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CASE SERIES

Multidisciplinary and personalized approach to the management of mycosis fungoides with chlormethine gel: a collection of clinical experiences

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Abstract

Topical chlormethine (CL) gel formulation was approved by the EMA in 2017 for the treatment of adult patients with mycosis fungoides (MF). To expand the knowledge on the management of MF, this paper provides an overview of clinical practice evidence about the MF diagnostic phase and a collection of clinical experiences to better characterize the use of CL gel in daily practice. Collected cases underline the importance of the concomitant biopsy and clinical evaluation in the diagnostic phase, with the contribution of a multidisciplinary team, and support the use of CL gel as a first-line or adjuvant treatment in selected patients.

Keywords: chlormethine gel, cutaneous T cell lymphoma, mycosis fungoides.

Citation

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Introduction

Mycosis fungoides (MF) is the most frequent sub-type of primary cutaneous T cell lymphoma, accounting for up to 65% of all cutaneous lymphomas.[1–3] MF in its classic form is defined by cutaneous red scaly patches, which can evolve over time to raised plaques and tumours.[4,5] Histologically, the MF cellular infiltrate consists of small-to-medium-sized atypical clonal T cells with convoluted, cerebriform nuclei often showing epidermotropic features.[4,5] The World Health Organization (WHO) lymphoma classification recognizes three MF variants other than the classic form, as follows: the folliculotropic MF, the pagetoid reticulosis (Woringer–Kolopp disease) and the granulomatous slack skin.[6] In contrast to classic MF, which presents in the patch and plaque stage with a 5-year survival rate of more than 90%, the folliculotropic variant has an impaired outcome with 5-year survival rates of ~60%.[7,8] The staging of MF is based on the 2007 TNMB revision and comprises four stages (I–IV) based on the extent of skin involvement and the presence of cancer cells in other organs.[9,10] IA, IB and IIA are considered early stages, whereas stages IIB, III and IV are classified as late-stage disease.

MF can be challenging to diagnose because its early symptoms resemble other skin conditions such as eczema or psoriasis, and a skin biopsy is often necessary for the integration of clinical and histopathological data

for a definitive diagnosis, which should include phenotype characterization and molecular analysis.[11–13] This can lead to a diagnosis delay and, consequently, to delayed treatment, which is mainly based on the stage and extent of the disease.[11] Treatment options for MF may include topical treatments, phototherapy (light therapy), radiation therapy and, in some cases, targeted or systemic therapies like chemotherapy.[1] In selected patients, allogeneic stem cell transplantation may be considered as a possible curative option in patients with advanced stages (IIB–IV), adequate control of the disease manifestations and an available donor,[11,14] with reported long-term survival in the range of 30–40% of cases.[15,16]

Early-stage disease is often managed with less aggressive topical therapies such as corticosteroids, retinoids (bexarotene), topical chemotherapy (chlormethine (CL)) or topical immunomodulators (imiquimod).[1] Recent developments in skin-directed treatments include optimizing the use of existing topical therapies, the introduction of dermatological agents and treatment modalities for the specific treatment of MF (such as CL gel, calcineurin inhibitor creams and photodynamic therapy), and novel local and topical agents.[17] Amongst these options, topical CL is currently recommended by the European Organization for Research and Treatment of Cancer (EORTC; level 2 recommendation), the National Comprehensive Cancer Network (NCCN; level 2A recommendation) and all major national guidelines as a first-line treatment for early-stage disease.[1,10,18,19] In particular, in 2013, a multicentre phase II, randomized, blinded study (201 study) demonstrated the non-inferiority of the 0.02% CL gel formulation compared with 0.02% CL ointment in terms of both safety and efficacy in patients with persistent or recurrent stage IA-IB or IIA MF.[20] As in previous literature evidence, no detectable systemic absorption of the drug was reported.[20,21] According to this evidence, the 0.02% CL gel formulation was approved by the FDA in 2013 and by the EMA in 2017 for the treatment of adult patients with MF and is now commercially available in several European countries.

In recent years, clinicians have developed effective protocols that allow for flexibility in CL gel treatment regimens in daily practice, and sometimes also concomitant use of topical corticosteroids and systemic therapies to increase patient adherence/compliance and prevent premature treatment discontinuation.[22–24]

To provide additional knowledge on the management of patients with MF, an overview of clinical practice evidence about the MF diagnostic phase is provided. Moreover, to better characterize the use of CL gel in daily practice, a collection of clinical experiences is presented. Collected cases underline the importance of the concomitant biopsy and clinical evaluation in the diagnostic phase, with the contribution of a multidisciplinary team (pathologist, dermatologist, haematologist) and the tailored approach to the management of MF. In this context, the multidisciplinary team plays a crucial role in the prompt diagnosis of the disease, which in turn has an impact on disease course and progression.

Mycosis fungoides: the diagnostic challenge

A correct MF diagnosis is crucial in defining therapeutic strategies and management but this goal requires a multidisciplinary approach with the close cooperation of different experts (dermatologist, pathologist, molecular biologist, haematologist and radiologist).

MF must be differentiated from benign and malignant conditions showing similar clinicopathological features. Several T cell lymphoma sub-types may show epidermotropic infiltrates, including, in particular, primary cutaneous γδ T cell lymphoma, cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T cell lymphoma, cutaneous $CD30^+$ lymphoproliferative disorders (including lymphomatoid papulosis and anaplastic $CD30^+$ large cell lymphoma), peripheral T cell lymphoma not otherwise specified, skin localization of an extranodal natural killer/T cell lymphoma nasal type, Sezary syndrome and cases of adult T cell leukaemia/lymphoma, the latter especially in countries endemic for human T-lymphotropic virus (HTLV1).[2,5,25] MF must also be distinguished from numerous benign inflammatory or reactive conditions, including atopic dermatitis, chronic eczematous dermatitis, psoriasis, lichenoid keratosis, lichen sclerosus and many others.

Different papers and guidelines dealing with major clinicopathological criteria for MF diagnosis have been published.[1,14,26] Nevertheless, the MF diagnosis is still challenging, particularly in its early phase; a histological examination of the lesional skin biopsy is mandatory.[26] Pathological features of MF, especially in early stages, include the presence of atypical T cells, often epidermotropic, with cerebriform, hyperchromatic nuclei, individual haloed atypical T cells scattered within the epidermis, alignment of single atypical T cells along the dermal–epidermal junction, fibrosis of the papillary dermis, and a band-like infiltrate in the dermis.[27] In some cases, atypical T cells in the epidermis may be the major pathological features but, in others, epidermotropism and nuclear atypia are not relevant. However, a variable degree of nuclear atypia of infiltrating lymphocytes as well as epidermotropism of single lymphocytes may also be observed in various benign inflammatory disorders. On such a basis, the role of the haematopathologist is crucial in favouring the correct diagnosis.

Immunohistochemical analysis also contributes to MF diagnosis despite the lack of specific tumour markers for MF cells.[28] MF lymphoma cells usually have a memory T-helper phenotype and express CD3 and CD4 but $CD8^+$ MF may occur more frequently in paediatric patients; a minority of MF cases may exhibit a cytotoxic phenotype (in these cases, other cytotoxic lymphomas must be ruled out). The loss of pan-T cell markers (CD3, CD2, CD5) in otherwise $CD4^+$ T cell skin lesional infiltrate favours an MF diagnosis. Notably, the loss of the T cell-related antigen CD7, previously retained to be sensitive and specific for MF, is now considered of limited diagnostic value because the partial loss of CD7 has been observed in various benign inflammatory T cell infiltrates.[29]

The assessment of T cell receptor (TCR) clonality by polymerase chain reaction (PCR) relies on the length determination of the most abundant PCR product, assumed to represent the predominant TCR clone. As in other T cell lymphoma, the demonstration of a clonal T cell rearrangement is relevant in corroborating the diagnosis of MF. However, clonality results should be carefully evaluated by expert molecular biologists and always correlated within the clinicopathological context. Indeed, TCR clonality by PCR can also be detected in some cases of benign inflammatory disorders. In this regard, the crucial role of the pre-analytical phase must be stressed. Very frequently, patients suspected of early MF receive small 'punch' biopsies in which neoplastic cells often account for as few as 5–10% of the entire T cell population. Recently, various groups have introduced high-throughput next-generation sequencing (NGS) to enhance the detection of malignant T cell clones in cutaneous T cell lymphoma, including MF.[30] Zimmerman et al. reported an increased specificity and sensitivity in the detection of T cell clonality in cutaneous T cell lymphoma by means of NGS technique.[31] Although would take a long time to implement NGS in all clinical facilities, NGS could prove a very useful diagnostic tool for early MF in the near future. However, despite the above-mentioned limitations, an accurate MF diagnosis requires that all skin lesions showing a lymphoid cellular infiltrate with epidermotropic features in the lymphoid population must undergo phenotypic and molecular characterization, including the search for Ebstein–Barr virus by *in situ* hybridization for differential diagnosis purpose. Such investigation should be coupled with proper clinical information, including lesional features, to provide for the correct diagnosis.

Clinical cases

Patients and methods

The authors retrospectively selected and reported clinical experiences related to patients treated with 0.02% CL gel as monotherapy or in addition to other concomitant therapeutic regimens. Clinical cases were selected to address the use of CL gel in patients with early-stage and late-stage disease in clinical practice. Inclusion criteria were age ≥18 years and, where applicable, an indication of treatment with CL gel based on the summary of product characteristics, current guidelines and physician judgment. Treatment response was evaluated according to EORTC criteria for complete response (CR; 100% improvement), partial response (PR; 50% to <100% reduction of the lesion from the baseline), stable disease (SD; <50% reduction of the lesion from the baseline) and progressive disease (PD; at least a 20% increase in the diameters of target lesions).[20] Due to the retrospective description of these clinical experiences, treatment regimens were not standardized. Data collection was conducted following the ethical principles of the revised version of the Declaration of Helsinki. The retrospective review of patient data was notified to the Ethics Committee of participating centres when required. In all cases, patients provided informed consent to treatment and anonymous publication of clinical data.

Eight clinical cases of patients with MF treated with CL gel are presented in the following paragraphs. Cases were related to the early-stage treatment (five cases) and late-stage treatment (three cases). The main demographic and clinical characteristics of patients treated with CL gel are presented in Table 1; a detailed description of each case is reported in the following paragraphs.

Management of early-stage MF

Case 1

A 58-year-old female patient presented with a diagnosis of stage IB follicular MF dating back to 2009. The disease had a diffuse presentation with follicular and granulomatous plaque lesions. The patient had been treated with intralesional steroids, topical steroids and phototherapy in cycles with good response but continuous relapses.

Since 2015, the patient experienced further clinical deterioration, with widespread plaque-infiltrated lesions. The patient started the therapy with low-dose oral bexarotene (225 mg/die) associated with seasonal phototherapy and radiotherapy on more infiltrated lesions, achieving stabilization of the disease.

As of June 2021, the patient was in therapy with bexarotene 75 mg (three tablets daily) for the treatment of plaques in the right buttock, calf and right plantar region (Figure 1). The patient was prescribed CL gel with application three times a week as topical monotherapy without any irritative or adverse reaction. In September 2021, hyperpigmented lesions were reported on the calf,

Table 1. Main demographic and clinical characteristics of patients

Case	Sex	Age (years)	Time from diagnosis	Disease stage	CL gel therapy modality	Therapeutic scheme
Early-stage disease						
1	Female	58	15 years	IB	Combined with oral bexarotene	Three-times a week
2	Female	50	9 years	IA	Monotherapy	Alternate days
3	Female	82	18 months	IA	Combined with mometasone furoate	Three-times a week
4	Male	35	5 years	IA	Combined with clobetasol	Alternate days
5	Male	58	15 years	IIA	Combined with clobetasol	Alternate days
Late-stage disease						
6	Female	38	7 years	IIB	Monotherapy on resistant areas	Single administration for 40 days, then alternate administration with clobetasol cream
7	Male	20	3 years	IIB	Combined with bexarotene/ clobetasol	Once every 3 days following an irritative reaction
8	Female	31	6 years	IIA	Combined with clobetasol	Every 3 days

plantar region and buttock (Figure 1). In April 2022, complete resolution of hyperpigmentation in the calf and plantar region was reported, with persistence of the lesion at the level of the buttock (Figure 1). The patient discontinued the use of bexarotene and continued treatment with CL gel. In August 2022, complete resolution of the treated lesions was reported. The patient discontinued therapy; at the last follow-up (February 2024), clinical remission of the disease persisted.

Case 2

A 50-year-old woman was diagnosed with epidermotropic $CD4^+CD8^+$ T cell lymphoma (MF) following a skin biopsy in 2015. The patient underwent a few cycles of phototherapy with narrowband UVB (nb-UVB), with discrete disease control. Subsequently, in 2022, the patient underwent a course of phototherapy with UVA without psoralen, reporting a marked improvement in the skin picture. At the follow-up visit in December 2022, erythematous-desquamative lesions of poikilodermal appearance were reported in the buttock area, extending towards the perianal region, as well as in the bilateral axillary, right breast and groin area (Figure 2A). CL gel monotherapy on alternate days was then initiated in December 2022. As of January 2023, a CR to treatment was observed (Figure 2B).

Case 3

An 82-year-old female patient featuring a stage IA MF presented with some patches on the trunk and one poikilodermal patch on the mammary region, with itching. Staging procedures showed a disease limited to the skin involving less than 10% of the body surface area. Treatment with CL gel in monotherapy three times a week was started in November 2022. After 2 months of therapy, an erythematous-crusted patch appeared on the mammalian area, and a diagnosis of CL-related irritative contact dermatitis was made. CL gel was temporarily discontinued (Figure 3A) for 2 weeks, whilst mild-potency class steroid (mometasone furoate) was started with a complete regression irritative area. After 2 weeks, CL gel was re-introduced for 3 days a week on alternate days with mometasone furoate. In the subsequent 2 months, a CR of the lesion on the breast was observed and it was therefore decided to discontinue CL gel application (Figure 3B).

Irritative events due to the use of CL gel can be experienced. However, it is possible to combine CL gel with corticosteroids or, if it is necessary to suspend the therapy, a subsequent rechallenge is possible, maybe reducing the frequency of administration.

Case 4

A 35-year-old male patient with a previous diagnosis of atopic dermatitis was diagnosed with stage IA MF (Figure 4A). The patient reported widespread injuries on his neck, face, armpits, back, and legs and was prescribed CL gel in March 2019, with daily applications on the neck and armpits. After 1 month, the patient developed

Figure 1. Case 1. A. Plaques in the right buttock (upper line) and right plantar region (lower line; T0). B. Plaques after 3 months of treatment with CL gel, the lesions appear partially reduced. C. After 12 months of treatment with CL gel, the lesions resolved with mild hyperpigmentation.

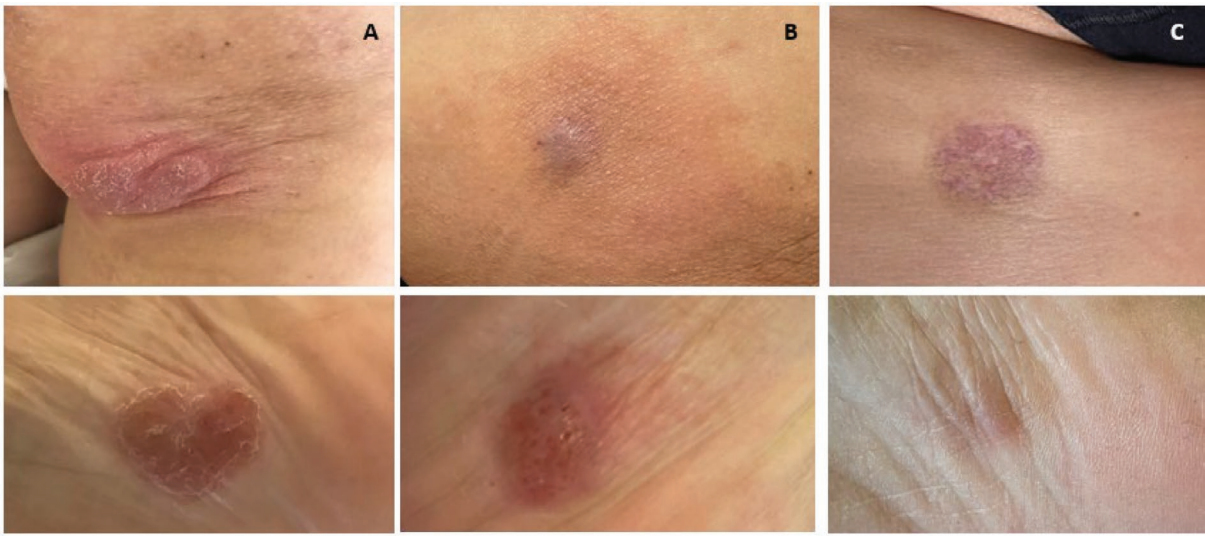


Figure 2. Case 2. A. Erythemato-desquamative lesions of poikilodermal appearance in December 2022. B. Complete clinical regression of the lesions after 1 month from the start of CL gel therapy.

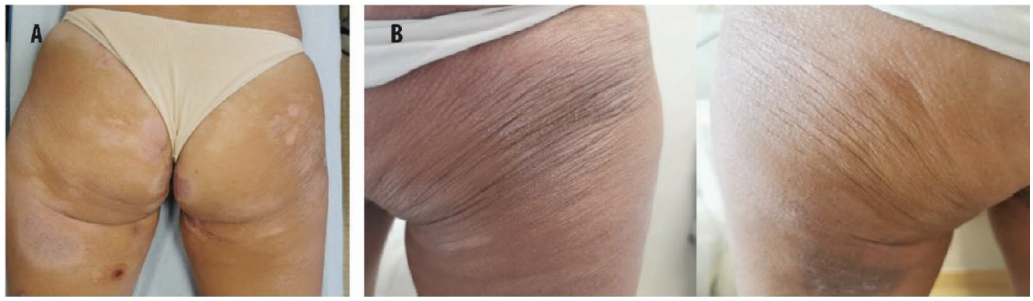
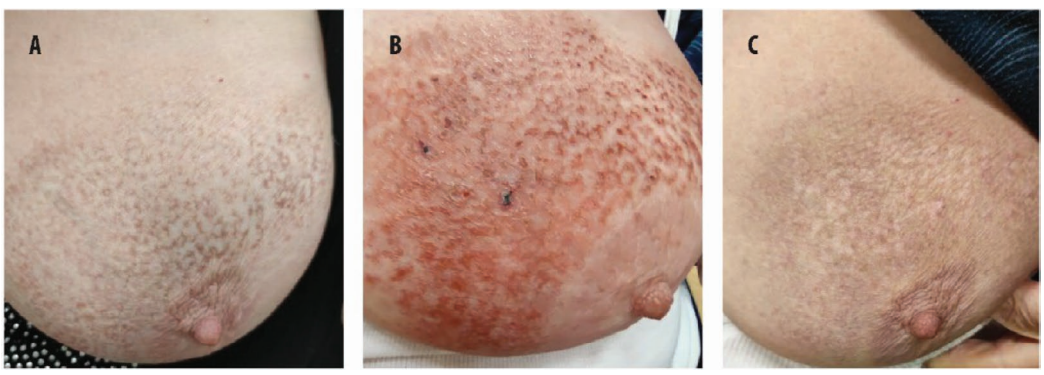


Figure 3. Case 3. A and B. Erythematous-crusted patch in the mammary region. C. After 2 months from the start of CL gel therapy.



itching, dermatitis and severe xerosis. The patient had been well-educated regarding possible local side-effects. Therapy was discontinued, and once the irritation resolved, it was resumed in combination with local steroids (clobetasol) every other day. After 2 months with this therapeutic regimen, a clinical response of the lesions was observed, and after a further 3 months of follow-up, a CR was achieved (Figure 4B). This case report suggests that CL gel is indicated in MF in the early stages, regardless of the extent of the lesions and the affected body surface area. Despite the application in sensitive areas, the skin reaction was limited and easily managed by the patient himself. In addition, the combination of topical steroids with CL gel can improve its tolerability and, therefore, adherence to therapy.

Case 5

A 58-year-old male patient presented with MF histologically diagnosed in 2009 and pretreated with numerous cycles of phototherapy nb-UVB, acitretin and topical corticosteroids with partial response. During the last follow-up, the patient showed erythematous desquamative patches on the scrotum, skin of the penis and intergluteal fold (Figure 5). Treatment with CL gel every other day in combination with topical clobetasol was started in March 2023. After 15 days, due to a skin reaction, the application of CL gel was reduced to 3 days a week. The patient reported complete clinical remission of the treated lesions 2 months after the start of therapy, maintained to date on the scrotum, skin of the penis and intergluteal fold (8 months after the treatment suspension).

Management of late-stage MF

Case 6

A 38-year-old female patient was diagnosed with severe atopic dermatitis in 2013, which was treated with several lines of therapy (steroid, azathioprine, cyclosporine in cycles since 2015, omalizumab). In 2017, the patient was diagnosed with erythrodermic MF with minimal blood involvement (absolute lymphocyte count 1440/μL, 23.5% $CD4^+CD7^-CD26^-$). The patient was sequentially treated with extracorporeal photopheresis, IFNα, gemcitabine and alemtuzumab, with a good – though not complete – final response. In 2018, the patient underwent allogeneic stem cell transplantation from an HLA-identical sister after reduced intensity conditioning according to the fludarabine–melphalan scheme. Prophylaxis of graft versus host disease included antithymocyte immuno-

Figure 4. Case 4. A. Dermatitis and severe xerosis localized on right armpit. B. Clinical response after 2 months from the start of CL gel therapy.

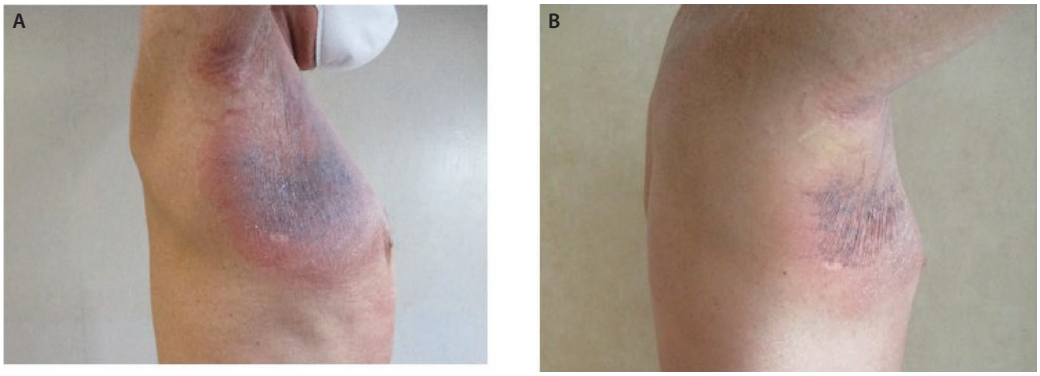
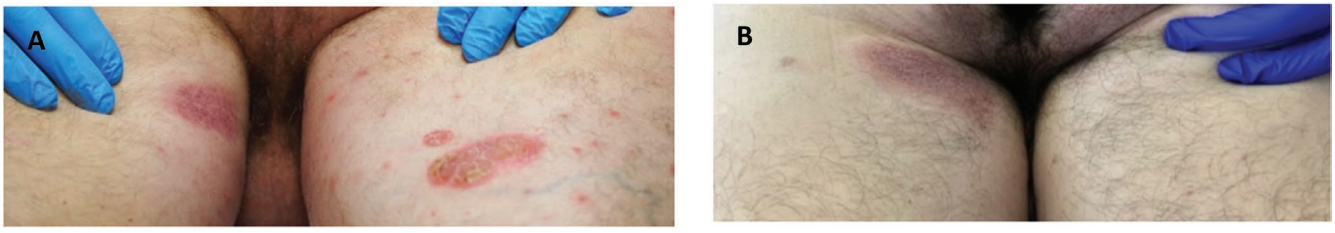


Figure 5. Case 5. A. Erythematous-desquamative patches on the posterior surface of the thighs. B. Clinical response 8 months after the treatment suspension with pigmentary outcomes.



globulins, cyclosporine and mycophenolate. In May 2019, cutaneous progression of the disease was observed, documented with a cutaneous punch (Figure 6). In the context of a well-structured multidisciplinary follow-up, the patient underwent total skin electron beam irradiation for a total of 24 Gy and, in September 2019, achieved complete clinical remission. In April 2020, small patches and erythematous papules reappeared, mainly located on the thighs, hips and upper limbs. The patient started therapy with CL gel, with the improvement of some lesions. In July 2021, CL gel was suspended, and the patient was treated with 24 sessions of nb-UVB followed by 16 sessions of localized nb-UVB for persistence of lesions on the feet. In April 2022, CL gel was resumed.

At the last follow-up visit (February 2023) there was only a persistence of a small, thickened plaque lesion in the right ankle and plantar region. Treatment with CL gel was continued for 40 days, then alternating it with clobetasol cream.

Case 7

A 20-year-old male patient was diagnosed with folliculotropic MF stage IIB with a Modified Severity-Weighted Assessment Tool score of 46 at diagnosis. The patient presented with multiple patches with areas of alopecia on the hair, armpits, and lower limbs and a plaque/nodule on the back (diameter of ~20 cm) and involvement of ~30% of the body surface (Figure 7). No fever, night sweats, weight loss or other symptoms were reported. Pruritus was moderate. On physical examination, no peripheral lymphadenopathy, no hepatosplenomegaly and no other skin abnormalities were identified. Other than slightly elevated LDH and alanine aminotransferase, blood work was normal and an abnormal lymphocytic population was found in the blood (B1 stage). Skin biopsy presented with an infiltrate of small lymphoid elements with cerebriform nuclei, eosinophils, thick sub-epidermal band-like patterns, frequent Pautrier abscesses in the epidermis, and marked tropism for follicles and eccrine glands (Figure 7C,D). Immunohistochemical stains showed that the predominant lymphocytic population was $CD3^+$ and $CD4^+$ and was negative for CD7, CD8 and CD30. The first-line therapy for this patient was oral psoralen plus UVA and pegylated interferon but, after 1 month, he had stopped his cycles due to liver toxicity. Subsequently, the patient underwent treatment with nb-UVB and oral bexarotene, first at 300 mg/day then reduced to 150 mg/day after 1 month due to hypertriglyceridaemia. Subsequently, in an attempt to improve the clinical response, treatment with a CL compound was initiated in July 2022; a PR was observed within 3 weeks. CL gel was discontinued after 4 weeks following an irritative reaction. Clobetasol cream was then initiated, with a concomitant resumption of CL gel treatment, achieving a good clinical response with a Modified Severity Weighted Assessment Tool score of 18. During the initial month of CL gel treatment, there was a notable occurrence of skin irritation. However, this issue was successfully addressed by incorporating topical steroids, adjusting the application frequency of CL gel to once every 3 days and ensuring the patient maintained proper hydration.

The difficulty in managing this case arises from the complex clinical condition, lymph node involvement and, above all, from a young age that imposes a long-term vision of the therapeutic objectives. In this case, bone marrow transplantation is a potentially successful option despite the high rates of morbidity and mortality.

Case 8

A 31-year-old female patient with a previous diagnosis of atopic dermatitis presented with MF stage IIA in 2017. The patient underwent treatment with psoralen plus

Figure 6. Case 6. A. Diffuse patches and plaque lesions at disease progression 8 months after allogeneic haematopoietic stem cell transplantation. B. Clinical CR following post-allogeneic stem cell transplantation total skin electron beam treatment. C. Small patch lesions at disease relapse 7 months after total skin electron beam, treated with CL gel. D. Residual plaque lesion still under treatment with CL gel at the last follow-up.

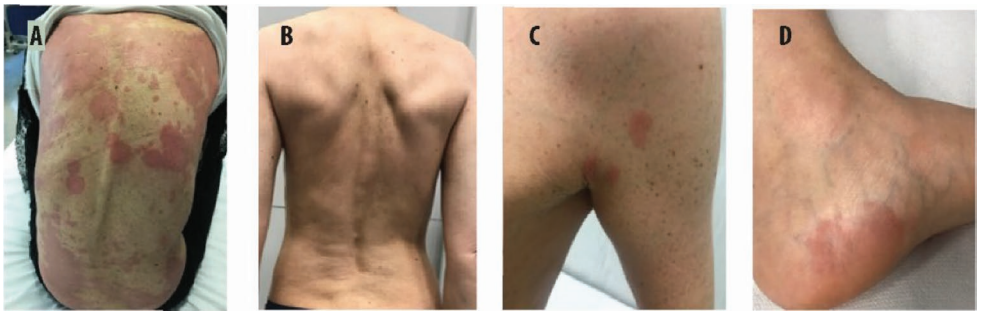
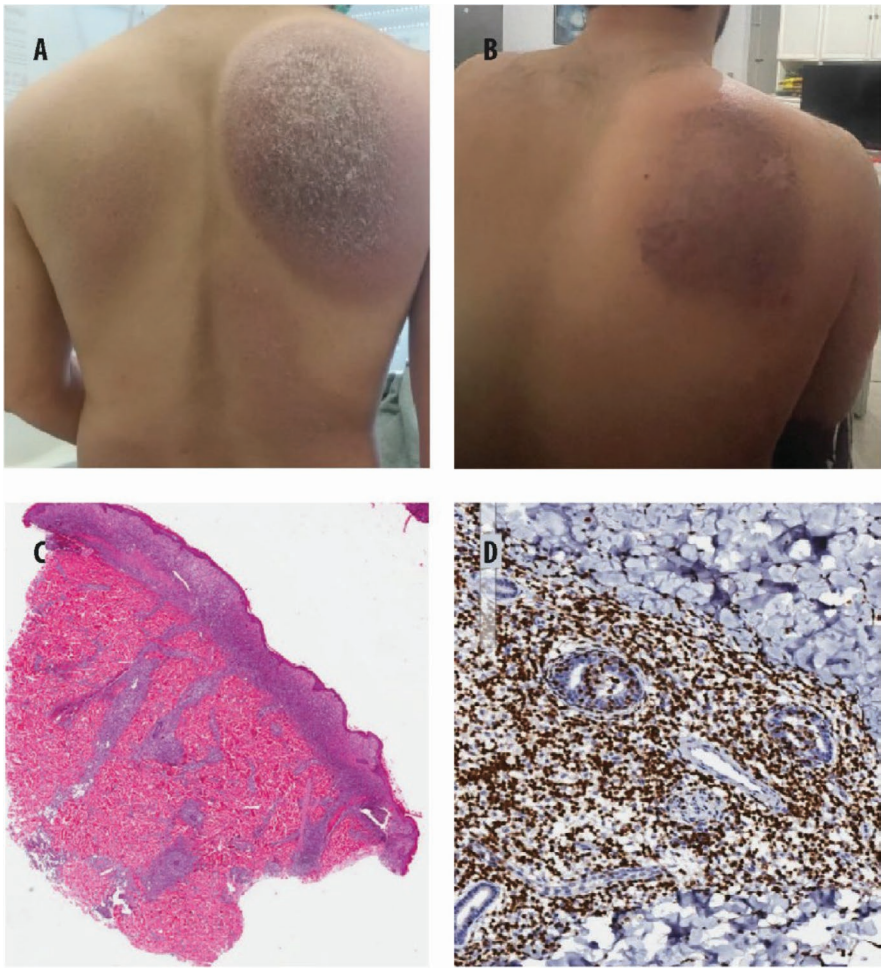


Figure 7. Case 7. A. First clinical presentation. B. After 7 months from the start of CL gel therapy. C and D. Lymphoproliferative process characterized by a lymphoid infiltrate of small elements with cerebriform nuclei with a thick subepidermal band-like pattern (C) and frequent Pautrier abscesses (D).

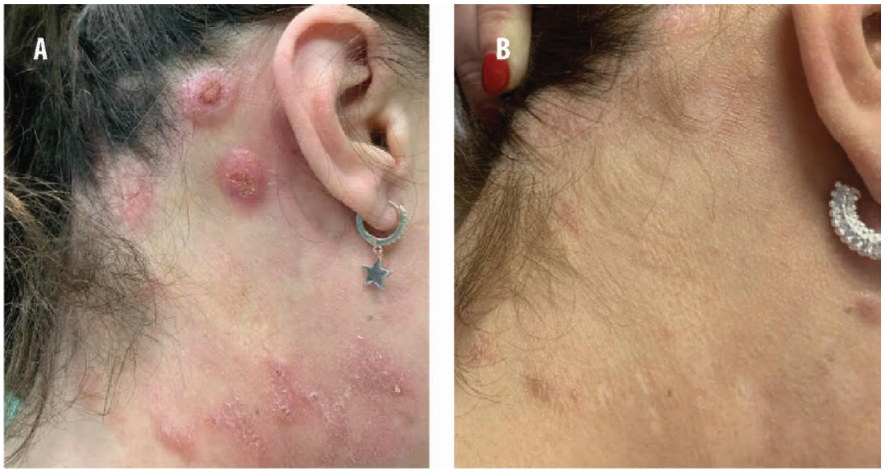


UVA therapy, bexarotene and methotrexate, yet due to rapid progression of the disease, treatment was intensified with brentuximab vedotin and low-dose total skin electron beam radiotherapy followed by allogeneic stem cell transplantation with complete disease response. After 6 months from stem cell transplantation, the patient relapsed with more indolent disease, and in the following years, she was treated with a second course of low-dose total skin electron beam radiotherapy, brentuximab vedotin and nivolumab. In July 2022, due to $CD30^-$ disease progression under brentuximab treatment, the patient was treated with mogamulizumab associated with low-dose radiotherapy on isolated nodules. Due to the recurrence of nodular lesions, in May 2023, CL gel was introduced to treat the right retro-auricular region, a left zygomatic nodule, and a plaque located at the right breast (Figure 8). CL gel was administered in combination with local steroids (clobetasol cream) every other day. The patient reported a worsening of the skin condition in the absence of symptoms 15 days after the start of CL on the right retro-auricular area and left zygomatic nodule and resolved to withdraw the treatment for 1 week. After resuming CL gel alternated with topical clobetasol every other day, a PR was observed within 3 months, ongoing to date after 8 months of treatment.

Discussion

Management of MF requires a multidisciplinary approach for a correct diagnosis, considering that different benign and malignant diseases as well as numerous inflammatory or reactive conditions present with similar clinicopathological features. Mostly in the early phase, a histological examination of the lesional skin biopsy is mandatory,[26] and immunohistochemical analysis can also contribute to MF diagnosis. Lastly, the assessment of TCR clonality by PCR, when required, should be carefully evaluated by an expert molecular biologist.

Figure 8. Case 8. A. Erythematous nodules and patches on the right retro-auricular area. B. 8 months after the treatment with CL gel.



The treatment goals of MF are focused on controlling symptoms, achieving remission and preserving quality of life. CL gel is a topical formulation recommended as a first-line treatment for early-stage MF thanks to its proven efficacy in inducing clinical responses and improving symptoms.[1,10,18–20] Despite its increasing use in clinical practice, there is still a paucity of real-world data regarding the clinical experiences with CL gel therapy for MF, especially with regard to the possibility of using combined therapeutic schemes to increase patient adherence.[32]

With this collection of clinical experiences, we aim to contribute to the existing literature by sharing real-practice experiences focusing on the multidisciplinary and personalized approach to MF management. In particular, the collected clinical experiences addressed the use of CL gel in early-stage and late-stage disease. Overall, our findings support the use of CL gel as an effective and tolerated treatment option for all patients with MF, regardless of the stage. The fast and high response rates observed in our case series are consistent with previous clinical trials and real-world studies evaluating CL gel in MF.[20,22,23,32–38]

Collected experiences show that the topical formulation offers several advantages, including localized delivery, reduced systemic exposure and convenience of self-administration, making it an attractive option for patients with limited skin involvement and those who prefer non-invasive therapies, in agreement with previous real-life experiences. The favourable safety profile of CL gel further enhances its utility, particularly in patients with comorbidities and those at risk of treatment-related complications.

It is important to recognize that, due to the mechanism of action, CL gel may cause local skin reactions, which can affect treatment adherence and quality of life. Of note, local skin reactions do not affect the likelihood of response and have often been correlated with response to treatment.[24,32,39] At the same time, strategies to minimize these adverse effects, such as proper skin care, dose adjustment and supportive measures, should be implemented to optimize treatment outcomes and patient adherence. Lastly, reported cases suggest that the combination of skin-directed treatment as CL gel with systemic therapy resulted in prolonged clinical benefit in patients with the most severe disease, underlining the need for tailored treatment approaches in this difficult-to-treat population. Multidisciplinary assessment of patients is a key element in providing this personalized intervention as dermatologists, haematologists and radiotherapists were often all involved in the clinical management.

Future research efforts should focus on identifying predictive biomarkers of response to CL gel and exploring its role in combination therapies and maintenance regimens. Overall, our clinical experiences underscore the importance of personalized treatment approaches and shared decision-making in the management of MF, considering patient preferences, disease characteristics, treatment goals and risk-benefit considerations.

Conclusions

CL gel represents a valuable therapeutic option for patients with MF, offering high response rates, a favourable safety profile and convenient topical

administration. Our case series highlights the real-world experiences and outcomes associated with CL gel therapy in MF, supporting its use as a first-line or adjuvant treatment in selected patients. Further research is warranted to optimize treatment protocols, refine response criteria and address unanswered questions regarding the long-term efficacy and tolerability of this treatment.

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