a patient with SLE and DLE whose scalp lesions and alopecia improved with topical ruxolitinib.

Abbreviations used:

AI:	antibody index
CLE:	cutaneous lupus erythematosus
DLE:	discoid lupus erythematosus
SLE:	systemic lupus erythematosus

CASE REPORT

A 28-year-old woman presented to our dermatology clinic with a recent diagnosis of SLE. She described rashes that started 6 months prior on the left cheek, upper portion of the left side arm, both the ears, and right side of the scalp, with right-sided scalp patchy alopecia. Laboratory testing revealed elevated antinuclear antibody titer ≥ 1:2560 (normal <1:80) with a speckled pattern, double stranded DNA antibody titer 1:160 (normal <1:10), ribosomal P antibody 4.5 antibody index (AI) (normal <1.0), Smith/ribonucleoprotein antibody >8 AI (normal <1.0), and Sjogren's Syndrome related antigen A antibody >8 AI (normal <1.0). Patient also had low complement C3c 76 mg/dL (normal 83-193 mg/dL) and C4c 9 mg/dL (normal 15-57 mg/dL). She had no oral sores, dry eye, eye pain, blurry vision, chest pain, dyspnea, abdominal pain, or muscle weakness. The skin examination revealed bilateral ear and conchal bowl hyperpigmented plaques; right scalp with a hyperpigmented, violaceous plaque with scale, and associated alopecia; nasal tip and left malar cheek with pink-brown, atrophic plaques; and left shoulder with 2 brown, violaceous plaques with

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2022;28:133-5.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.08.038

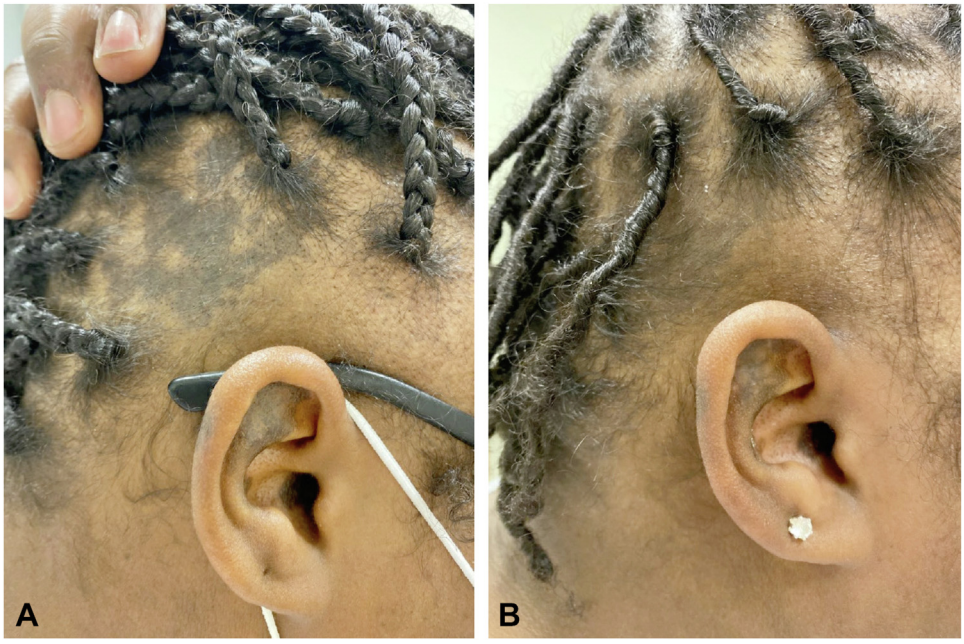

Fig 1. Improvement of hyperpigmented, violaceous plaques with scale and associated alopecia after 2 months of topical ruxolitinib therapy. **A,** before treatment. **B,** after treatment.

scale. Skin biopsy of the upper portion of the left arm revealed a focally thinned epidermis with vacuolar alteration of the dermoepidermal junction, a focally thinned basement membrane, and edema of the papillary dermis, along with perivascular and periadnexal lymphocytic infiltrate. Biopsy results and clinical impressions were consistent with a diagnosis of DLE.

The patient was diagnosed with SLE and began treatment with hydroxychloroquine titrated up to 400 mg daily, and skin lesions were initially treated with halobetasol 0.05% ointment. Two months later, the patient was started on belimumab for SLE. Six months after the initial presentation, the patient reported experiencing fatigued, that DLE lesions appeared worse with a new lesion on the upper portion of the left eyelid, and that overall halobetasol 0.05% ointment had minimal benefit. As a result, she was started on topical ruxolitinib 1.5% cream daily for right scalp plaques (Fig 1, *A*). After 2 months of treatment with topical 1.5% ruxolitinib cream, plaques on her right side of the scalp showed improvement and subtle hair regrowth (Fig 1, *B*).

DISCUSSION

This case suggests that topical ruxolitinib is an effective therapy for CLE and associated alopecia. Ruxolitinib, a small-molecule inhibitor of JAK1/2, is effective for several immunologic skin disorders, including alopecia areata.[7] Oral treatment with JAK inhibitors ruxolitinib and tofacitinib are effective in improving cutaneous lesions in lupus-prone mouse models[8,9] and also for a patient with chilblain lupus.[5] However, given that the systemic use of oral JAK inhibitors for CLE is limited by side effects such as anemia and thrombocytopenia, whether topical formulations can penetrate the skin barrier and still have efficacy is of particular interest. One recent study demonstrated that the lesional skin from patients with subacute CLE and chronic DLE had increased phosphorylated JAK1 expression in the epidermis and dermis and that topical treatment with JAK inhibitors could significantly improve CLE-like skin lesions in lupus-prone mouse models.[10] There has also been 1 case report of the use of 2% tofacitinib ointment, a topical JAK1/3 inhibitor, for treating periorbital DLE.[6] However, there have otherwise been limited data on the use of topical JAK inhibitors for CLE. To our knowledge, there are no prior reports of improvement of alopecia associated with CLE lesions of the scalp after treatment with topical JAK inhibitors. In addition to the emerging evidence on the role that JAK-STAT dysregulation plays in CLE pathogenesis, this case suggests that topical JAK inhibitors may be a promising therapeutic avenue for CLE, particularly as adjunctive therapy along with systemic immunosuppression. Further investigation is necessary to continue to evaluate the safety and efficacy of this approach.

Conflicts of interest

None disclosed.

REFERENCES

1. Little AJ, Vesely MD. Cutaneous lupus erythematosus: current and future pathogenesis-directed therapies. *Yale J Biol Med*. 2020;93:81-95.
2. Kuhn A, Aberer E, Bata-Csörgő Z, et al. S2k guideline for treatment of cutaneous lupus erythematosus — guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol*. 2017;31(3):389-404. https://doi.org/10.1111/jdv.14053
3. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. *Nat Rev Rheumatol*. 2019;15(9):519-532. https://doi.org/10.1038/s41584-019-0272-0
4. Kuhn A, Landmann A, Wenzel J. Advances in the treatment of cutaneous lupus erythematosus. *Lupus*. 2016;25(8):830-837. https://doi.org/10.1177/0961203316641771
5. Wenzel J, van Holt N, Maier J, Vonnahme M, Bieber T, Wolf D. JAK1/2 inhibitor ruxolitinib controls a case of chilblain lupus erythematosus. *J Invest Dermatol*. 2016;136(6):1281-1283. https://doi.org/10.1016/j.jid.2016.02.015
6. Mazori DR, Min MS, Kassamali B, et al. Use of tofacitinib, 2%, ointment for periorbital discoid lupus erythematosus. *JAMA Dermatol*. 2021;157(7):880-882. https://doi.org/10.1001/jamadermatol.2021.1198
7. Xing L, Dai Z, Jabbari A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. *Nat Med*. 2014;20(9):1043-1049. https://doi.org/10.1038/nm.3645
8. Chan ES, Herlitz LC, Jabbari A. Ruxolitinib attenuates cutaneous lupus development in a mouse lupus model. *J Invest Dermatol*. 2015;135(7):1912-1915. https://doi.org/10.1038/jid.2015.107
9. Furumoto Y, Smith CK, Blanco L, et al. Tofacitinib ameliorates murine lupus and its associated vascular dysfunction. *Arthritis Rheumatol*. 2017;69(1):148-160. https://doi.org/10.1002/art.39818
10. Fetter T, Smith P, Guel T, Braegelmann C, Bieber T, Wenzel J. Selective janus kinase 1 inhibition is a promising therapeutic approach for lupus erythematosus skin lesions. *Front Immunol*. 2020;11:344. https://doi.org/10.3389/fimmu.2020.00344