e-ISSN 3050-8460
Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Case Report

Amastigote-Negative Cutaneous Leishmaniasis without Visceral Involvement: Caused by *Leishmania donovani* in a Traveler to Spain: A Polymerase Chain Reaction (PCR)-Confirmed Case Report

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Citation: Sharara Z, et al. Amastigote-Negative Cutaneous Leishmaniasis without Visceral Involvement: Caused by *Leishmania donovani* in a Traveler to Spain: A Polymerase Chain Reaction (PCR)-Confirmed Case Report. J Dermatol Res. 2026;7(2):1-6.

https://doi.org/10.46889/JDR.2026.7203

Received Date: 25-04-2026

Accepted Date: 29-05-2026

Published Date: 05-06-2026

Abstract

Background: *Leishmania donovani* is the primary causative agent of Visceral Leishmaniasis (VL), but its emergence as a cause of purely Cutaneous Leishmaniasis (CL) is an increasing challenge to public health. Conventional diagnosis relies on microscopic identification of amastigotes, a method that frequently fails in pauciparasitic lesions.

Case Presentation: We report the case of a 60-year-old Caucasian female, who presented with a persistent, non-healing, non-painful ulcer on her right mid-arm with positive travel history to Spain. Despite a high clinical suspicion for Cutaneous Leishmaniasis (CL), two separate skin biopsies have failed to detect amastigotes on Giemsa staining, although histology showed non-caseating granuloma. The definitive diagnosis was achieved when tissue from the second biopsy was subjected to Polymerase Chain Reaction (PCR) analysis, which returned a positive result for the *Leishmania donovani* complex. Systemic workup, including blood Leishmania PCR and rK39 serology, were negative, confirming the absence of visceral involvement. She started Miltefosine 50 mg TDS for 28 days with cessation of her immunosuppressive medication to avoid developing resistance.

Conclusion: This case highlights the diagnostic pitfall of relying solely on histopathology for CL, particularly in pauciparasitic and immunosuppressed patients. The failure of two biopsies, contrasted with the definitive molecular confirmation, underscores the critical role high index of clinical suspicion and the PCR as indispensable tool for accurate diagnosis and species identification. This case contributes to the growing evidence of *L. donovani* causing purely cutaneous disease and advocates for the routine use of molecular diagnostics in challenging leishmaniasis cases.

Keywords: *Leishmania donovani*; Atypical Cutaneous Leishmaniasis; Pauciparasitic Lesion; Polymerase Chain Reaction (PCR); Tropical Disease; Amastigote-Negative Ulcer; Miltefosine

Introduction

Leishmaniasis is a complex vector-borne disease caused by protozoan parasites of the genus Leishmania, presenting in three main clinical forms: Visceral (VL), Cutaneous (CL) and Mucocutaneous (MCL) [1]. VL, often caused by I and Leishmania infantum, is the most severe form, characterized by systemic involvement and high mortality if untreated. CL, the most common

form, is typically caused by species such as *L. major, L. tropica and L. mexicana* and is generally confined to the skin resulting in chronic and often, self-healing lesions [2].

The traditional epidemiological and clinical boundaries of Leishmania species are becoming increasingly blurred. In recent years, there have been growing reports of *L. donovani* causing purely cutaneous disease without any evidence of visceral involvement, particularly in endemic regions like the Indian subcontinent and East Africa [3].

Diagnosis of leishmaniasis relies on a combination of clinical suspicion and laboratory confirmation. The gold standard remains the microscopic identification of amastigotes (Leishman-Donovan bodies) in tissue smears or biopsies [4]. However, in pauciparasitic lesions this method will be of low sensitivity [5]. False negative results can lead to delayed treatment and potential disease progression. PCR offers significantly higher sensitivity and specificity than conventional methods, enabling the detection and species identification of Leishmania DNA [5].

Case Presentation

A 60-year-old Caucasian female, resident in the United Kingdom, was referred to the community dermatology clinic for evaluation of a persistent, non-healing, non-painful ulcer on her right mid-arm. The lesion was first noted in April 2024 and had been slowly progressing since its onset, Fig. 1 (A).

Clinical History and Initial Workup

The patient's medical history was significant for Crohn's disease, for which she was receiving azathioprine and alternate weekly adalimumab injections. On examination, the lesion was an indurated, erythematous plaque with a central, weeping ulceration located on the right mid-arm. The lesion was non-tender and the patient denied any associated systemic manifestations, such as fever, weight loss or fatigue. There was no evidence of lymphadenopathy or hepatosplenomegaly, clinically ruling out visceral involvement.

The patient reported a history of travel to Spain/ Alicante several months prior to the appearance of the lesion, however, she did not recall an insect bites. This travel history, combined with the chronic, non-healing nature of the ulcer, prompted the consideration of Cutaneous Leishmaniasis (CL) as a key differential diagnosis. The immunosuppressed state raised other differential diagnosis of opportunistic infections or a primary inflammatory process, such as cutaneous Crohn's disease.

Diagnostic Challenge and Molecular Confirmation

The initial diagnostic approach focused on histopathology. A first biopsy was performed in August 2024 at Community Dermatology outpatient surgery, clinically the lesion was persistent Fig. 1 (B). Histological examination revealed a non-caseating granuloma, a finding consistent with a variety of inflammatory conditions, including Crohn's disease and leishmaniasis. However, no amastigotes (Leishman-Donovan bodies) were identified on Giemsa staining (Fig. 2).

Given the persistent clinical suspicion of CL, a second biopsy was performed in May 2025. Clinically, the lesion maintained its indurated, erythematous state even after 1 year of appearance (Fig. 1). Like the first, this biopsy failed to reveal any amastigotes on microscopic examination, reinforcing the pauciparasitic nature of the lesion. However, tissue from the second biopsy was subjected to Polymerase Chain Reaction (PCR) analysis. The PCR assay targeting Leishmania DNA returned with a positive species identification of the *Leishmania donovani* complex.

To further exclude systemic disease, abdominal ultrasound and blood tests were performed, including a peripheral blood Leishmania PCR and an rK39 serological test for Visceral Leishmaniasis (VL). Both systemic tests were negative, confirming the absence of visceral involvement and supporting the diagnosis of purely cutaneous leishmaniasis caused by *L. donovani*.

Clinical Photography

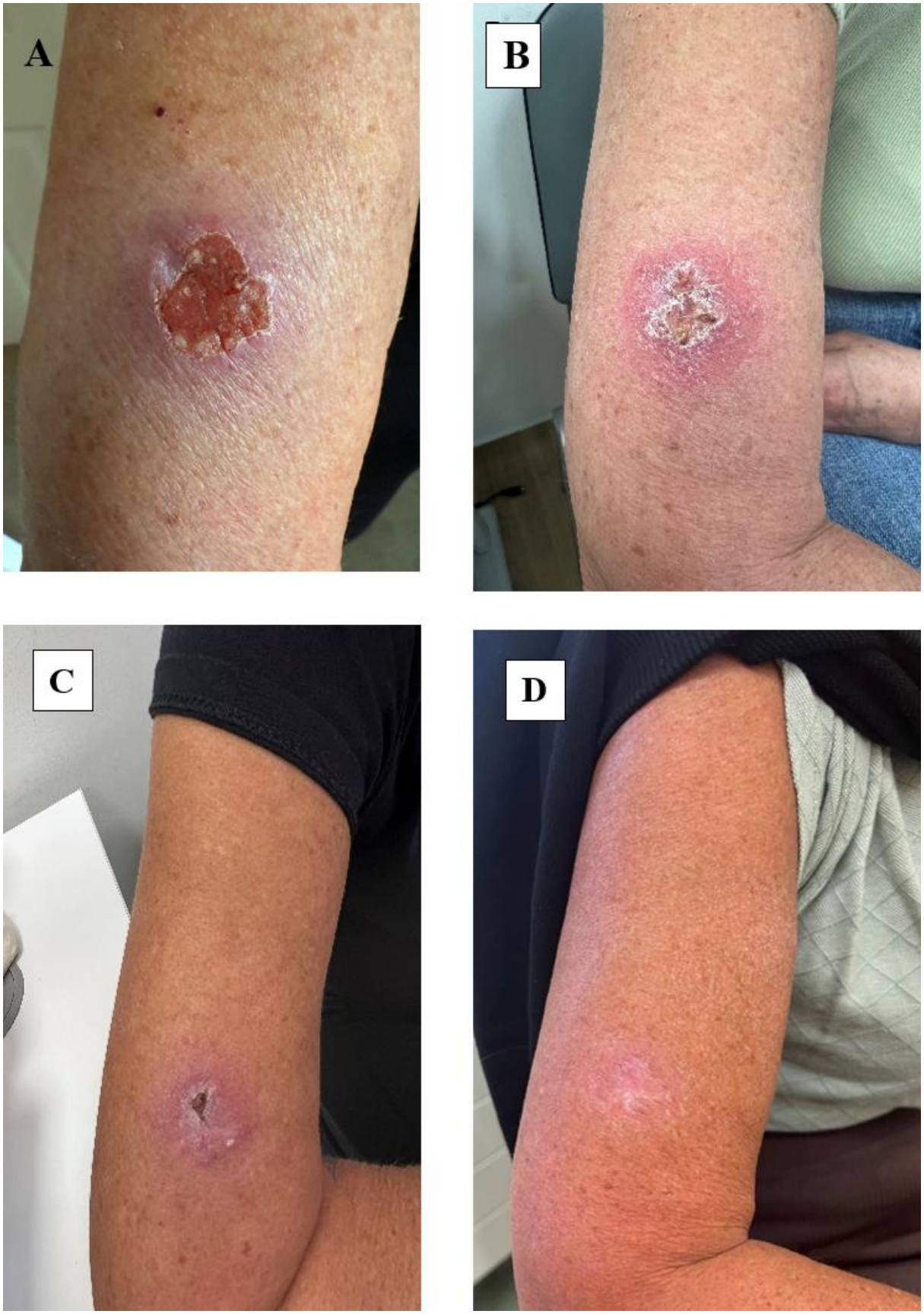

Figure 1: (A)Ulcerated plaque at presentation; B) and(C) weeping non healing at the biopsy appointments; (D) After treatment.

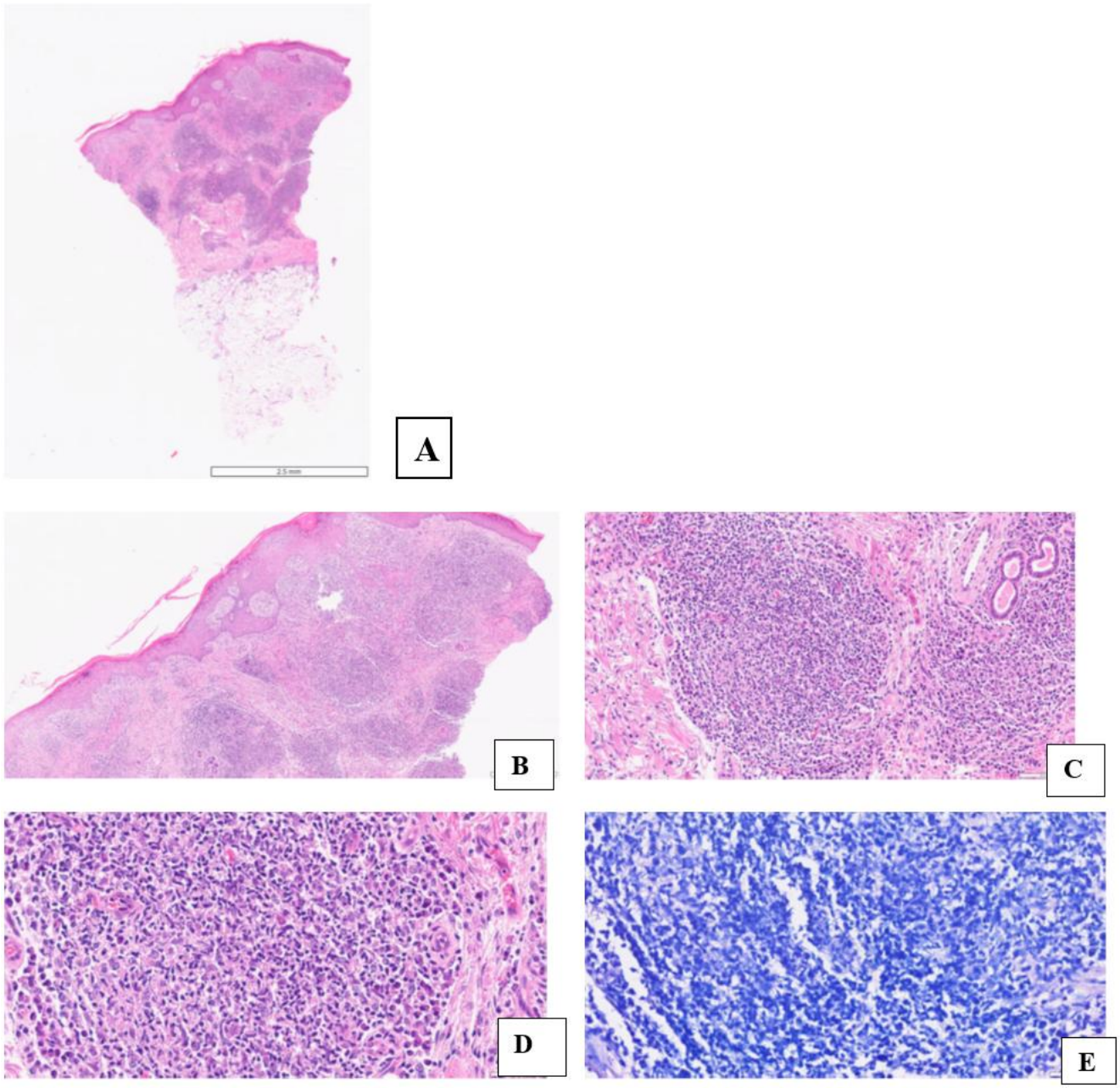

Figure 2: A) (H+E stain, 10x magnification): Low power view shows skin punch biopsy with focal epidermal acanthosis and a prominent, dense inflammatory infiltrate in both the superficial and deep dermis B: (H+E stain, 50x magnification): Medium power view shows focal basal epidermal damage, focal epidermal hyperplastic change and a dense, perivascular, nodular and granulomatous pattern of lymphohistiocytic inflammation within the dermis; C: (H+E stain, 200x magnification): High power view shows lymphoplasmacytic rich granulomatous inflammation. No amastigotes are visible within macrophages present; D: (H+E stain, 400x magnification): High power view shows lymphoplasmacytic rich granulomatous inflammation. No amastigotes are visible within macrophages present; E: (Giemsa, 400x magnification): No amastigotes are identified within macrophages present.

Discussion

Leishmania donovani is classically known as the agent of Visceral Leishmaniasis (VL) or kala-azar, the most severe form of the disease. The occurrence of purely cutaneous disease caused by this species, particularly in non-endemic VL regions, represents a significant deviation from the established paradigm. This phenomenon, often termed Atypical Cutaneous Leishmaniasis (ACL), is increasingly recognised [6,7]. Recent literature, particularly from the Indian subcontinent, has documented the emergence *of L. donovani* lineages that are dermotropic, challenging the traditional visceral tropism and highlighting that these emerging *L. donovani* variants causing CL are a new challenge [8,9].

The reported patient's clinical presentation; a persistent, non-healing, indurated plaque with central ulceration; was highly suggestive of CL, but the diagnosis was complicated by two factors: the patient's immunosuppression due to Crohn's disease treatment (azathioprine and adalimumab), which raised the possibility of cutaneous Crohn's disease and the repeated failure of biopsies to prove the diagnosis.

The two separate biopsies have shown non-caseating granulomatous inflammation but failed to detect amastigotes on Giemsa staining. This failure is characteristic of a pauciparasitic lesion, where the parasite load is too low for microscopic detection. This can occur in chronic lesions, in cases with a strong host immune response in this patient potentially this is due to an altered immune status from immunosuppressive therapy and the chronic nature of the lesion [10].

The definitive diagnosis was achieved solely through the high sensitivity of the Polymerase Chain Reaction (PCR) assay performed on the tissue from the second biopsy. PCR detects parasite DNA, making it far superior to microscopy in pauciparasitic lesions. This case serves as a powerful illustration of the necessity of molecular testing to overcome the diagnostic limitations of histopathology.

The use of PCR not only confirmed the presence of Leishmania but also identified *L. donovani* complex. Amare, et al., demonstrated the utility of advanced PCR techniques (ITS-1 HRM PCR and HSP70 sequencing) to confirm *L. donovani* CL in a new focus, emphasising that molecular methods are often the only reliable way to achieve a definitive diagnosis and species typing in atypical presentations [6]. The ability to identify the species is paramount, as it guides treatment decisions, which may differ for *L. donovani* compared to other CL-causing species.

Furthermore, the negative systemic workup (peripheral blood Leishmania PCR, rK39 serology and normal scanning of viscera) was essential. While the *L. donovani* complex was identified in the skin, the negative systemic tests confirmed that the infection was confined to the skin, supporting the diagnosis of purely cutaneous leishmaniasis and ruling out the more severe visceral form.

The patient's concurrent treatment for Crohn's disease with azathioprine and adalimumab is a significant factor. It has been proven that resolution of lesions correlates with an effective Th1 cellular immune response mediated by IL-12- and IFN-γ-mediated expression of TNF-α and inducible Nitric Oxide Synthase (iNOS), with Nitric Oxide production and parasite destruction [12,13]. T regulatory cells have been demonstrated in localised Leishmania skin lesions due to *L. braziliensis*, however, it is documented that sterile immunity is not attained [14]. The ability of Leishmania to sustain a chronic infectious state within the host relay on its immune circumvention potential utilising several virulence factors against the host immune response [14]. This case emphasises that in immunosuppressed patients with chronic non-healing skin lesions, we need to maintain a high index of suspicion for atypical infections, including CL. When conventional methods fail, molecular diagnostics are indispensable for accurate and timely management, especially when the causative agent is a species typically associated with life-threatening visceral disease.

Conclusion

This case report of Cutaneous Leishmaniasis (CL) caused by the *Leishmania donovani* complex in an immunosuppressed patient highlights two critical contemporary issues in the diagnosis and management of leishmaniasis. First, it reinforces the growing recognition of *L. donovani* as an agent of purely cutaneous disease, challenging the traditional species-tropism paradigm and draw attention to the need for vigilance regarding atypical presentations, even in non-endemic areas. This case strongly advocates for the routine incorporation of molecular diagnostics as a first-line confirmatory tool in all clinically suspected cases of CL, particularly those that are chronic, atypical or occur in immunosuppressed hosts, to ensure timely and accurate treatment.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement
The authors have no acknowledgments to declare.

Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Informed consent was obtained from all participants included in the study.

Authors' Contributions
All authors contributed equally to this paper.

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