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BRIEF REPORT

Topical Mechlorethamine for the Treatment of Psoriasis: A Report of Two Cases and Literature Review

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ABSTRACT

Introduction: Psoriasis is a common inflammatory skin disease that significantly impacts patients' psychosocial wellbeing. Despite increasingly effective treatment options, the recurrence of plaques after discontinuation of therapy in many patients highlights the need for additional therapies.

Methods: We report two cases of patients with concurrent psoriasis and mycosis fungoides who were treated with topical mechlorethamine (MCH). A literature review was performed by searching PubMed using the keywords *psoriasis, mechlorethamine, chlormethine,* and *nitrogen mustard*.

Results: Both patients had significant improvement in their psoriasis following treatment with topical MCH gel, which was well tolerated and maintained clearance after 1 and 3 years of follow-up. Seven prospective cohort studies investigating the use of topical MCH were identified through literature review. Out of five studies reporting clinical outcomes by patient, 68 of 77 patients (88%) experienced an improvement in their psoriasis, with 47 of 77 (61%) achieving complete or near-complete clearance. The remaining two studies reported clinical outcomes by lesion, demonstrating improvement in 40 of 45 lesions (88%) and complete or near-complete clearance in 32 of 42 lesions (76%). Contact dermatitis was the most frequent adverse effect, observed in 56 of 125 patients (45%).

Conclusions: Topical MCH may be an option for patients with psoriasis who fail or have incomplete responses to other treatments. Published studies are limited by lack of standardized treatment regimens and well-defined outcome measures, highlighting the need for prospective clinical trials to better understand the utility of this topical agent in psoriasis.

Keywords: Chlormethine; Cutaneous T-cell lymphoma; Mechlorethamine; Mycosis fungoides; Nitrogen mustard; Psoriasis

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Key Summary Points

Why carry out this study?

Psoriasis can be challenging to treat, and many patients on long-term therapy never achieve complete clearance of their psoriatic lesions. Topical mechlorethamine is an alkylating agent commonly used to treat mycosis fungoides, a disease that has overlapping clinical, pathological, and immunological features with psoriasis.

The aim of this study was to present two cases of psoriasis treated with topical mechlorethamine and review clinical evidence regarding the use of this topical agent in psoriasis.

What was learned from the study?

In two patients with concurrent psoriasis and mycosis fungoides, topical mechlorethamine was well tolerated and maintained clearance of psoriatic lesions after 1 and 3 years of follow-up.

Considering its mechanism of action and limited clinical data, topical mechlorethamine may be used to treat psoriasis and warrants further investigation with prospective clinical trials.

INTRODUCTION

Although significant advancements have been made in developing targeted therapeutics for psoriasis, a large proportion of patients never achieve long-term, complete disease resolution on even the most effective biologic [1], and disease recurrence is common. Topical mechlorethamine (MCH) is an alkylating agent that has been widely used to treat mycosis fungoides (MF) for over 50 years. Given its mechanism of action as a DNA crosslinking agent, we hypothesized that topical MCH would be an effective treatment for psoriasis, which responds favorably to other DNA crosslinking treatment modalities such as psoralen ultraviolet A phototherapy [2]. Here, we share our experience successfully treating psoriasis with MCH gel in individuals with concurrent MF. These cases prompted us to review the clinical evidence demonstrating the efficacy of topical MCH in psoriasis, explore mechanistic similarities between psoriasis and MF, and consider the biologic rationale for MCH use in psoriasis.

METHODS

We present two cases and conduct a PubMed literature review using the following keywords: *psoriasis, mechlorethamine, chlormethine,* and *nitrogen mustard*. Studies were included if topical MCH monotherapy was used for psoriasis treatment. Studies unavailable in English were excluded. There were no date restrictions. For each study, the following information was extracted: MCH strength and application schedule, clinical response, number of patients achieving clear or almost clear skin, response duration, number of patients who developed contact dermatitis, and number of patients who discontinued use of topical MCH due to contact dermatitis. Given that all included studies were published prior to the widespread use of standardized outcome measures, such as Psoriasis Area and Severity Index (PASI), clinical response was defined as any improvement in psoriatic lesions with the use of topical MCH. The two patients whose cases are described in this study provided informed consent according to protocols approved by the Columbia University Irving Medical Center Institutional Review Board.

RESULTS

Report of Cases

Case 1

A 70-year-old man with a 50-year history of plaque psoriasis and psoriatic arthritis was referred to us after skin biopsy of a plaque

unresponsive to his usual psoriasis treatments showed MF. His past psoriasis treatments included tar preparations, corticosteroids, calcipotriene, and phototherapy. He used etanercept and then infliximab for several years until he developed *Pseudomonas* bacteremia and pneumonia while on infliximab. His biologic therapy was discontinued out of concern for increased risk of infection. His psoriasis was moderately controlled on topical corticosteroids at the time of presentation to us. Physical examination revealed two types of lesions. First, he had well-demarcated, erythematous plaques with silver scale typical of psoriasis located on the elbows, knees, and bilateral lower legs involving 7% total body surface area (TBSA) with a PASI score of 5.8. He also had patches and thick plaques in a bathing trunk distribution involving < 10% TBSA, consistent with stage IA MF.

After discussing multiple treatment options, the patient elected to begin therapy with commercially available 0.016% MCH gel. He was instructed to use MCH to the entire body surface from the neck down three times weekly with increasing frequency as tolerated. Full-body application is commonly recommended in our practice for MF patients as this method of application may prevent relapses and/or treat patches that are not easily appreciated on clinical examination, a phenomenon well known as "invisible MF" [3]. The patient experienced significant improvement within a few months, with near-complete response of both his MF and psoriatic lesions by one year, achieving a 75% reduction in PASI score (Fig. 1). He discontinued topical corticosteroids shortly after MCH initiation and did not increase the frequency of MCH application more than three times weekly as he had a favorable clinical response on this regimen. Full-body application was used for 4 months until clinical improvement was achieved; thereafter topical MCH was applied only to residual affected areas. His response was maintained on three-times-weekly application of MCH for 3 years of follow-up.

Case 2

A 74-year-old man with a 3-year history of stage IA MF with < 1% TBSA involvement presented to a clinic for evaluation of a new-onset rash. On physical examination, he had sharply demarcated, erythematous plaques with silver scale on the extensor elbows and knees, nail pitting, and sharply demarcated palmoplantar keratoderma clinically consistent with psoriasis involving 5% TBSA with a PASI score of 4.0. He had thin erythematous patches on the right lower thigh and popliteal fossa comprising 0.9% TBSA consistent with MF. Topical clobetasol, urea cream, and apremilast led to modest improvement of his psoriatic plaques and no

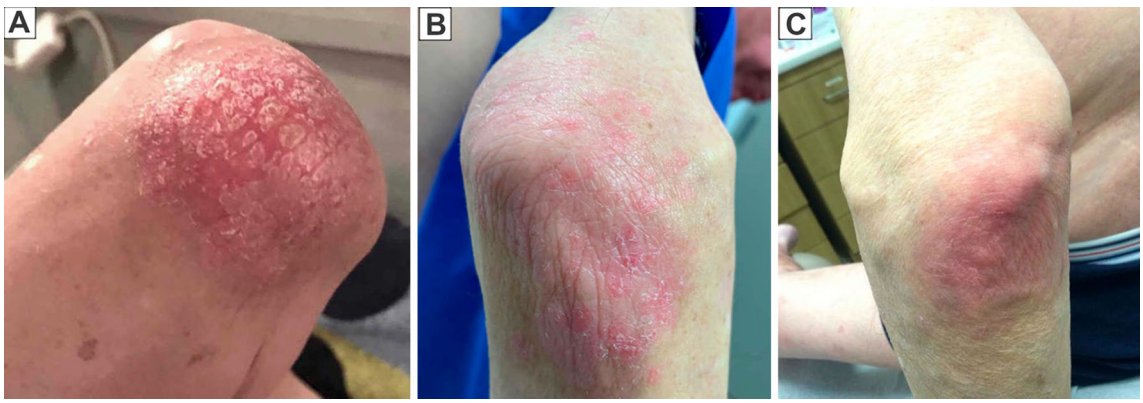

Fig. 1 Clinical images at baseline and following initiation of topical mechlorethamine in case 1. **A** An erythematous plaque with silver scale on the elbow is seen at baseline. **B** Marked improvement in the erythema and scale is seen after 11 months of treatment. **C** Complete response with residual erythema is seen at 17 months

improvement of his keratoderma. The patient was concerned about the safety of using other systemic therapies due to his MF, and his insurance did not cover phototherapy. He agreed to begin topical, commercially available 0.016% MCH gel. Application of topical MCH to the body surface area neck-down including to palms and soles three times weekly led to improvement of both his psoriatic plaques and keratoderma after 2 months. Upon clinical improvement, he applied topical MCH only to residual affected areas and had nearly complete resolution by 6 months with a 90% reduction in PASI score. His response was maintained for 1 year of follow-up with weekly application of MCH gel (Fig. 2).

Literature Review: Efficacy of Topical MCH in Psoriasis

Seven prospective cohort studies investigating the use of topical MCH in psoriasis were included [4–10] (Table 1). Clinical outcomes were either reported by patient or by lesion. Among five studies reporting by patient, 68/77 (88%) experienced improvement in their psoriasis and 47/77 (61%) achieved complete or almost complete clearance, which was maintained for 1–77 months on maintenance therapy and 0 to > 10 months after treatment discontinuation. Two studies reported clinical outcomes by lesion: 40/45 lesions (88%) improved, and 32/42 lesions (76%) had complete or almost

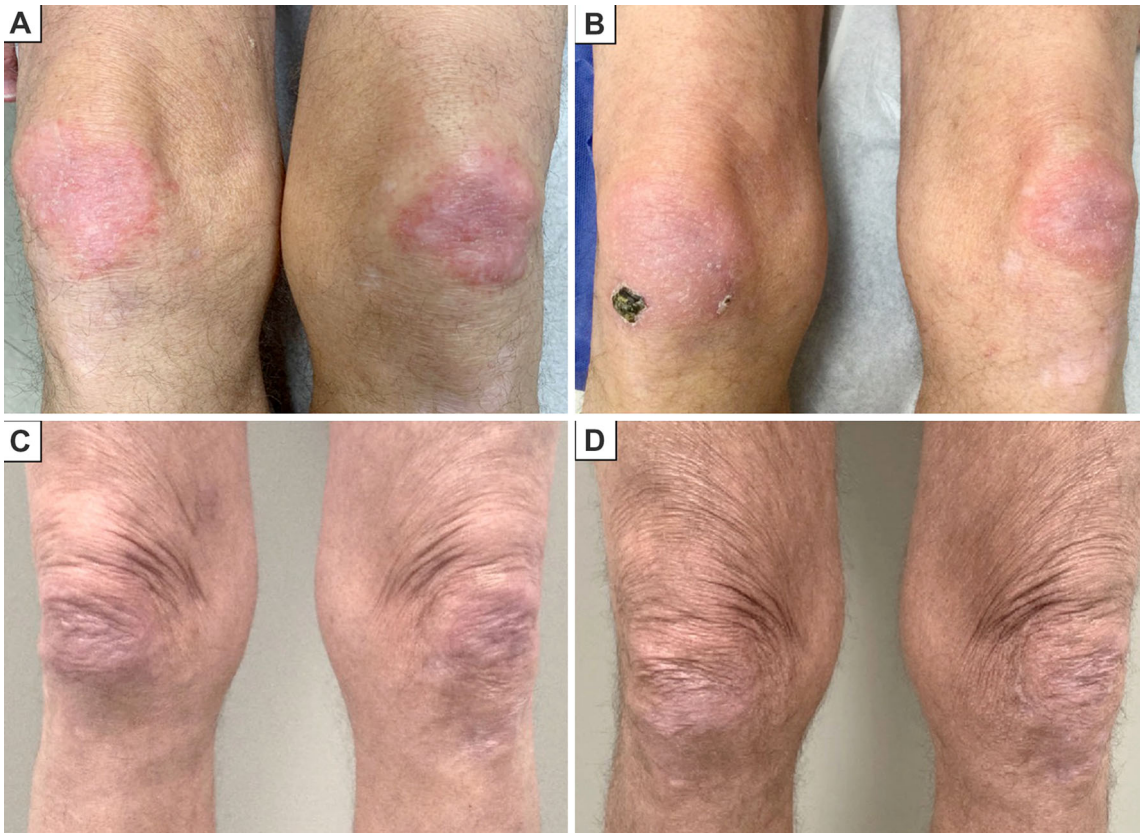

Fig. 2 Clinical images at baseline and following initiation of topical mechlorethamine in case 2. **A** Sharply demarcated erythematous plaques are seen on the bilateral knees. **B** Improvement in the scale and texture is seen by 2 months of treatment. **C** Almost complete clearance is seen by 5 months. **D** Clinical response is maintained at 10 months

Table 1 Studies investigating the use of topical mechlorethamine in psoriasis

Study	No. of patients	Strength[a]	Application schedule	Clinical response[b]	Clear or almost clear	RD after treatment discontinuation or on maintenance[c]	No. of patients with CD (%)	No. of patients with treatment discontinuation due to CD (%)
Van Scott et al. [4]	3	0.002% to 0.025%	Single dose to 1 lesion under occlusion	3/3 (100%) lesions	Not reported	Not reported	Not reported	Not reported
Epstein et al. [5]	12	0.05%	Weekly to lesions	10/12 (83%) patients	3/10 (30%) patients	2 to > 10 months after discontinuation	9/12 (75%)	6/12 (50%)
Mandy et al. [6]	7	0.02%	Once daily to lesions	7/7 (100%) patients	7/7 (100%) patients	1–5 months on maintenance	1/7 (14%)	0/7 (0%)
Zackheim et al. [7]	42	0.0125%, 0.025% and 0.05%	Once daily to up to 4 lesions	37/42 (88%) lesions	32/42 (76%) lesions	0–6 months after discontinuation	23/42 (55%)	Not reported
Purdy [8]	29	0.02%	Once daily to lesions	27/29 (93%) patients	27/29 (93%) patients	2–16 months on maintenance	10/35 (29%)	4/35 (43%)
Price [9]	10	0.00001% to 0.01%	Once daily to lesions	9/10 (90%) patients	2/10 (20%) patients	6–38 weeks on maintenance	7/10 (70%)	Patients with CD discontinued MCH per protocol
Handler et al. [10]	19	0.02%	No consistent posology reported	15/19 (79%) patients	8/19 (42%) patients	4–77 months on maintenance	6/19 (32%)	6/19 (32%)

CD contact dermatitis, *MCH* mechlorethamine, *RD* response duration

[a]w/v in aqueous solution

[b]Clinical response was defined as any improvement in psoriatic lesions with the use of topical MCH

[c]Maintenance therapy regimens were heterogeneous among and within studies. In general, the least frequent application schedule that allowed the patient to remain clear was used as maintenance, ranging from daily to once every 6 weeks

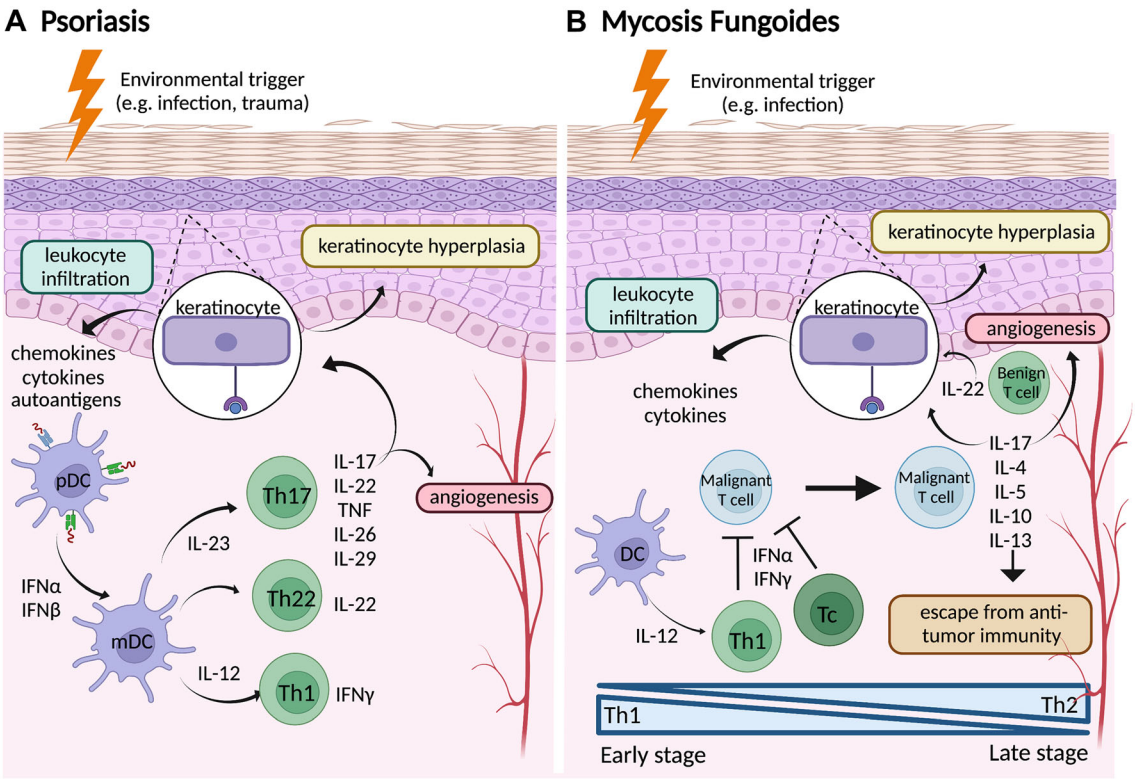

Fig. 3 Similarities and pertinent differences in the mechanisms driving psoriasis and mycosis fungoides (MF). **A** In psoriasis, autoantigens, including self-nucleotides bound to antimicrobial peptides released from keratinocytes, stimulate plasmacytoid dendritic cells (pDC) to produce interferons (IFN) that activate myeloid dendritic cells (mDC). mDCs secrete IL-12 and IL-23, which drives the development and proliferation of T helper 17 (Th17), T helper 22 (Th22), and T helper 1 (Th1) cells. Numerous inflammatory cytokines are produced, including IL-17, which binds to receptors on keratinocytes and activates an inflammatory feed-forward cycle that leads to upregulation of chemokines, cytokines, autoantigens, and angiogenic factors. IL-22 promotes keratinocyte hyperplasia. **B** In MF, the early stage of disease is characterized by an abundance of Th1 cytokines produced from Th1 cells and cytotoxic T-cells (Tc), which act to suppress malignant T-cells. As the disease progresses, there is a shift to a Th2-dominated microenvironment, which allows tumor cells to escape from anti-tumor immunity. Some malignant T-cells upregulate IL-17, which stimulates keratinocytes to release chemokines, cytokines, and angiogenic factors. IL-22, produced by benign T-cells in the microenvironment, stimulates epidermal hyperplasia and may promote tumor invasion and metastasis. The pathogenesis of both psoriasis and MF involves chronic inflammation, T-cell activation, leukocyte infiltration, angiogenesis, and keratinocyte hyperplasia. Created with BioRender.com

complete clearance. Allergic contact dermatitis was seen in 56/125 patients (45%). The severity of contact dermatitis ranged from mild to severe but did not preclude continued use of topical MCH in many cases.

DISCUSSION

We report two cases of psoriatic plaque resolution in patients with concomitant psoriasis and mycosis fungoides who used MCH gel to treat their psoriasis. Near-complete responses were

achieved and maintained at 1 and 3 years of follow-up. The successful treatment of these patients is consistent with findings from our literature review, which revealed clinical improvement with topical MCH in most psoriasis patients. Our cases add to previous literature as our patients were treated with commercially available MCH gel, a formulation that was recently approved and is generally better tolerated than the aqueous-based MCH used in previously published studies [11]. The tolerability of MCH gel observed in our patients suggests that topical MCH should be revisited as a treatment for psoriasis now that more elegant formulations are available.

MCH, also known as nitrogen mustard, is an alkylating agent that was initially used in the 1940s as systemic chemotherapy for lymphoid malignancies. In the 1950s, topical MCH was first reported as a successful skin-directed therapy in MF [12]. Today, topical MCH is widely used to treat cutaneous T-cell lymphoma (CTCL) as a first-line agent. MCH acts by alkylating guanine residues in a manner that leads to mispairing of guanine with thymine, depurination of guanine, and intra- and inter-strand DNA crosslinking. Inter-strand crosslinking prevents separation of DNA strands during DNA replication and transcription, which ultimately causes cell-cycle arrest and apoptosis [13, 14]. Cells with rapid turnover are disproportionately affected, hence MCH's utility as a chemotherapeutic agent [15]. Data from in vitro and ex vivo studies suggest that topical MCH selectively targets malignant T-cells in MF, likely through induction of DNA damage and apoptosis [16, 17]. Interestingly, topical MCH applied to the skin of alopecia areata-affected mice selectively depletes infiltrating lymphocytes in the skin and reduces expression of pro-inflammatory cytokines [18]. This suggests topical MCH may be an effective therapy for T-cell-mediated inflammatory skin disease that works by depleting pathogenic T-cells resident in the skin.

MF shares many similarities with psoriasis: both can present with erythematous scaly plaques that can be difficult to distinguish clinically [19]. In some cases of MF, histological hallmarks such as epidermotropism may be lacking and there can be significant overlap in the histopathological features of psoriasis and MF. Patients with psoriasis may be at increased risk for developing MF [19]. Several theories postulate why this is observed, including use of carcinogenic therapies to treat psoriasis, misdiagnosis of MF as psoriasis, and chronic T-cell stimulation leading to malignant transformation [19]. The pathophysiology of both diseases is characterized by aberrant T-cell activation, chronic inflammation, leukocyte infiltration, angiogenesis, and epidermal hyperplasia (Fig. 3) [20–28]. Given the clinical, pathological, and immunologic overlap between psoriasis and MF, and the efficacy of topical MCH in MF, it is conceivable that MCH could have similar favorable effects in psoriasis via apoptosis of pathogenic T-cells and/or hyperproliferative keratinocytes.

A key challenge of treating psoriasis is the tendency for psoriatic plaques to recur in the same anatomic locations as previously cleared plaques. This is likely due to a population of tissue-resident memory T-cells that remain within resolved psoriatic lesions, primed to drive local inflammation upon exposure to the appropriate trigger for recurrence [29]. Skin-resident memory T-cells may be derived from the expanded population of disease-initiating T-cells in psoriasis [29], suggesting that depletion of these cells may be required for long-term disease control. If topical MCH indeed functions by inducing apoptosis of pathogenic T-cells in psoriasis, this mechanism may allow MCH to have long-lasting effects on psoriatic lesions, consistent with the responses we observed in our patients. MCH may be an ideal topical agent for stubborn plaques that recur with other treatments.

In our literature review, the most common adverse effect reported with topical MCH was allergic contact dermatitis. However, all included studies utilized aqueous-based MCH preparations, which are associated with higher rates of allergic contact dermatitis than ointment- or gel-based formulations [11]. Strategies to minimize local cutaneous reactions to MCH include decreased application frequency and concomitant topical corticosteroid use [11].

MCH gel was well tolerated by our patients using a three-times-weekly regimen.

Topical MCH has a well-characterized safety profile. Its long-term use was studied in the pivotal 201 study, a randomized controlled safety and efficacy study of 260 MF patients who used 0.02% MCH gel or ointment once daily for up to 12 months [12]. The most common side effects reported were contact dermatitis, pruritus, erythema, skin hyperpigmentation, and folliculitis. There were no drug-related serious adverse events. Similarly, a retrospective cohort analysis of 203 MF patients treated with topical nitrogen mustard reported no serious adverse events; side effects were mainly skin-limited [30]. Immediate hypersensitivity reactions to topical MCH have been reported but appear to be exceedingly rare [31–33]; treatment discontinuation is recommended in these cases. If patients experience symptoms of anaphylaxis, urgent medical evaluation is warranted.

Systemic absorption of topical MCH was evaluated in 31 patients from the pivotal 201 study and an open-label extension study. Most of these patients used topical MCH daily, with 8/31 using full-body application and many applying the product to skin with a compromised barrier (e.g., erosions). Bioanalytic assays performed on serum from patients before and after application of MCH gel at different time points showed no detectable blood level of MCH in any patient, including those who had been on treatment for 6 months. Hematologic and serum chemistries showed no abnormal trends throughout the 12-month treatment period [12, 34]. These findings suggest negligible systemic absorption of topical MCH, even with application to large body surfaces over a period of several months.

There is a paucity of data on the risk of developing non-melanoma skin cancer (NMSC) due to topical MCH. Only one study that has evaluated the rate of NMSC development with topical MCH monotherapy; among 203 patients, the rate of NMSC was reported to be low at 1.4% [30]. The notion that topical nitrogen mustard is associated with an increased risk of NMSC comes from observational and retrospective cohort studies performed in the 1980s [35–37]. These studies examined NMSC rates in patients who used topical MCH in the context of prior treatments known to be carcinogenic, including local radiotherapy, total skin electron beam therapy, PUVA phototherapy, systemic methotrexate, and systemic alkylating agents. Further studies are needed to investigate the relationship between topical MCH and NMSC development, and patients using this therapy should undergo regular skin cancer screening examinations.

LIMITATIONS

This study is limited by the lack of standardization among reported treatment regimens and limited information regarding baseline demographics and psoriasis severity. The results of the literature review should be interpreted with caution as the outcome measures were heterogenous between studies and did not rely on well-defined endpoint criteria. Further, the included studies were unblinded and observational in nature. The relatively small number of patients may limit the generalizability of these findings.

CONCLUSIONS

We report the successful use of topical MCH for the treatment of psoriatic lesions in two patients with both psoriasis and MF. Several small cohort studies demonstrate favorable clinical outcomes with the use of topical MCH in psoriasis. Further studies, including prospective clinical trials, are required to better understand the clinical effects of topical MCH in psoriasis.

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Compliance with Ethics Guidelines. The patients described in this study provided informed consent according to protocols approved by the Columbia University Irving Medical Center Institutional Review Board.

Data Availability. Consent to publish clinical images in Figs. 1 and 2 was obtained from patients. Figure 3 was created with BioRender.com and a publication license is available upon request.

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