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Case Report: Local Treatment of a *Leishmania tropica* Infection in a Syrian Child with a Novel Filmogenic Preparation of Pharmaceutical Sodium Chlorite (LeiProtect®)

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Abstract. Cutaneous leishmaniasis (CL) frequently entails chronic skin lesions that heal only slowly. Until now, the available therapeutic options are very limited. Here, we present a case of a 5½-year-old Syrian refugee with two progressive lower-leg skin ulcers caused by *Leishmania tropica*. The patient received topical treatment with LeiProtect®, a newly developed, hydroxypropylcellulose-based, filmogenic gel containing nontoxic concentrations of pharmaceutical sodium chlorite. The skin lesions completely healed within 8 weeks and did not relapse during 1 year of follow-up, underlining the efficacy of this novel local therapy of CL.

INTRODUCTION

Cutaneous leishmaniasis (CL) is a neglected tropical disease caused by different species of the protozoan parasite *Leishmania*. Infections of humans with *Leishmania* (*L.*) *tropica* are transmitted by sand flies and are highly prevalent in North Africa and the Near and Middle East. In Syria, humans form the primary reservoir for the parasite. Cases of CL in Syria have strongly increased following the massive destructions during the civil war. Consequently, CL has become a true epidemic among Syrian refugees. Clinical characteristics of cutaneous *L. tropica* infections are a variable incubation period of weeks to months, the development of nodular or ulcerative skin lesions and a long period of self-healing of up to 2 years.[1,2] Locally injected or systemically applied pentavalent antimony drugs (meglumine antimonite or sodium stibogluconate) are still the treatment of choice in endemic regions according to WHO recommendations.[3] Thermotherapy using radiofrequency waves, cryotherapy, photodynamic therapy, intravenous injection of liposomal amphotericin B, or oral application of miltefosine have also been effective in case studies or trials of *L. tropica* infections,[4–8] but require instrumentation (thermo-, cryo-, photodynamic therapy) or are much more costly (miltefosine, amphotericin) than antimonials. In contrast, therapeutic strategies that focus on sterile wound care and aim to promote the wound healing process, are inexpensive, easy to apply, and appear to be at least as effective as antiparasitic drug regimens.[9,10]

Here, we present a case of ulcerative CL in a Syrian child following *L. tropica* infection that was successfully treated with a novel filmogenic gel containing pharmaceutical sodium chlorite.

CASE PRESENTATION

In autumn 2017, an otherwise healthy 4-year-old boy, living in the Syrian district of Aleppo, developed two nodular, reddish lesions on the lateral and dorsal side of his left lower leg following insect bites. A general practitioner diagnosed CL without histological or laboratory analyses and perilesionally injected one dose of an antimonial drug. Thereafter, the lesions remained untreated for 20 months, until the child and his parents, after staying in various refugee camps in Syria and Lebanon, arrived as asylum seekers in Germany in July 2019. From August to November 2019, a practicing dermatologist saw the boy and sequentially treated the two skin lesions, which in the meantime had ulcerated, with topical antiseptics (clioquinol), antibiotics (fusidic acid), and steroids (triamcinolone, betamethasone) as well as with oral amoxicillin. As these therapies were unsuccessful, the boy was referred to our Department of Dermatology. On admission, the child had a 2×2 cm and a 1.5×1.5 cm ulcer on the lateral and the dorsal side of the left calf, respectively. As a bacterial superinfection was suspected, topical treatment with fusidic acid and polyhexanide and a 7-day-course of oral cefuroxime (2×250 mg/day) were initiated. Two punch biopsies were taken. Histopathological analysis revealed a chronic granulomatous inflammation of the skin including multinucleated giant cells, notably in the adipose tissue. The parasitological analysis yielded a positive 18S *Leishmania* rRNA gene-based real-time PCR (c_t value 27.1) and the growth of *L. tropica* in modified Schneider's insect cell medium as described.[11] The grown *Leishmania* promastigotes were identified as *L. tropica* using *Leishmania* cytochrome b sequencing.[11]

On January 10, 2020, local therapy with LeiProtect® containing *sodium* (*Na-*)*chlorosum* was started after detailed instructions of the parents.

- *Na-chlorosum*, formerly listed as DAC N-055 in the German Drug Codex,[12] is a pharmaceutical form of sodium chlorite

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that was prepared in a two-stage process, the chemical details of which will described in detail elsewhere. Briefly, in step 1, chlorine dioxide gas (ClO_2) was generated using the well-established peroxodisulfate-chlorite route. In step 2, ClO_2 reacted with an alkaline solution of hydrogen peroxide, yielding chlorite and molecular oxygen as main products. The obtained stock solution of *Na-chlorosum* contained up to 1 M chlorite and very low levels of chlorate and chloride (~10–20 mM, all anion concentrations determined by ion chromatography [IC]). Ultraviolet (UV) vis and Raman spectroscopy revealed that *Na-chlorosum* did not contain significant residual concentrations of the two reactants ClO_2 or H_2O_2. Using cyclic voltammetry chlorite was the only detectable redox-active species.

- The LeiProtect gel was prepared with hydroxypropylcellulose (Klucel GF®, Caelo, Hilden, Germany), gum Arabic (Caelo), poloxamer 407 (Caelo), propane-1,2-diol (Caelo), water for injection (prepared under GMP-conditions in the university hospital pharmacy, Erlangen) and *Na-chlorosum* (final chlorite concentration: 10 mM), using a Conti-TDS 1 mixing and dispersing machine (Ystral GmbH, Ballrechten-Dottingen, Germany). The gel (lot no. H080219.1) was allowed to degas spontaneously, was aliquoted in 10 mL syringes and then stored at 4°C. Ion chromatography chromatograms confirmed the expected chlorite content and the stability of chlorite within the gel for at least 1 year with only minimal chlorate formation (~0.2 mM). The LeiProtect gel, for which the nonprofit organization *Waisenmedizin e.V.* (Freiburg, Germany) holds a license, has been approved by the *German Federal Institute for Drugs and Medical Devices* (BfArM, Bonn, Germany) according to §11 of the German Medical Device Regulation. The approval is temporary (currently prolonged until September 30, 2021) and so far only valid for the treatment of CL within Germany.

Following initial wound disinfection with polyhexanide, a thin layer of the LeiProtect gel (0.15–0.3 mL gel) was applied to each of the two ulcers using gloved fingers and allowed to form a dry film (~20 minutes). Every day, a new layer of gel was gently spread on the layer of the previous day. After 7 days, the accumulated film was carefully removed with 70% ethanol- or polyhexanide-soaked cotton wool swabs, without disrupting the newly formed epithelial cell layers. The daily application of LeiProtect was then restarted until wound closure. To ascertain the correct application of the gel by the parents, the treatment was carried out during the first week in our day-care clinic. Thereafter, the patient was

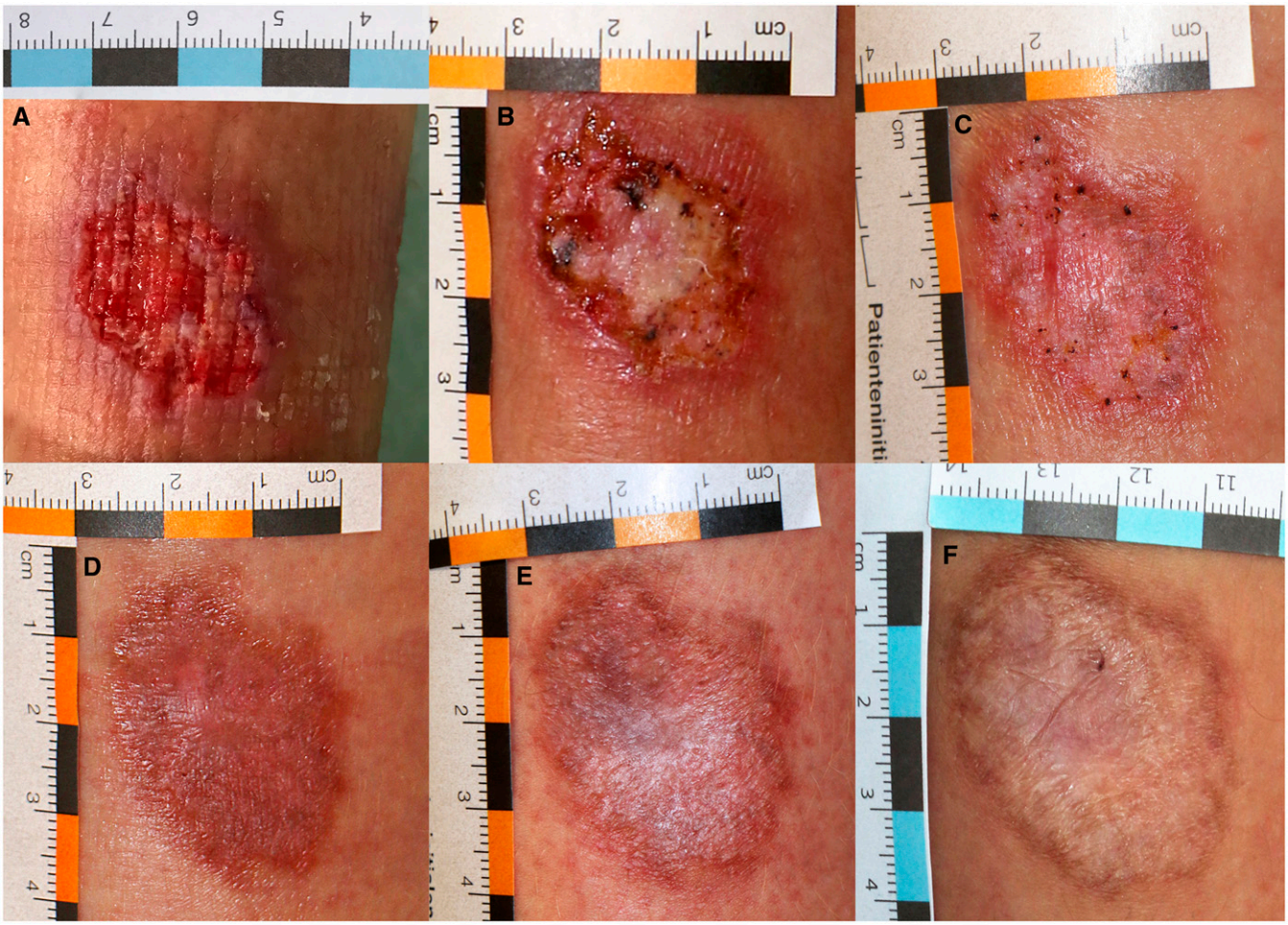

FIGURE 1. Clinical course of the skin lesion located lateral of the left tibia of the patient. (**A**) 11 days before the start of LeiProtect® treatment, (**B**) 7 days, (**C**) 4 weeks, (**D**) 9 weeks after initiation of LeiProtect® treatment, (**E**) 4 months, and (**F**) 13 months after termination of LeiProtect® treatment.

seen once per week with detailed photodocumentation of the healing process. Complete wound closure was achieved on March 6, 2020, after 8 weeks of topical therapy with LeiProtect, which was stopped after 12 weeks on April 3, 2020. There were monthly clinical follow-ups until the end of July 2020 and quarterly follow-ups until April 29, 2021, which showed stable scar formation (Figure 1). There was no clinical evidence for disease recurrence, which is in line with the time course of the anti-*Leishmania*-antibody titer of the patient's serum as determined by indirect immunofluorescence using viable *L. major* promastigotes (April 3, 2020: 1:200; July 20, 2020: 1:400; October 9, 2020: 1:200; January 15, 2021: $<$ 1:100; April 29, 2021: $<$ 1:100).

DISCUSSION

Na-chlorosum is known to promote the healing of different types of wounds, including skin lesions caused by *L. major* or *L. tropica*.[10,12,13] In our previous studies on CL, the application of *Na-chlorosum* entailed occlusive moist wound treatment causing micro milieus that might favor bacterial growth.[10,12] The innovative preparation of LeiProtect, in contrast, leads to a translucent, dry film on the wound surface, can be easily applied by the patient and does not require any additional wound dressing. The present case illustrates the potential of this novel therapeutic approach and underlines that *Leishmania* wounds caused by *L. tropica* rapidly heal even in the absence of classical antileishmanial drugs. In contrast to antimonial drugs (for which there is no authorization in Germany), treatment with LeiProtect is completely painless and nontoxic, which, along with the cosmetic outcome of the therapy, was very much appreciated by the child and its parents.

LeiProtect is thought to act by generating a protective wound coverage that helps to prevent bacterial superinfections. *Na-chlorosum* itself is a pre-oxidant that leads to the generation of reactive (chloro)oxygen species in the presence of heme ([10,12] and references therein), which might promote wound healing via balanced pro- and anti-inflammatory activities[14] (C. Bogdan, unpublished observations) according to the concept of "oxidative shielding".[15] It also exerts leishmanicidal effects against extracellular and intracellular *L. tropica*.[12]

Our case highlights the successful use of the filmogenic LeiProtect gel for the treatment of CL, which will hopefully help to initiate urgently needed randomized clinical trials in countries endemic for CL.

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