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Cutaneous Langerhans Cell Histiocytosis Responsive to Topical Nitrogen Mustard

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ABSTRACT

Langerhans cell histiocytosis (LCH) limited to the skin is rare in adult patients. Given the challenges of prospective clinical trials for this rare disease, there is paucity in data to guide the management of cutaneous LCH. Topical nitrogen mustard is a possible treatment for cutaneous LCH with positive responses in five known adult cases in the literature. In this report, we present two adult patients with recalcitrant cutaneous LCH and no evidence of systemic involvement who had rapid and complete response on topical nitrogen mustard therapy. We provide support for topical nitrogen mustard as a treatment option for primary cutaneous LCH which may spare patients from requiring systemic immunosuppressive treatments.

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare clonal proliferation of pathologic langerhans cells that accumulate in organs including skin, bone, liver, or spleen.[1] LCH that is limited to the skin is rare in adult patients;[1] larger studies estimate that up to 11% of LCH is limited to the skin.[2] While cutaneous LCH has better prognosis than multisystem LCH, response to skin-directed therapies remains variable particularly for recalcitrant disease.[1]

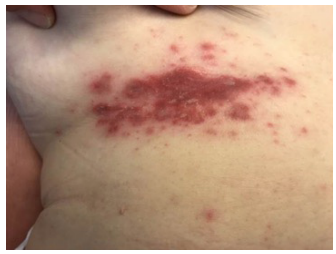
There are a lack of guidelines and consensus in the management of cutaneous LCH.[3] Current reported therapies include topical corticosteroids, topical imiquimod, radiation therapy, methotrexate, hydroxyurea, phototherapy, thalidomide, or vinblastine.[1,4-7] Topical nitrogen mustard therapy, or mechlorethamine, is a treatment with positive responses in six known pediatric cases[5] and five known adult cases of cutaneous LCH without systemic involvement.[5,8-11] It has also shown positive response in larger pediatric cohort studies of multisystem LCH.[5,6] We present two adults with skin-limited LCH with complete response after treatment with topical nitrogen mustard.

Report of Cases

Case 1

A 75-year-old woman presented in dermatologic consultation with a painful, pruritic eruption of 8 years' duration. Physical examination showed scattered, red-brown crusted papules without ulcerations in her inguinal folds and vulva, extending onto the perineum and labia. There were also scattered papules on a background of macular erythema on the bilateral inframammary folds (Figure 1). The patient did not have systemic symptoms at diagnosis but was diagnosed at subsequent follow-up with chronic myelomonocytic leukemia (CMML) and immune thrombocytopenic purpura.

FIGURE 1. Clinical presentation of Case 1 showing scattered papules on a background of erythema on the right inframammary fold.



A punch biopsy from her vulvar area found focal parakeratosis overlying a superficial dermal proliferation of medium-sized discohesive cells, positive for CD1a, langerin, S100, and cyclin D1, and negative for CD123 (Figure 2). She was positive for the BRAFV600E mutation. Positron emission tomography, pituitary MRI, and bone survey did not show multisystem involvement. The final diagnosis was of LCH, limited to cutaneous involvement.

FIGURE 2. Histopathology of Case 1 showing focal parakeratosis overlying a superficial dermal proliferation of medium-sized discohesive cells.

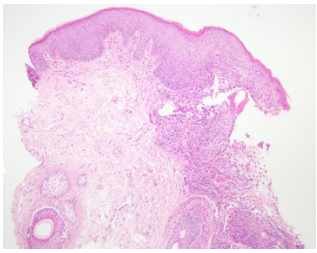
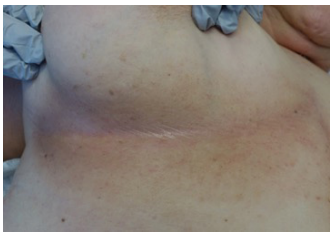


FIGURE 3. Clinical image of Case 1 showing complete resolution of lesions with PIH 6 months after topical nitrogen mustard on the right inframammary fold.



She attempted high-potency topical corticosteroids, topical tacrolimus, and a combination of amitriptyline, ketamine, and lidocaine patch 5% without relief. A 12-week course of topical imiquimod 5% cream to the inframammary folds was discontinued due to progression of cutaneous disease. She experienced significant irritation from brachytherapy to her vulvar lesions.

She was prescribed topical nitrogen mustard, or mechlorethamine 0.016% gel, to the inframammary folds daily. At 6 months' follow-up, she had complete response and clearance of disease on the inframammary folds with post-inflammatory hyperpigmentation (PIH; Figure 3). Despite complete response on topical nitrogen mustard, topical therapies were eventually discontinued due to patient's intolerance of all topical applications including petrolatum. She is being treated with hydroxyurea for her CMML.

Case 2

An 85-year-old woman presented in dermatologic consultation for a pruritic eruption of 9 years' duration. Physical examination showed crusted red-brown papules on her bilateral axillae (Figure 4), inframammary folds, inguinal folds, and left vulva.

A punch biopsy from the left popliteal fossa showed a dense superficial dermal polymorphous infiltrate composed of small lymphocytes, histiocytes, and numerous eosinophils. Immunohistochemical studies showed positivity for CD1a and CD4, and negative for langerin, S100, and CD68. Evaluation for systemic disease including brain MRI was negative. The final diagnosis was of LCH, limited to cutaneous involvement.

FIGURE 4. Clinical presentation of Case 2 showing small crusted red-brown papules on the left axilla.

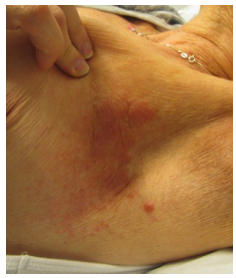
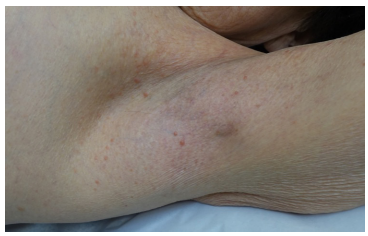


FIGURE 5. Clinical image of case 2 two years after topical nitrogen mustard therapy. Resolution of lesions with mild PIH and few small papules.



She was prescribed topical corticosteroids and topical imiquimod 5% cream without relief. She was initiated on topical nitrogen mustard therapy, or mechlorethamine 0.016% gel daily to affected lesions. She experienced complete response; all large nodules in her bilateral axilla and inguinal folds resolved completely with mild PIH (Figure 5). At 2 years' follow-up, patient's cutaneous LCH remained in remission. She was eventually maintained on triamcinolone 0.01% cream to her axilla and inframammary folds as needed for itch.

DISCUSSION

Topical nitrogen mustard therapy, an alkylating agent that induces breaks in DNA, has traditionally been used for treatment of limited-stage mycosis fungoides and cutaneous T-cell lymphoma.[1] There is a paucity of data to guide management of adult patients with unisystem LCH, particularly disease limited to the skin.[1,3] While systemic treatments are more varied, options for topical therapies typically include topical corticosteroids or topical imiquimod.[1,5,7] The data on topical nitrogen mustard as treatment for primary cutaneous LCH in adults is limited to 5 known cases in the literature.[8-11] In these cases, patients had clearance within an average of 2 to 3 weeks. Therapy was well-tolerated, with limited short-term side effects including hyperpigmentation and mild to moderate allergic contact dermatitis.[8-11]

Our two cases support topical nitrogen mustard as a possible treatment for primary cutaneous LCH recalcitrant to other treatment modalities, inducing complete response of lesions in a rapid manner. In our two cases, patients experienced com-

plete response of cutaneous LCH with PIH and mild irritation at 6-month and 2-year follow-up, respectively. In the first case, the patient eventually became intolerant to all topical therapies, including petrolatum in all affected areas even in areas not treated with topical nitrogen mustard. She also developed CMML. Interestingly, patients with cutaneous LCH have been observed to develop secondary hematologic malignancies in small cohort studies.[3] In the second case, our patient experienced complete response and remission.

The literature on the short-term effects of topical nitrogen mustard therapy is inconsistent, ranging from mild hypopigmentation or hyperpigmentation to urticarial, bullous reactions, and severe allergic contact dermatitis in treated adults.[6,8,12,13] Long-term side effects have not been well-studied. There is concern regarding increased incidence of epithelial skin cancer in patients treated with topical nitrogen mustard for mycosis fungoides.[12] Moreover, a possible carcinogenic effect has been observed in animal models.[14] Long-term outcomes remain to be studied. The literature is scant regarding mitigation of allergic or irritant contact dermatitis from topical nitrogen mustard, but dilution with water, concomitant use of topical corticosteroids, and desensitization may help minimize side effects.[5,6] In conclusion, our cases support the use of topical nitrogen mustard as a possible treatment for primary cutaneous LCH with positive responses that may spare patients from requiring systemic immunosuppressive treatments.

DISCLOSURES

The authors have no conflicts of interest to report.

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