Cureus
Part of SPRINGER NATURE

Open Access Case Report

Multibacillary Lepromatous Leprosy in an Endemic Area: A Two-Year Diagnostic Delay and the Role of Slit-Skin Smear and PCR

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Review began 09/24/2026
Review ended 10/10/2026
Published 10/17/2026

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DOI: 10.7759/cureus.118084

Abstract

Multibacillary lepromatous leprosy can mimic other dermatological conditions, delaying diagnosis. In areas with limited access to histopathology, the slit-skin smear (SSS) is an accessible tool that, together with clinical findings, can support the diagnosis and the start of treatment, while PCR of SSS material may provide complementary confirmation.

A 63-year-old male from Montería (Córdoba, Colombia), with a history of chronic venous insufficiency, presented with a two-year history of characteristic skin lesions, including nodular infiltration of the earlobe, a hyperkeratotic plaque with hypoesthesia on the right elbow, and diffuse cutaneous involvement of the chest and abdomen. SSS of the earlobe showed acid-fast bacilli with a bacterial index of 4+ (Ridley scale). Based on the clinical findings and the smear result, multibacillary lepromatous leprosy was diagnosed, and multidrug therapy was started per the WHO regimen without histological confirmation. Real-time PCR performed approximately two and a half months later was positive for *Mycobacterium leprae*, and a skin biopsy performed about 18 months after diagnosis showed foamy histiocytes consistent with the lepromatous pole. After completing 12 months of treatment, the patient showed favorable clinical progress.

In endemic areas with limited access to histopathology, clinical suspicion of characteristic leprosy lesions, supported by SSS, can allow the diagnosis and the start of multidrug therapy without depending on histological confirmation. As a single case, it does not demonstrate that this approach shortens time to treatment or prevents disability.

Categories: Internal Medicine, Infectious Disease, Dermatology
Keywords: colombia, delayed diagnosis, lepromatous leprosy, mycobacterium leprae, polymerase chain reaction test, primary health care

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* that remains a public health concern, with more than 170,000 new cases reported annually worldwide [1]. Lepromatous leprosy represents the most advanced end of the disease spectrum, characterized by a high bacillary load and diffuse skin involvement, and is classified as multibacillary for treatment purposes [2]. Unlike paucibacillary forms, it lacks well-demarcated hypopigmented anesthetic patches and instead presents with symmetric macules, papules, nodules, or diffuse infiltration. This pleomorphic presentation can mimic other dermatological and systemic conditions, delaying diagnosis and increasing the risk of irreversible nerve damage, permanent disability, and continued community transmission; hypoesthesia associated with characteristic skin lesions remains the key clinical clue that should raise suspicion [1-4].

In endemic areas with limited access to timely histopathology, the slit-skin smear (SSS), in which dermal fluid is scraped from selected sites such as the earlobe and examined for acid-fast bacilli, is a widely accessible tool. A positive smear, together with characteristic clinical findings, can allow treatment to begin without histological confirmation. PCR on SSS material can provide complementary confirmation, but it may require referral facilities and is not necessary before starting treatment. We present a case of multibacillary lepromatous leprosy with an approximately two-year diagnostic delay, illustrating the importance of maintaining a high index of clinical suspicion for characteristic lesions and describing a stepwise diagnostic sequence based on primary-care-level tools.

Case Presentation

A 63-year-old male, resident of Montería (Córdoba, Colombia), with a history of chronic venous insufficiency and right inguinal herniorrhaphy, presented with a two-year history of progressively appearing skin lesions.

Physical examination revealed shiny, erythematous, scaly, and warm skin, with multiple ulcers on the left lower limb located on the distal anterior surface (2×2 cm), distal anterolateral surface (8×3 cm), and distal posterior region (5×2 cm). Nodular erythematous-violaceous infiltration was observed on the right earlobe (Figure *1A*), and a nodular erythematous-violaceous plaque with raised borders and a hyperkeratotic surface, with associated hypoesthesia, was found on the posterior aspect of the right arm/elbow (Figure *1B*). Additionally, diffuse cutaneous involvement of the anterior chest and abdomen was documented, with multiple infiltrative nodular lesions in a bilateral distribution (Figure *1C*). Neurological examination revealed hypoesthesia as the predominant sensory abnormality. Motor strength was preserved, and no palpable thickening of peripheral nerves was found. Peripheral pulses were also preserved.



FIGURE 1: Cutaneous manifestations of the patient before (A-C) and after (D-E) completing multibacillary multidrug therapy (MDT-MB).

(A) Right earlobe with nodular erythematous-violaceous infiltration, the site where the slit-skin smear (SSS) was performed. (B) Nodular erythematous-violaceous plaque with raised borders and a hyperkeratotic surface, located on the posterior aspect of the right arm/elbow. (C) Diffuse pretreatment cutaneous involvement of the anterior chest and abdomen, with multiple infiltrative nodular lesions in a bilateral distribution. (D) Anterior chest and abdomen one month post-treatment, showing resolution of nodular lesions with residual hyperpigmented macules. (E) Posterior chest one month post-treatment, showing similar resolution of nodular infiltration and residual pigmentation.

Based on these findings, the differential diagnosis included varicose ulcer, peripheral venous insufficiency, and Hansen's disease, and an SSS was obtained from the earlobe, the usual site for this test. At 21 days, the smear, stained with the Ziehl-Neelsen method, reported acid-fast bacilli with a bacterial index of 4+ (++++) on the Ridley logarithmic scale, indicating a high bacillary load.

Eight days later (29 days from the initial visit), based on clinical findings (more than five skin lesions and sensory impairment) and the slit-skin smear result, a diagnosis of multibacillary lepromatous leprosy was confirmed, and multidrug therapy (MDT) was initiated per the World Health Organization regimen [5].

Approximately two and a half months after diagnosis, real-time PCR (qPCR) was performed on the same SSS

material obtained from the earlobe, using the Bio-Rad CFX96 Real-Time System (Bio-Rad Laboratories, Hercules, California, USA). The result was positive for *M. leprae* (reported by the laboratory as ++++, reference value ++++). Because PCR was performed after MDT had already been started, it served only as complementary confirmation and did not influence the decision to initiate treatment.

The therapeutic regimen consisted of rifampicin 600 mg, clofazimine 300 mg, and dapsone 100 mg administered under supervision on the first day of each month, followed by self-administered clofazimine 50 mg/day and dapsone 100 mg/day on days 2 through 28, for a total duration of 12 months. The patient was enrolled in a specific leprosy program, and blister pack delivery was recorded under the supervision of the public health program coordinator; adherence was good. Treatment was supplemented with local ulcer care, education on treatment adherence, multidisciplinary management, and surveillance for leprosy reactions. Follow-up complete blood count and liver function tests were normal.

Approximately 18 months after diagnosis, an abdominal skin biopsy was performed, showing orthokeratotic epidermis without significant changes and, in the dermis, a dense inflammatory infiltrate of foamy histiocytes arranged in a nodular pattern, extending into the deep reticular dermis with associated edema, findings consistent with lepromatous leprosy. Special stains (Fite-Faraco and Ziehl-Neelsen) could not be performed due to limited access to specialized diagnostic resources, related to the patient's geographic context and care conditions.

The patient continued monthly clinical follow-up and, after completing multidrug therapy, showed favorable progress, with a reduction in the size of skin lesions and no serious adverse events (Figures *1D*, *1E*). The timeline of the main diagnostic and therapeutic events is shown in Figure *2*.

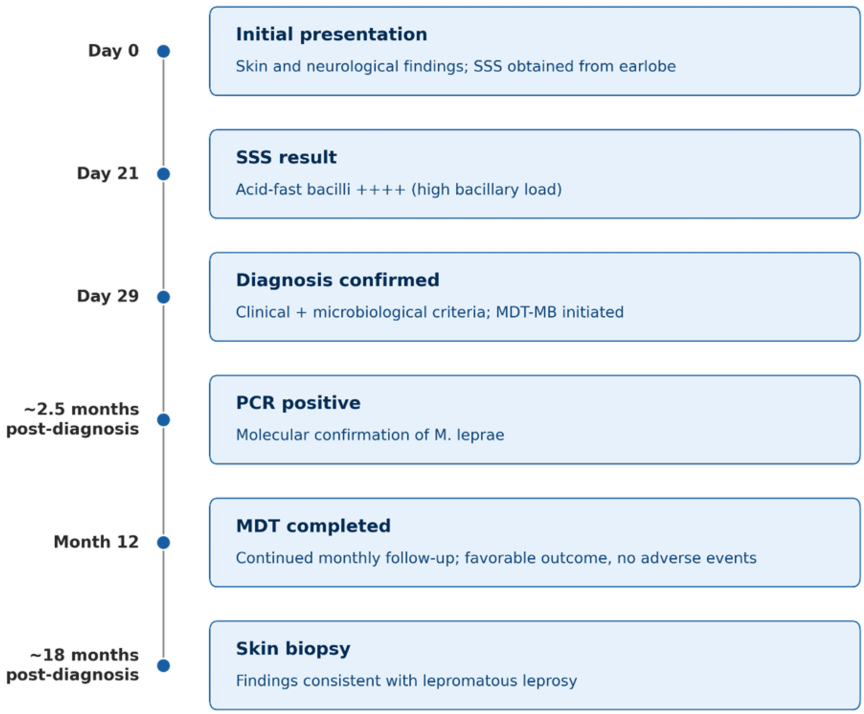


FIGURE 2: Timeline of the clinical case.

Diagnostic and therapeutic milestones are shown from the initial visit through completion of the multibacillary multidrug therapy (MDT-MB) regimen and the subsequent confirmatory skin biopsy. AFB: acid-fast bacilli; SSS: slit-skin smear; PCR: polymerase chain reaction; MDT: multidrug therapy.

Discussion

This case illustrates a diagnostic delay of approximately two years, frequently reported in multibacillary/lepromatous leprosy owing to its pleomorphic presentation, which can mimic chronic dermatoses and vascular conditions such as venous ulcers, favoring underdiagnosis. Hypoesthesia associated with skin lesions remains the most useful clinical clue for raising suspicion; delayed recognition increases the risk of disability and sequelae [1,2].

This pattern of diagnostic error is not uncommon: a systematic review of 20 studies on factors contributing

to delayed leprosy detection identified misdiagnosis as the main intermediate link in the delay chain, reporting that up to 32.5% of patients lived with an incorrect diagnosis for periods ranging from three months to ten years, most frequently arthritis, photosensitivity, and other chronic dermatoses [3]. Among chronic lower-limb ulcers, venous insufficiency and varicose ulcers are among the most frequent alternative diagnoses: their phenotype (shiny, erythematous, scaly, warm skin with distal ulcers) closely replicates that of diffuse lepromatous leprosy, generating a diagnostic anchoring bias toward the vascular cause when both conditions coexist, as in this patient. A series of eight cases of multibacillary leprosy presenting primarily with ulcers documented a mean delay of 17.4 months to diagnosis, with grade 2 disability already established in seven of eight patients, initially attributed to vascular or mechanical causes [4]. This reinforces that, for any chronic lower-limb ulcer, particularly in endemic areas, systematic assessment for hypoesthesia should keep leprosy within the active differential diagnosis.

SSS is the most accessible microbiological method at the primary care level, with a practical specificity close to 100% (a positive result constitutes direct confirmatory evidence) [2,6], but its overall sensitivity is limited, particularly in paucibacillary forms: 24.5% in a Brazilian cohort (n=345, specificity 100%) [6] and only 18% in Nepal (n=50) [7]. However, its performance improves markedly in multibacillary disease (78% vs. 44% in paucibacillary cases, Nepal) [7], which is consistent with the high positivity observed in this patient, whose earlobe smear showed a bacterial index of 4+ on the Ridley scale. Operationally, SSS requires no cold chain, uses basic microscopy, and has low cost [2,8]. In this patient, however, the smear result took 21 days and treatment began eight days later. Therefore, this case does not demonstrate that the SSS-based approach shortened the time to treatment.

PCR performed on the same SSS material increases sensitivity by detecting *M. leprae* DNA: 72% in Nepal, confirming 66% of AFB-negative cases [7]. A meta-analysis of 78 studies reported pooled sensitivity/specificity of 75.3%/94.5% (conventional PCR) and 78.5%/89.3% (qPCR) [9]; in Brazil, PCR reached 41%/100% and was positive in 51.3% of SSS-negative cases [6]. Performance depends critically on the extraction method: in Ethiopia, tissue sensitivity reached 91.1%, increasing from 84.6% to 96.8% when mechanical lysis was used instead of enzymatic digestion [10]. These estimates come from different populations, specimens, and methods and are not directly comparable. The WHO emphasizes the need for "ASSURED/REASSURED" tests in these settings, acknowledging that molecular tests still face operational barriers [8]. Variability across platforms also depends on the genomic target: the multicopy RLEP element is more sensitive than single-copy targets such as 16S rRNA, whose performance has been questioned in recent reviews [11,12]. In practice, a positive SSS is usually sufficient in multibacillary cases with high pretest probability, whereas PCR provides greater clinical impact in paucibacillary cases with a negative SSS [7,9]. In this patient, MDT was started on the basis of clinical findings and the SSS result alone. The qPCR was performed approximately two and a half months later and served only as complementary confirmation; it did not influence the decision to start treatment.

M. lepromatosis also circulates in Colombia: a study of 92 multibacillary patients documented co-infection with *M. leprae* in 5.4% of cases, with universal qPCR positivity [13], and systematic reviews place the country among those reporting this species [14], reinforcing the value of molecular confirmation at reference centers.

Based on the literature reviewed and on our experience with this case, we outline a stepwise algorithm for endemic areas with limited access to biopsy (Figure *3*). This algorithm is literature-informed and has not been validated by this single case; minimally invasive strategies such as anti-PGL-I serology could complement it in selected programs [15,16].

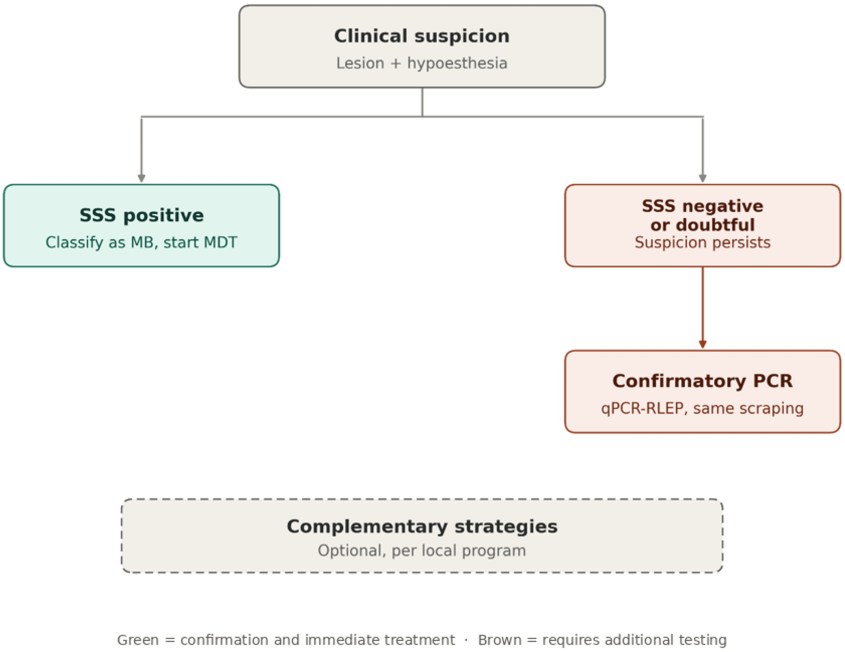


FIGURE 3: Proposed, literature-informed stepwise diagnostic pathway for endemic areas with limited access to biopsy.

This pathway has not been validated by the present case. In cases of clinical suspicion of leprosy (skin lesion associated with hypoesthesia), earlobe slit-skin smear (SSS) may be used as the initial test: a positive result, together with the clinical findings, supports classification as multibacillary and the start of multidrug therapy without awaiting histological confirmation. In a negative or doubtful smear, confirmatory PCR (preferably qPCR targeting the RLEP element) may be considered on the same material or at a reference center. PCR may require referral to a reference laboratory, and in the present patient it was performed after treatment had started and served only as complementary confirmation. In parallel, and optionally, depending on availability and local program context, complementary non-invasive strategies such as anti-PGL-I serology may be considered. SSS: slit-skin smear; PCR: polymerase chain reaction; MB: multibacillary; MDT: multidrug therapy.

The histopathological findings (a dense dermal infiltrate of foamy histiocytes (“Virchow cells”) extending deeply, with edema) are consistent with the lepromatous pole of the Ridley-Jopling spectrum, characterized by vacuolated macrophages with a high bacillary load and scant granulomatous organization, reflecting an ineffective immune response and correlating with cutaneous and neural dissemination [17,18]. However, the biopsy was performed approximately 18 months after diagnosis, after MDT had been completed, and no special stains were available; therefore, it was not used to establish the diagnosis, and the corresponding microscopy images could not be provided.

The patient received the standard WHO regimen (rifampicin, clofazimine, dapsone for 12 months) [5], supported by a network meta-analysis of 60 trials (9,256 patients) showing comparable efficacy and safety across regimens [19]. Adherence was good, with supervised delivery of blister packs through a specific leprosy program, and follow-up blood counts and liver function tests were normal. Post-MDT relapse is uncommon (~4% pooled, meta-analysis of 26 studies, 71,385 participants), though more frequent in multibacillary patients with a high bacillary load, justifying prolonged follow-up and surveillance for reactions, particularly erythema nodosum leprosum [20].

Strengths of this report include: (i) the use of accessible primary-care tools (SSS and clinical assessment) that supported the diagnosis and the start of MDT in a setting without timely histopathology; (ii) good documented adherence through a supervised program; and (iii) documentation of an underreported mimicking presentation. Limitations include: (i) absence of special stains (Fite-Faraco/Ziehl-Neelsen) on the biopsy and of histopathological images, due to resource and administrative constraints; (ii) a single-case design, precluding estimation of diagnostic performance or generalization to paucibacillary forms; (iii) lack of standardized objective markers for post-treatment follow-up to detect treatment failure [21]; and (iv) the case does not demonstrate that this diagnostic approach shortens time to treatment or prevents disability or transmission.

Conclusions

This case of multibacillary lepromatous leprosy illustrates how the pleomorphic clinical presentation of the disease can delay its recognition and reinforces that, in the presence of characteristic skin lesions associated with hypoesthesia, clinical suspicion must remain active even in areas with limited access to timely histopathology. In such settings, the earlobe SSS is an accessible tool that, together with clinical findings, can support the diagnosis and the initiation of multidrug therapy without depending on biopsy, while PCR of SSS material may serve as complementary confirmation. As a single case, it does not demonstrate that this approach shortens time to treatment or prevents disability or transmission. Nevertheless, it underscores the need to strengthen access to timely microbiological and molecular diagnostic tools at the primary care level in endemic regions.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Carlos Berrocal

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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