Sumerianz Journal of Medical and Healthcare, 2025, Vol. 8, No. 1, pp. 18-21
ISSN(e): 2663-421X, ISSN(p): 2706-8404
Website: https://www.sumerianz.com
DOI: https://doi.org/10.47752/sjmh.8.1.18.21

Original Article Open Access

Complicated Skin Ulcer from Misdiagnosis and Inappropriate Treatment of a Cutaneous Leishmaniasis Lesion. Case Report

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Article History

Received: 07 August 2024

Revised: 01 November 2024

Accepted: 10 February 2025

Published: 13 March 2025

How to Cite

Néstor Añez; Agustina Rojas; Gladys Crisante; José V. Scorza-Dagert; Johnny Bullón (2025), Complicated Skin Ulcer from Misdiagnosis and Inappropriate Treatment of a Cutaneous Leishmaniasis Lesion, Case Report. *Sumerianz Journal of Medical and Healthcare*, Vol.8. No.1, pp.18-21.

Abstract

Introduction. American cutaneous leishmaniasis, a sand fly transmitted neglected tropical disease caused by *Leishmania spp.* parasites, is endemic in most Latin-American countries. Case report. We present a 54-year-old-woman case, showing a grade II ulcer in the left leg's malleolar zone with a presumptive clinical diagnosis of skin neoplasia lesion. For 6 weeks this patient received antibiotic treatment after being subject to a surgical skin grafting. However, biopsies from the ulcer did not reveal neoplasia components, the lesion was unresponsive to antibiotic therapy and reject the skin grafting. The ulcer was treated with antibiotic for six additional weeks, without size reduction. Months later, we diagnosed the patient's lesion as leishmaniasis, based on: i. positive Leishmanin skin test, ii. detection of amastigotes from the lesion and iii. positive PCR assay. Treatment with a pentavalent antimony compound was administered in a perilesional infiltration (PLI) combined with daily applications of an antimony based nanoemulsion cream. After 60 days of treatment, the ulcer was observed epithelialized with a scar. Conclusion. Combined Sb^{5+}-PLI-meglumine antimoniate and nanoemulsion cream, is a cost effective and safe anti leishmanial therapy option, accessible to all people, including the poorest of the poor infected with cutaneous leishmaniasis.
Keywords: Cutaneous leishmaniasis; Sb^{5+}Perilesional infiltration; Nanoemulsion cream.

1. Introduction

Cutaneous leishmaniasis (CL) is a neglected tropical disease, transmitted by *Leishmania*-infected female sand flies during blood feeding. It is endemic in most Latin-American countries. CL is caused by several parasite species,

including *L. mexicana* and *L. braziliensis*. The human CL-clinical infection ranges from inapparent or asymptomatic cases, spontaneous skin ulcers healing to severe cutaneous lesions and/or disfigurating processes to mucocutaneous infections [1-3].

The infection, generally, starts with a papule after several weeks at the site of a bite from an infected sand fly, which changes into a nodule, and then ulcerates, with the ulcers growing with time in the absence of treatment. In some cases, lymph nodes near the lesion can be noticed enlarged, individually or showing a small chain. Following the growth of CL skin lesions, it is frequent that patients start treatment without laboratory confirmation. Often these treatments include risky and toxic compounds such as corrosive chemicals and /or topical steroids [4]. When healthcare is sought, the lack of knowledge about tropical diseases among practitioners in health centers and/or the incomplete medical histories, may lead to inappropriate treatments for CL, including the use of antibiotics and/or other unspecific drugs.

For CL-diagnosis, parasitological methods detecting tissular amastigote-forms of the parasite remain the gold standard because of its high specificity and the use of DNA-based molecular methods, such as PCR, is recommended due to their high sensitivity and specificity against other skin pathologies.

Several authors have been recently highlighted that atypical CL development physically and clinically resembles various neoplasia lesions [5, 6]. The above statement is supported by: **a**. the clinical outcome of both diseases maintained under the control of innate and adaptive immunity and **b**. their progressive effect characterized by an impaired host Th1 response. As a consequence, the Th2 cytokine led to parasite proliferation in target organs or uncontrolled neoplasia progression [6, 7]. Thus, malignancy process should be considered in the differential diagnosis of leishmaniasis in endemic regions.

We report a CL case, initially misdiagnosed, in a patient who received clinical, surgical and many weeks of inadequate antibiotic treatments.

2. Case Presentation

A 54-year-old woman was hospitalized during 1 month showing a grade II ulcer in the left leg's malleolar zone with presumptive clinical diagnosis of skin cancer. Despite ulcer tissue biopsies did not show neoplasia components, the patient was submitted to a local tissue resection and a skin grafting in an area of 4.5x4.0 cm in diameter showing granular tissue, oedema and trophic changes around the lesion, followed by antibiotic therapy (Amikacin/Rivaroxaban) for six weeks. However, the rejection of skin grafting generated 20% epidermal lysis and necrosis and the ulcer was debrided trying to promote epithelialization with not success at all. The patient's ulcer was then kept under control using intravenous (IV)-antibiotic during six more weeks, without reduction in size or healing. Details on the process are shown in Figure 1.

One year post the initial lesion, the patient came to our research team looking for diagnosis for her complicated ulcer. During the anamnestic interview the patient declared to have visited a village located in the Colombia-Venezuela border, where leishmaniasis is highly endemic. After reading and accepting our informed consent to participate in our study this patient was diagnosed with the following methods: **i.** a leishmanin-skin test (Montenegro's intradermic reaction). **ii.** a scalpel scraping sample from the lesion-surface, smeared on glass slide, fixed with methanol and stained with Giemsa in 10% phosphate buffer at pH 7.2, examined under an Axioscop microscope (Zeiss Germany) linked to a 480 Noticam camera connected to a computer to record morphology of the tissue-amastigote-forms, and **iii.** 1mm^3 tissue biopsy taken to be proceeded for a multiplex conventional PCR assay using primers for the spliced leader (mini-exon) gene sequence [8].

The obtained outcomes from the methodological procedures revealed: **i.** a 10x10mm positive LST reaction, 48h post injection. **ii.** an active ulcer of 3.5x2.0 cm in size, from which a microscopically observed sample, revealed few *Leishmania*-amastigote forms and, **iii** the PCR assay showed bands of 148 bp, confirming the presence of *Leishmania braziliensis*- DNA (Figure 2).

Once confirmed CL-diagnosis; to fulfill ethical criteria established by the Biomedical Committee of the National Research Council of Venezuela, a written informed consent was obtained from the patient previous to start the proposed treatment.

Taking into consideration the long time traumatic clinical history suffered by the patient, we decided, to combine previous experience with patients suffering CL-infection treated in our research team. This consisted of using perilesional infiltration (PLI) of a pentavalent antimony compound combined with Lidocaine and daily application of a nanoemulsion cream based on 10% generic antimony compound [1, 9]. Briefly, PLI of a generic meglumine antimoniate compound in solution at concentration of 90 mg/mL Sb^{5}combined (1:3) with 2% lidocaine, was weekly injected using a 27G13/8"0.40 x 35 mm needle adapted to a dental carpool syringe. In addition, 150 mg nanoemulsion cream containing 10% (w/v) meglumine antimoniate, was applied twice daily all around the ulcer border.

Due to the complication of this case, a complementary treatment was suggested and accepted by the patient, which consisted of the use of Trimethoprim 80 mg/Sulphametoxazol 400 mg (Bactrimel®) twice a day until bacterial coinfection disappeared. In addition, to produce a soft scar after lesion healing, fresh *Aloe vera* crystal was daily applied on the lesion. The patient was weekly evaluated to check out the process of skin regeneration and reduction of ulcer size with time. After eight weeks of treatment, no discomfort or other adverse effects were detected. The ulcer was replaced with healthy skin tissue and a soft clean scar. Details of the process of healing are shown in Figure 3.

3. Discussion

Here, we present a clinical case consisting of a complicated CL-lesion caused by *Leishmania braziliensis* in a patient who was, initially, misdiagnosed and inappropriately treated for several months, before consulting with our research team. Once the CL-diagnostic was confirmed, perilesional infiltrations of a 90mg/mL solution of pentavalent antimony compound, combined with two daily applications (~150mg each) of a 10% meglumine antimoniate nanoemulsion cream, a successful CL lesion healing was obtained in 60 days.

The overall amount of Sb^{5+} the patient received with 5 PL-infiltrations (450mg) and 120 applications of the nanoemulsion (1,800mg) was equivalent to 2.25g during the complete treatment. Comparing these figures with those of the systemic treatment of 20mgSb/kg/day, recommended for CL by WHO [10] our 60kg-weight patient, would receive 1.2gSb/kg/day, equivalent to 53% in a day of the total Sb given during 60 days to the present complicated clinical case.

In previous work, our research team has obtained successful results with two therapy options for CL lesions using, separately, either low dose of Sb-intralesional infiltrations or 10% meglumine antimoniate nanoemulsion cream, both leading to CL lesion healing in a similar time, while showing no adverse effects or patient disconfort, as well as, considerable cost-savings, compared with the more conventional systemic treatments [1, 9].

In conclusion, the combination of Sb-PLI and local application of meglumine antimoniate nanoemulsion cream described here, is an excellent anti leishmanial therapy option, with the advantage of being safe (without adverse effects) and cost effective.

4. Conflict of Interest

The authors declare they have not conflict of interest.

Acknowledgements

We thank M. Arteaga for collaboration received during the case study. The financial support received from FONACIT (Project-CFP-202300084/CFP-2024000056 and Project-CFP-2024000071) is grateful acknowledged. We are deeply indebted to Professor Dr. L F Chaves at the School of Public Health, Indiana University, Bloomington, USA, for reviewing the manuscript.

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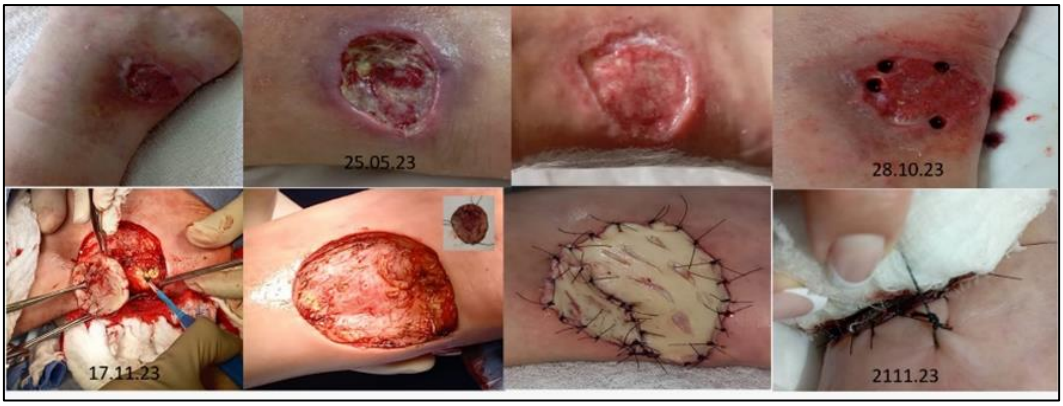

Figure-1. Primary lesion submitted to antibiotic treatment and skin grafting before diagnosing cutaneous leishmaniasis

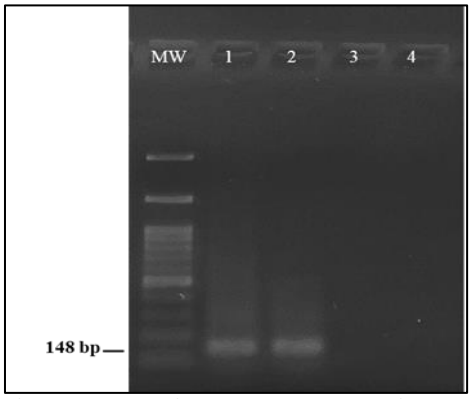

Figure-2. Leishmania braziliensis-DNA amplification in sample from complicated lesion of a patient with cutaneous leishmaniasis. Ethidium bromide-stained 2% Agarose gel showing PCR amplification products: Lane 1, sample from active CL-lesion; Lane 2, Positive control sample; Lane 3, Negative control sample; Lane 4 H2O; MW: Molecular weight marker

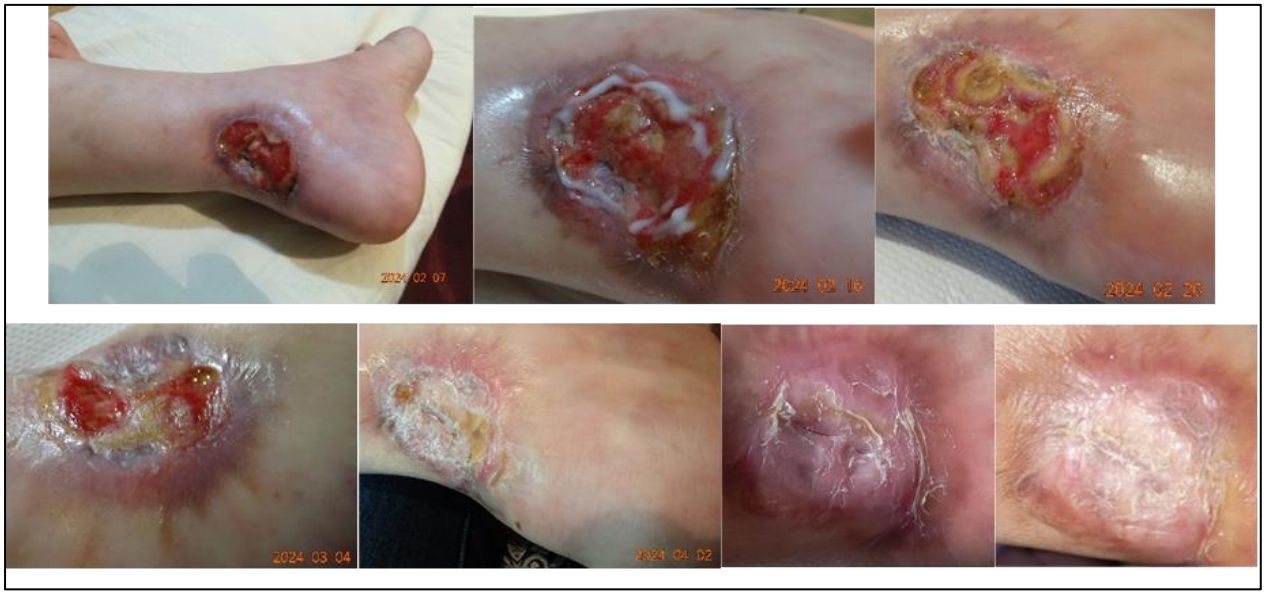

Figure-3. Healing process with time after receiving combined Sb 5+ perilesional infiltrations and nanoemulsion cream based on 10% generic antimony compound treatment