

# Ultra-high-frequency Ultrasound in the Objective Assessment of Chlormethine Gel Efficacy: A Case Report

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## ABSTRACT

Mycosis fungoides (MF) represent the most frequent form of cutaneous T-cell lymphoma (CTCL). Chlormethine gel has been approved as first-line therapy in MF. The classification of early forms of MF is clinically and histologically complex even for experienced clinicians. Ultra-high-frequency ultrasound (UHFUS) is a new non-invasive method that is capable of supporting clinical evaluation, thus providing both a diagnostic guide for distinguishing different stages of the disease and a therapeutic method in terms of monitoring the treatment. In our case report, we clinically and ultrasonographically evaluated the efficacy of chlormethine gel treatment on patches resistant to previous local treatments. A 63-year-old patient was treated for MF stage 1B with cycles of topical clobetasol cream and PUVA and UVB narrow-band phototherapy for 2 years, with a partial therapeutic response. Patches remained at the level of the left and right hips and lower legs. The patient began treatment with chlormethine gel 3 times a week for 2 months. We performed clinical and ultrasound evaluations on the left hip at baseline and after 2 months. The ultrasound examination was performed using (VEVO MD, VisualSonics), both in B-mode and C-mode, with a 70 MHz frequency probe. At baseline, we found a hypoechoic band of 0.94 mm named the Subepidermal Low Echogenicity Band (SLEB), localized under the dermo-epidermal junction. Multiple dilated hair follicles with vascular invasion, disrupting the dermo-epidermal junction, and numerous vascular lacunae at the dermal level were found using C-mode. After 2 months of treatment, the lesions had clinically healed with the persistence of a pigmentary outcome. UHFUS identified minimal thickness of the SLEB and minimal vascularization. Chlormethine gel was an effective and well-tolerated treatment in patches unresponsive to other topical treatments. The use of a non-invasive diagnostic technique can allow objective assessment of lesions with a better therapeutic approach.

**KEY WORDS:** cutaneous lymphoma, chlormethine gel, mycosis fungoides, non-invasive diagnostics, ultra-high-frequency ultrasound

## INTRODUCTION

Mycosis fungoides (MF) represent the most frequent form of cutaneous T-cell lymphoma (CTCL) and usually have an indolent course. In the early stages, MF clinically manifests as patches and plaques, and diagnosis may be difficult due to its similarity to inflammatory skin conditions such as eczema and

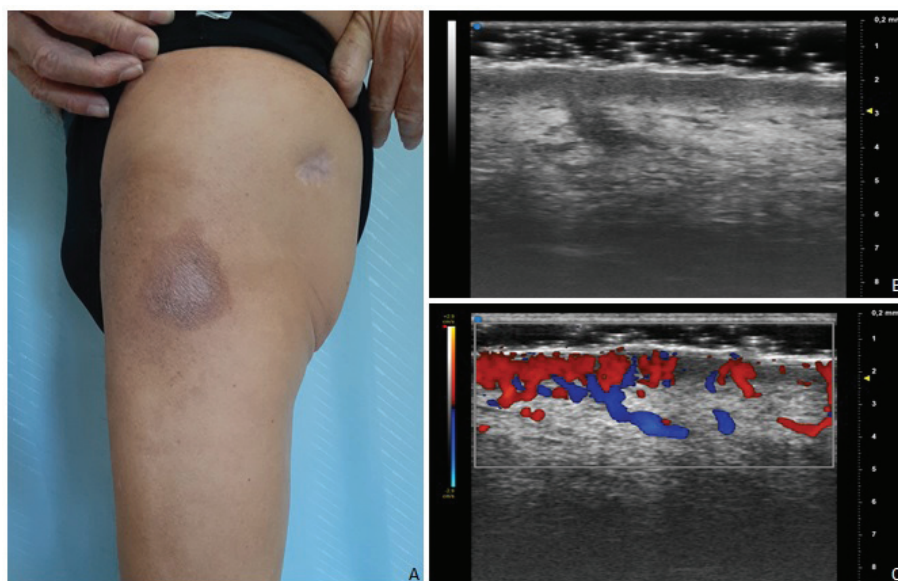
psoriasis (1). Multiple biopsies are often required for histologic and immunohistochemical confirmation, and the diagnostic delay for early forms is about 3 years (2). In the early stages, treatment consists of skin-directed therapies such as high-potency topical corticosteroids, retinoids, PUVA therapy, and

narrowband ultraviolet B (NB-UVB) (3). In recent years, a new topical therapy has been developed. Chlormethine gel was approved by the Food and Drug Administration (FDA) in 2013 and by the European Medicines Agency (EMA) in 2017 as first-line therapy for MF in adult patients. In advanced stages, this treatment can be associated with systemic therapies, extracorporeal photopheresis, and/or bone marrow transplantation. Daily application is the recommended frequency of chlormethine gel use, although the dose can be adjusted to 2-3 times a week to reduce possible skin reactions. Discontinuation of therapy may occur for severe and long-lasting skin reactions (4). The most frequent side-effects are irritant contact dermatitis and hyperpigmentation (5). Ultra-high-frequency ultrasound (UHFUS) is a new non-invasive method that has numerous applications in the study of morphological features and pre- and post-treatment mapping of skin tumors. Unlike reflectance confocal microscopy (RCM) and optical coherence tomography (OCT), it allows a better assessment of lesion depth and therapy response (6). In our case report, we clinically and ultrasonographically evaluated the efficacy of chlormethine gel treatment on patches resistant to previous topical treatments.

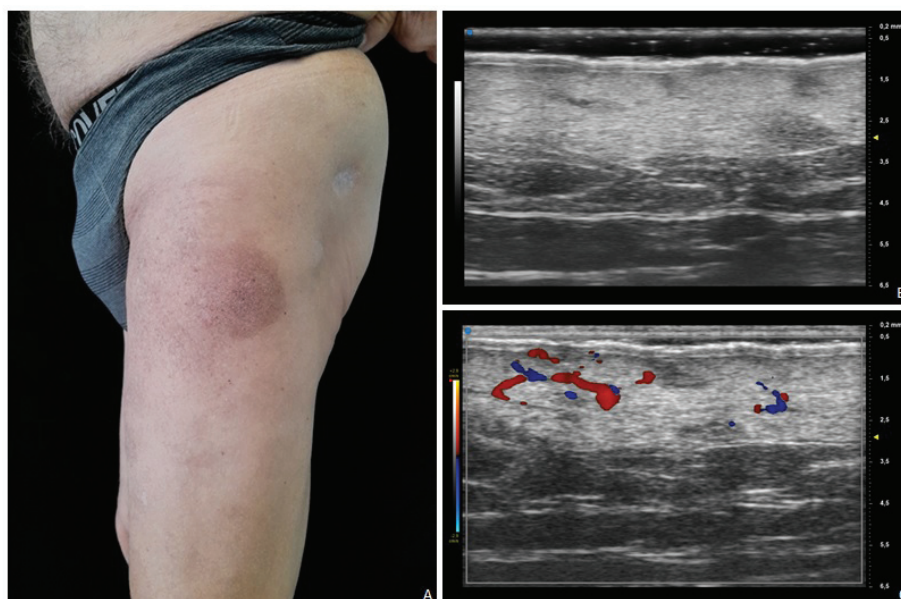
### CASE REPORT

A 63-year-old patient had been treated at our clinic since 2019 for MF stage 1B. During the initial evaluation, the patient presented with thin plaques and patches distributed across the upper and lower limbs, trunk, and back. The patient's medical history

revealed dyslipidemia, spinal arthritis, and centrofollicular Non-Hodgkin lymphoma currently in clinical remission. The MF had been previously treated with cycles of topical clobetasol cream and PUVA and NB-UVB phototherapy from 2020 for 2 years, resulting in a partial therapeutic response. Patches persisted on the left and right hips and lower legs (Figure 1, A). In September 2022, the patient initiated treatment with chlormethine gel 3 times a week for 2 months. Clobetasol cream was prescribed to reduce potential side-effects. We performed clinical and ultrasound evaluations on the left hip at baseline and after 2 months. The ultrasound examination was performed using VEVO MD, VisualSonics, FUJIFILM SonoSite, Inc., employing both B-mode and C-mode with a 70 MHz frequency linear probe, which provided an axial resolution of 30  $\mu$ m. At baseline, we observed the following: an increased thickness of the hyperechogenic layer corresponding to the stratum corneum (0.18 mm), localized between the beginning of the echo entrance and the end of the first hyperechogenic layer; a hypoechoic band of 0.94 mm referred to as the Subepidermal Low Echogeneity Band (SLEB), localized under the dermo-epidermal junction (Figure 1, B). C-mode revealed multiple dilated hair follicles with vascular invasion, disrupting the dermo-epidermal junction, and numerous vascular lacunae at the dermal level (Figure 1, C). After 2 months of treatment, the lesions clinically resolved with persistence of a pigmentary outcome (Figure 2, A). UHFUS identified the same skin layers observed at baseline: a reduced thickness of the epidermis (0.11 mm) and minimal



**Figure 1.** A) Patch on the left hip before the treatment with chlormethine gel. B) UHFUS\* B-mode examination: a hypoechoic band of 0.94 mm referred to as SLEB# localized under the dermo-epidermal junction. C) UHFUS\* C-mode examination: multiple dilated hair follicles with vascular invasion, disrupting the dermo-epidermal junction, and numerous vascular lacunae at the dermal level.



**Figure 2.** A) Pigmentary outcome after 2 months of treatment. B) UHFUS\* B-mode examination: minimal thickness of the SLEB# (0.15 mm). C) UHFUS\* C-mode examination: lower vascular invasion of hair follicles with no increase in vascular signal.

\*Ultra-high-frequency ultrasound

#Subepidermal Low Echogenicity Band

thickness of the SLEB (0.15 mm) (Figure 2, B). Lower vascular invasion of hair follicles with no increase in vascular signal in C-mode was observed (Figure 2, C). At a 4-month follow-up after treatment, there was no recurrence in the treated areas. New erythematous squamous patches at the trunk level are currently undergoing therapy with chlormethine gel.

## DISCUSSION

The classification of early forms of MF is clinically and histologically complex. The clinical distinction between patches and thin plaques as well as thick plaques and nodules is not well-defined and often proves challenging even for experienced clinicians (7). UHFUS, with its sub-millimeter resolution comparable to histology, can serve as an instrumental and noninvasive examination to support clinical evaluation. It can provide diagnostic guidance for distinguishing different stages of the disease and therapeutic assistance in monitoring the treatment. UHFUS has been used to study melanomas, establishing a correlation between Breslow (8) thickness and ultrasound measurements. It has also been applied to non-melanoma cancers for clinical characterization (9) of various subtypes and pre-and post-treatment evaluation (10). Real-life and official clinical trials have shown that chlormethine gel is an effective treatment with few side-effects and high patient tolerability (5). In our clinical case, we reported clinical and instrumental responses after 2 months with no

side-effects except transient hyperpigmentation. To our knowledge, this is the first article evaluating the efficacy of chlormethine gel in MF using UHFUS.

Chlormethine gel has proven to be an effective and well-tolerated treatment for patches that do not respond to other topical treatments. The use of a non-invasive diagnostic technique such as UHFUS can allow objective assessment of lesions and increases the likelihood of choosing the best treatment approach. Undoubtedly, further case series are necessary to evaluate the potential of this new technique in MF treatment.

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