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CASE REPORT

Revisiting Imiquimod for Treatment of Folliculotropic Mycosis Fungoides: A Case Report and Review of the Literature

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ABSTRACT

Folliculotropic mycosis fungoides (FMF) is an aggressive variant of mycosis fungoides (MF) characterized by infiltration of the hair follicle epithelium by neoplastic T cells. FMF demonstrates poor response rates to standard skin-directed therapies such as phototherapy and topical corticosteroids. Imiquimod, an immunomodulatory agent that stimulates the antitumor immune response, has been used successfully in treatment of early-stage MF. We report a 21-year-old patient with unilesional FMF who achieved clinical remission with imiquimod application. This case highlights a potential for use of imiquimod as a treatment option for patients with FMF and limited skin involvement.

Keywords: Folliculotropic mycosis fungoides; Imiquimod; Toll-like receptor 7 agonist

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INTRODUCTION

Mycosis fungoides (MF) is the most common variant of cutaneous T cell lymphoma (CTCL) and is primarily characterized by the proliferation of neoplastic $CD4^+$ T cells in the skin [1]. Early-stage MF presents as patches and plaques that may progress to a more advanced stage with tumors, blood, lymph node or visceral involvement [2]. Several skin-directed therapies (SDTs), including topical corticosteroids, phototherapy, mechlorethamine gel, and topical retinoids, are commonly used in the treatment of early-stage MF [3–5].

Folliculotropic MF (FMF) is an aggressive subtype of MF with distinct histopathological features demonstrating the infiltration of the pilosebaceous unit with atypical $CD4^+$ T cells. Clinically, it has variable presentations and can frequently involve the scalp and face, areas spared in classic MF [6, 7]. Folliculotropic mycosis fungoides is associated with worse prognosis than conventional MF and has a poor 5-year overall survival rate [6, 8, 9]. More importantly, it has often been difficult to treat FMF patients with the standard SDTs used in classic MF, with many patients being refractory to initial treatments and requiring systemic medications earlier [6, 8]. It is proposed that the deep extension of lymphocytes into the follicular units may limit the response to superficial therapies such as phototherapy and topical corticosteroids [8, 10].

Imiquimod, a topical immune modulator that activates toll-like receptor 7 (TLR7), has demonstrated therapeutic benefit in small case series of MF patients [11–19]. When applied on MF lesional skin, it often creates erosions or ulcerations, presumably by triggering an exuberant immune response with significant depth [12, 14, 17]. Thus, the inflammatory response triggered by imiquimod may be of sufficient depth to target the deeper folliculotropic lymphocytes in FMF. Herein, we present the case of a young female with a single FMF lesion whom we successfully treated with topical imiquimod application. Informed consent for publication was obtained from all patients for whom identifying information is included in this article.

CASE

A 21-year-old female patient initially presented to our cutaneous lymphoma clinic after histopathology findings of a single persistent lesion on the breast were concerning for MF. The lesion had been present for approximately one year despite three months of treatment with topical corticosteroids; it was pruritic but not painful. Physical examination revealed a pink 1.5-cm indurated plaque with mild surrounding erythema on the left anteromedial breast. The patient had no other lesions and no lymphadenopathy. Histopathology review revealed atypical $CD4^+$ lymphocytes infiltrating the follicular epithelium, consistent with FMF (Fig. 1a, b). Immunohistochemistry analysis showed predominantly $CD3^+$ $CD4^+$ T cells (Fig. 1c) with an increase in CD4/CD8 ratio. Peripheral blood flow cytometric analysis revealed no abnormal cell populations.

Topical steroid was discontinued, and treatment with daily topical 5% imiquimod was started. One month after therapy, the patient presented with an indurated plaque with shallow erosions and reported some application-site irritation and pruritus. After another month of treatment, shallow ulcerations developed at the site (Fig. 2a). At this visit, imiquimod therapy was discontinued. One month after imiquimod discontinuation, the plaque had completely resolved, leaving an atrophic pink patch without scale (Fig. 2b). There was no reappearance of the lesion on follow-up five months after imiquimod discontinuation.

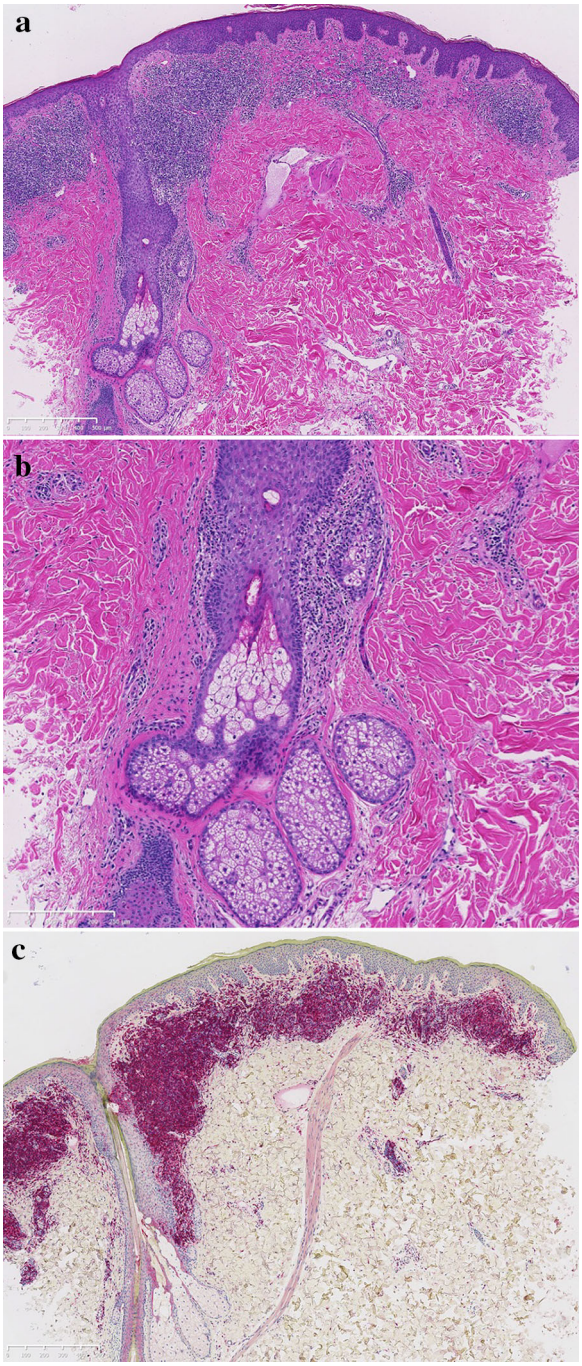

Fig. 1 **a**, **b** Atypical $CD4^+$ lymphocytes infiltrating the dermis (**a**; H&E, 40 ×) and follicular epithelium (**b** H&E, 100×). **c** Immunohistochemistry analysis showing predominantly $CD4^+$ T cells in the infiltrate (CD4 stain, 40×)

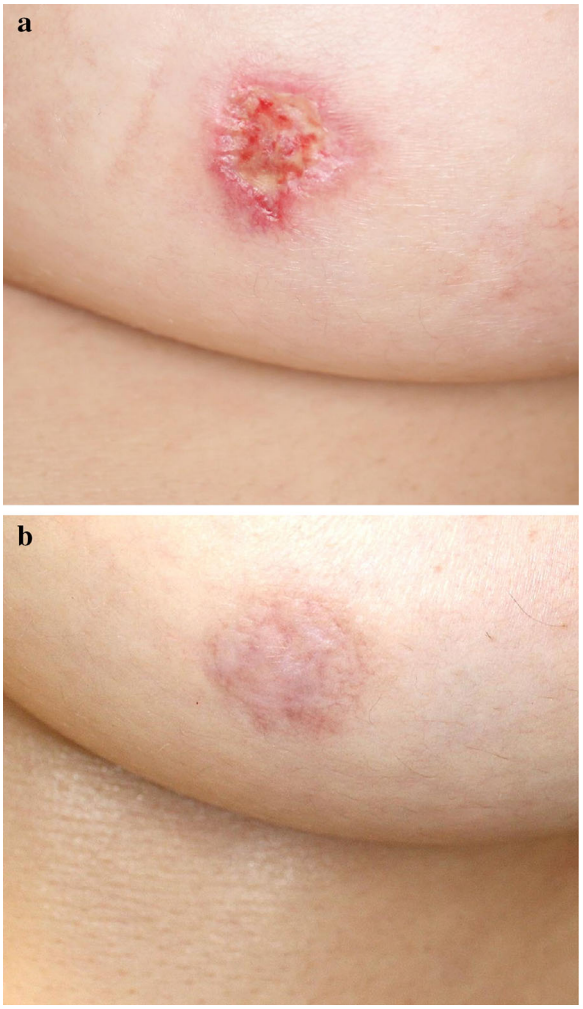

Fig. 2 **a** Shallow ulceration with surrounding erythema on left breast after two months of imiquimod therapy. **b** Atrophic pink patch seen one month after imiquimod therapy discontinuation

DISCUSSION

Unlike conventional MF, patients with FMF demonstrate poor response rates to SDTs. In Gerami et al.'s study, 13 of 43 patients with FMF received SDTs as initial therapy, including topical corticosteroids, psoralen plus ultraviolet A (PUVA), narrow-band ultraviolet B, localized irradiation, nitrogen mustard, and topical bexarotene [6]. Only three patients demonstrated a partial response (PR) or complete response (CR), with two of these patients requiring localized irradiation to achieve this effect. More importantly, patients who showed PR or CR had limited disease with less than 3% body surface area involvement. Therefore, in cases of FMF with limited skin involvement, potent SDTs may be effective. Similarly, imiquimod therapy in our patient with limited skin involvement led to an exuberant reaction and demonstrated efficacy in FMF.

Several studies indicate that the innate and cytotoxic antitumor responses in MF are dysfunctional. This is supported by reduced T-helper type 1(Th1) activity levels and proinflammatory cytokines including interferon (IFN)-α, IFN-γ, and interleukin (IL)-12 [20, 21] and a dominant T-helper type 2 (Th2) phenotype [22, 23]. FMF is a distinct entity with a similar pathogenesis, consisting of a $CD4^+$ lymphocytic infiltrate with a shift towards a Th2 environment [6]. Therefore, therapies that can promote immune activation and enhance the Th1 response can be beneficial in both MF and FMF. One example of such therapies that can be used topically is imiquimod.

Imiquimod is an immunomodulatory agent that induces TLR7 activity on plasmacytoid dendritic cells. Once activated, TLR7 signaling leads to release of proinflammatory cytokines including IFN-α, IFN-γ, and IL-12 that promote the innate immune response and shift the microenvironment to a Th1-dominant milieu [24, 25]. Subsequently, imiquimod enhances antigen presentation and cellular cytotoxicity, inducing an effective antitumor response [26]. It is likely that the exuberant skin reaction that occurred in our patient resulted from the release of imiquimod-induced proinflammatory cytokines. A subsequent increase in the antitumor immune response might have led to the resolution of her lymphoma lesion.

Several small-scale studies describe imiquimod's efficacy in early-stage MF (Table 1) [11–19, 27]. In our review of these studies, we found a total of 24 MF patients, stage IA–IIB, treated with topical imiquimod therapy. Only one patient was identified with FMF [18]. In patients who had documented clearance of treated lesions (N = 13, 54%), CR was achieved after an average of 4.3 months of imiquimod treatment. Patients who developed more severe inflammatory skin reactions were more likely to

Table 1 Cases of imiquimod therapy in mycosis fungoides

Author (year)	Patient(s) and MF presentation	Prior treatment(s)	Duration of imiquimod treatment	Adverse events (AEs)	Results
Suchin et al. (2002) [11]	52-year-old female Stage IA, one lesion on abdomen	TS, NM, and carmustine	Nightly × 4 months	Erythema, vesiculation, erosions, xerosis, pruritus during month 1 of treatment • Therapy discontinued for 2 days	Biopsy-proven CR of lesion No recurrence 10 months after therapy completion
Dummer et al. (2003) [12]	65-year-old male* Multiple lesions on face, trunk, extremities	PUVA, acitretin	Daily × 8 weeks only to facial plaques • PUVA continued on trunk and extremities	Ulceration during day 10 of treatment	CR of all facial and trunk/extremity lesions No recurrence 12 months after therapy completion
Chong et al. (2004) [13]	4 male patients, ages 39–61 years All stage IB	Not specified	Daily × 16 weeks One patient received placebo	Mild lesional irritation**	Mean decrease in surface area of 8.9% of treated lesions Mean increase in surface area of 39.9% of distant control lesions Mild improvements in erythema and lesion thickness Patient on placebo had increase in lesion thickness, surface area, and scaling
Deeths et al. (2005) [14]	2 male and 4 female patients, ages 41–79 years Stage IA (N = 3), IB (N = 2), IIB (N = 1)	None in 2 patients PUVA, NM, EB, SR, TS, IMQ, IFN, and MTX in 4 patients	3× weekly × 12 weeks on selected lesions Concurrent PUVA in 2 patients (stage IB and IIB) Concurrent IFN in 1 patient (stage IB)	Application-site irritation in 4 patients Erosion during week 3 of treatment in 1 patient Ulcer and erythema during week 3 of treatment in another patient Therapy frequency decreased in some patients	No change in 1 patient Slight improvement in 2 patients Moderate improvement in 1 patient Marked improvement in 1 patient Almost clear in 1 patient

Table 1 continued

Author (year)	Patient(s) and MF presentation	Prior treatment(s)	Duration of imiquimod treatment	Adverse events (AEs)	Results
Coors et al. (2006) [15]	4 male patients, ages 43–78 years Stage IA (N = 3), IB (N = 1)	PUVA in all patients, IFN in 2 patients, and SR in 1 patient	3–7× weekly × 8–24 weeks depending on initial response Concurrent PUVA in 1 patient Concurrent chlorambucil and prednisolone in 1 patient	Erythema, papules, and pruritus**	CR of treated lesions in 2 patients after 8 and 16 weeks of treatment PD in 1 patient No change in 1 patient
Chiam et al. (2007) [16]	32-year old male Stage 1A, penile plaque	TS	Every other day × 4–5 months	Local pain during week 1 of treatment Skin erosion during month 3 of treatment	CR of lesion No recurrence 6 months after treatment completion
Martínez-González et al. (2008) [17]	1: 70-year-old male • Stage IIB (tumor) 2: 62-year-old male • Stage IA 3: 79-year-old male • Stage IA 4: 60-year-old female*	1: TS, XRT, PUVA, IFN, NM 2: TS, PUVA 3: TS, PUVA 4: TS, nbUVB, PUVA	1: 3× weekly × 3 months 2: 3× weekly × 14 months 3: 3× weekly × 7 months 4: 3× weekly × 4 months	1: Erythema and ulcerations at month 1 2: Not specified 3: Minimal erythema 4: Intense inflammatory response during initial days	1: CR of treated lesions, CR of some nearby untreated lesions 2: CR of treated lesion; new lesion elsewhere 3: CR of treated lesions; CR 3 months after treatment completion 4: CR of treated lesion

Table 1 continued

Author (year)	Patient(s) and MF presentation	Prior treatment(s)	Duration of imiquimod treatment	Adverse events (AEs)	Results
Gordon et al. (2015) [18]	1:80-year-old female • Stage IB (folliculotropic) 2:60-year-old male • Stage IIB (tumor)	1: TS, carmustine, TR, PUVA, MTX 2: TS, nbUVB	1: 2× weekly titrated to 3× weekly × 6 months; concomitant INF therapy 2: 5 × weekly × 3 months	1: Mild erythema during initial few weeks 2: Inflammatory response during 2 months of treatment	1: CR of treated lesion; no recurrence of lesions 10 months after treatment, but new lesions elsewhere 2: CR of treated lesions; no recurrence of lesions 9 months after treatment, but new lesions elsewhere
Lewis et al. (2017) [19]	1: 68-year-old male • Stage IIB 2: 65-year-old female • Stage IIB with LCT	1: XRT, SR, NM, TS 2: SR, nbUVB	1: Nightly × 4 weeks 2: 5× weekly × 4 weeks	1: None 2: Irritation and flu-like symptoms**	1: CR of treated lesion; no recurrence of lesion 8 years after treatment; new lesions elsewhere 2: CR of treated lesion; no recurrence 2 years after treatment

PUVA psoralen plus ultraviolet A light, *NM* nitrogen mustard, *EB* electron beam, *SR* systemic retinoids, *TS* topical steroids, *IMQ* imiquimod, *IFN* interferon, *MTX* methotrexate, *TR* topical retinoids, *nbUVB* narrow-band ultraviolet B phototherapy, *XRT* radiation, *LCT* large cell transformation, *PD* progressive disease

*Staging not specified

**Timing of AE not specified

achieve clearance of their lymphoma lesions. We did not notice an association between time to CR with imiquimod and number of prior treatments or presence of simultaneous treatments. Interestingly, in one case, imiquimod treatment potentiated the patient's response to PUVA [12]. As expected, the most commonly reported adverse events were skin reactions including erythema, erosions, and ulcerations at the site of application.

CONCLUSIONS

Our patient with FMF who failed to respond to topical steroid treatment achieved CR after 2 months of imiquimod therapy. Given the tendency of FMF to resist SDTs, the rapid response to imiquimod observed in this case supports the unique role of topical imiquimod as an early treatment agent for FMF subtype with limited skin involvement. Overall, these findings highlight the need for large-scale studies to evaluate efficacy of imiquimod in treatment of MF and FMF.

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