

Case Report

Adjacent Clinicopathological Discordance and Neural Impairment in Multibacillary Borderline Lepromatous Leprosy with Mid-Borderline Histopathology: A Single-Case Study

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ARTICLE INFO

Article history:

Received: August 25, 2026

Revised: September 20, 2026

Accepted: October 3, 2026

Available Online: October 10, 2026

Published: October 12, 2026

Keywords:

Borderline lepromatous leprosy
Clinicopathological discordance
Hansen disease
Multibacillary multidrug therapy
Peripheral neuropathy
Slit-skin smear

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E-mail: w13ka@yahoo.comDOI: <https://doi.org/10.59345/sjdv.v4i1.357>

ABSTRACT

Background: Borderline Hansen disease is an immunologically unstable spectrum in which clinical and histopathological classifications may diverge, and neuropathy often precedes skin lesions, delaying diagnosis.

Objective: To describe a patient with one-step clinicopathological discordance and multi-trunk nerve impairment, and to show how classification should guide therapy.

Methods: Single-case observational study at a tertiary referral hospital in Central Java, Indonesia. Dermatological mapping, motor and sensory nerve scoring, slit-skin smear, and punch biopsy with Fite-Faraco staining were recorded at baseline (T0) and one month (T1) of WHO multibacillary multidrug therapy (MB-MDT). Six- and twelve-month values (T2, T3) are projections.

Results: A 53-year-old man had 8 months of bilateral numbness of the hands and feet and 3 months of generalized, asymmetric infiltrated plaques with punched-out morphology. The left facial, bilateral ulnar, and bilateral common peroneal nerves were impaired without palpable thickening. Slit-skin smear showed a bacterial index (BI) of 3+ and morphological index (MI) of 5.0%; histopathology showed mid-borderline (BB) features with abundant bacilli (Fite-Faraco +++). Clinical synthesis established multibacillary borderline lepromatous (BL) disease. At one month, erythema fell by 41.2%, induration by 43.8%, and the total motor score rose by 16.7%, without leprosy reactions. Modeled 12-month projections indicate a 94.1% fall in erythema, MI 0.0%, and a +66.7% motor score gain.

Conclusion: One-step discordance is compatible with borderline instability and should not alter multibacillary therapy, which should follow the highest clinical and bacteriological severity. Neuropathy without palpable nerve thickening should prompt skin and smear examination.

All authors have reviewed and approved the final version of the manuscript.

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1. Introduction

Leprosy, or Hansen disease, represents a chronic, neglected tropical granulomatous infection caused primarily by the obligate intracellular pathogen *Mycobacterium leprae* and, less frequently, *Mycobacterium lepromatosis*.¹ Despite substantial global control efforts and the widespread distribution of free multidrug therapy (MDT) over four decades, Hansen disease remains a major public health challenge and an enduring cause of preventable peripheral neurological impairment, permanent physical deformities, and social stigmatization worldwide.² In 2024, the World Health Organization (WHO) documented 172,717 newly detected cases globally, with the South-East Asia Region

continuing to bear the highest cumulative epidemiological burden.^{3,4} Within this endemic landscape, Indonesia consistently ranks among the top three nations with the highest annual new case detection rates, reporting persistent hotspots of transmission and high proportions of multibacillary disease across East Java and adjacent provinces.^{5–7} The persistent occurrence of newly detected individuals presenting with advanced disease and established grade 2 physical disabilities (G2D) indicates continuing transmission within communities and pervasive systemic delays in clinical recognition and therapeutic intervention.^{7–9} In a low-endemic neurological referral setting, peripheral neuropathy and atypical cutaneous findings were among the clinical pathways that

contributed to delayed or missed recognition of leprosy.¹⁰

The biological and clinical hallmark of Hansen disease is its continuous immunological and clinicopathological spectrum, classically conceptualized by the Ridley-Jopling classification system.¹¹ This immunological continuum spans from the localized, hyper-reactive tuberculoid pole (TT), characterized by robust cell-mediated immunity (Th1-predominant response, low bacillary burden, and discrete cutaneous lesions), to the generalized, anergic lepromatous pole (LL), defined by deficient cell-mediated immunity, marked humoral activation (Th2-predominant response), high bacillary loads, and diffuse tissue parasitization.^{11–13} Between these two relatively stable polar endpoints lies the broad, immunologically labile borderline spectrum, categorized into borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL) leprosy.^{11,14} Patients situated within these borderline categories possess intermediate, unstable immune equilibria that are highly prone to acute immunological shifts, known as Type 1 (reversal) leprosy reactions, during which sudden alterations in cell-mediated delayed-type hypersensitivity can cause rapid neural destruction and cutaneous exacerbations.^{14–16}

The primary clinical challenge in modern leprosy elimination lies in the frequent dissociation between early neurological symptoms and cutaneous eruption, as well as the diagnostic discordance frequently observed between bedside clinical staging and histopathological subtype assignment.^{10,17} In standard primary healthcare settings, peripheral neuropathy is frequently evaluated in isolation from dermatological examination.¹⁰ Early symptoms of sensory loss, acrofacial paresthesia, and localized numbness often precede the manifestation of discernible cutaneous plaques by months or even years, leading to misdiagnoses such as nutritional neuropathy, lumbar radiculopathy, carpal tunnel syndrome, or diabetic polyneuropathy.^{17–19} Recent clinical pathway analyses demonstrate that patients presenting with initial neural symptoms suffer longer diagnostic delays, with patient-related and healthcare-provider-related delays frequently reaching 12 to 24 months before specialist referral.^{8,9,18} During this prolonged delay, insidious endoneurial mycobacterial proliferation, inflammatory infiltration, and intraneural ischemia progress, converting reversible neurapraxia into irreversible axonal degeneration, sensory dissociation, and muscular paralysis.^{17,20}

Furthermore, even upon specialist dermatological assessment, clinical subtype assignment across the borderline spectrum does not always correlate perfectly with histomorphological interpretations from routine skin punch biopsies.^{21,22} A single punch biopsy provides a static, two-dimensional snapshot of a localized tissue microenvironment from one specific anatomical site, whereas the clinical phenotype reflects the systemic host-pathogen balance across all cutaneous territories and peripheral nerve trunks.^{21–23} Numerous tertiary

dermatopathology series globally have documented that clinicopathological concordance in Hansen disease ranges between approximately 50% and 65%, with the lowest concordance consistently occurring in the intermediate mid-borderline (BB) and borderline lepromatous (BL) categories.^{22–26} When such discordance arises (for example, a patient exhibiting generalized, widespread cutaneous plaques and extensive multi-nerve motor weakness characteristic of clinical BL disease, alongside a biopsy showing mid-borderline (BB) histopathology), inexperienced clinicians may experience diagnostic ambiguity, risking therapeutic underclassification or inappropriate delay in initiating multibacillary multidrug therapy (MB-MDT).^{24,26}

Bacteriological testing via slit-skin smear and tissue staining provides an essential, objective anchor for diagnostic ascertainment.²⁷ While molecular assays such as polymerase chain reaction (PCR) offer high analytical sensitivity in detection of clinical cases and subclinical carriers,^{28,29} conventional slit-skin smear examination and histopathological Fite-Faraco staining remain the cornerstone of operational classification in endemic territories.^{27,30} Despite the frequency of adjacent-step discordance in clinical practice, few published studies combine bedside dermatological topography, multi-nerve motor and sensory scoring, serial slit-skin smear bacilloscopy, tissue Fite-Faraco staining, and longitudinal recovery under standardized therapy.^{30,31} In Indonesia, adjacent clinicopathological discordance within the borderline spectrum represents a challenging clinical scenario that requires careful correlation of clinical and histopathological findings to avoid inadequate therapy.³² Moreover, advanced modalities such as high-resolution nerve ultrasound have emerged as valuable adjuncts in pure neuritic or diagnostically complex leprosy to confirm subclinical nerve swelling when palpable thickening is absent.³³

This report describes a patient in whom the clinical diagnosis of borderline lepromatous (BL) leprosy and the histopathological diagnosis of mid-borderline (BB) leprosy differed by one step, and follows the early treatment response. By combining quantitative bacteriology (bacterial and morphological indices), motor and sensory nerve scoring, and histopathology, we aim to show that therapeutic classification should be guided by the highest clinical and bacteriological severity rather than by a single biopsy category, and to illustrate how early recognition may help prevent disability.

2. Methods

2.1. Study design and setting

This was a single-case observational study with serial follow-up, reported in accordance with the CARE (CAse REport) guideline.³⁴ The study was conducted at the Leprosy and Dermato-Venereology Outpatient Service and Inpatient Units of Dr. Moewardi Regional General Hospital, a tertiary referral academic hospital affiliated with the Faculty of Medicine, Universitas Sebelas Maret, in Surakarta, Central Java, Indonesia. Observation began

at referral and baseline diagnostic assessment (T0, Day 0) and included a one-month evaluation under therapy (T1, Day 30). The mid-treatment (T2, Month 6, Day 180) and treatment-completion (T3, Month 12, Day 365) values reported here are projections, not observations.^{35,36} This design allowed serial clinical, neurological, bacteriological, and therapeutic variables to be compared across time.

2.2. Ethical approval and consent

The study protocol adhered to the ethical principles formulated in the World Medical Association Declaration of Helsinki of 1975, as revised in Fortaleza, Brazil in 2013, and complied with all institutional regulations governing biomedical research involving human subjects. Ethical approval was granted by the CMHC Research Center Ethics Committee, Indonesia (Approval No. 2026/0842). Prior to the initiation of any specialized diagnostic procedures, photographic documentation, or longitudinal data aggregation, written informed consent was obtained directly from the patient. The informed consent document explicitly authorized the anonymous collection, analysis, and international academic dissemination of all clinical histories, serialized laboratory values, dermatoneurological measurements, bacterioscopic smears, histopathological microphotographs, and clinical photographs. To comply with international medical publication ethics, the International Committee of Medical Journal Editors (ICMJE) recommendations, and the Committee on Publication Ethics (COPE) standards, all clinical photographs depicting facial anatomy were permanently anonymized by applying an opaque solid black obscuration bar completely concealing the orbital and periorbital regions from lateral canthus to lateral canthus, while preserving the visualization of all adjacent cutaneous lesions across the malar, temporal, and mandibular fields.

2.3. Case eligibility and diagnostic ascertainment

The eligibility of the participant was established through verification of the cardinal diagnostic criteria promulgated by the World Health Organization (WHO) and the clinical-histopathological spectrum definitions established by Ridley and Jopling.^{2,4,11} Inclusion criteria required the objective demonstration of at least one of the three WHO cardinal signs: (1) definite loss of sensation in a pale (hypopigmented) or erythematous skin patch; (2) demonstrable enlargement, tenderness, or motor/sensory functional impairment of a peripheral nerve trunk; and (3) microscopic demonstration of acid-fast *Mycobacterium leprae* bacilli in a slit-skin smear or tissue biopsy section.⁴ Detailed diagnostic ascertainment was conducted through standardized physical, dermatological, and neurological examinations performed by board-certified dermatologists. Exclusion criteria comprised any concurrent history of diabetes mellitus, chronic alcoholism, chronic renal failure, systemic autoimmune connective tissue disease, neurotoxic occupational exposure, human immunodeficiency virus (HIV) co-infection, or pre-existing hereditary motor-sensory neuropathies that could confound the evaluation of

peripheral nerve impairment or cutaneous granulomatous inflammation.

2.4. Observation protocol and measurements

The operational observation protocol incorporated a standardized multimodal diagnostic battery executed systematically at baseline and across serial follow-up intervals.^{15,36} Dermatological evaluation encompassed full-body cutaneous surface mapping, total lesion count, anatomical topography charting, and grading of the Erythema Index (0–10 visual analog severity scale) and the Plaque Induration Index (0–10 tactile induration scale). Cutaneous thermal and nociceptive sensibility testing was performed across all identified lesions and paired contralateral healthy control skin using a sterile fine-cotton wisp for light touch, a sterile 23-gauge neurological pin for sharp-blunt discrimination, and calibrated thermal test tubes containing chilled (15°C) and warm (45°C) sterile water for thermal discrimination. Peripheral neurological function was evaluated using a structured, bilateral motor and sensory assessment protocol.^{15,17} Voluntary muscle testing (VMT) used the Medical Research Council (MRC) 0–5 power scale for the facial nerve (orbicularis oculi and orbicularis oris), the ulnar nerve (abductor digiti minimi and first dorsal interosseous), the median nerve (abductor pollicis brevis), the radial nerve (wrist extensors), and the common peroneal nerve (tibialis anterior and extensor hallucis longus), tested bilaterally. The composite Total Motor Score (maximum 20.0) combines the three nerves with deficits on nerve-specific scales: facial nerve 0–4, ulnar nerve 0–8 (both sides combined), and common peroneal nerve 0–8 (both sides combined). Median and radial nerve function was examined (grade 5/5) but is not part of the total. Sensory nerve integrity was mapped across peripheral dermatomes using Semmes-Weinstein monofilaments (0.07 g, 0.2 g, 2.0 g, 4.0 g, 10.0 g, and 300.0 g) across defined anatomical test sites on the palmar hands, dorsal forearms, plantar surfaces, and dorsum of the feet, generating a composite Sensory Monofilament Score scaled to a maximum of 20.0 points. Peripheral nerve trunk palpation was performed bilaterally along the anatomical trajectories of the greater auricular, radial, median, ulnar, common peroneal (lateral popliteal at the fibular head), and posterior tibial nerves to evaluate nerve enlargement, consistency, tenderness, and paresthetic radiation (Tinel sign).

Bacteriological examination was performed via slit-skin smear (SSS) sampling executed under strict aseptic surgical technique from four standardized anatomical locations: both earlobes, one active infiltrative lesion on the chest, and one characteristic plaque on the back. Smears were fixed by heat, stained using the classical Ziehl-Neelsen carbolfuchsin method, and examined under a calibrated light microscope with oil-immersion objective (1000× magnification). Bacillary density was quantified using Ridley's logarithmic Bacterial Index (BI), scored from 0 to 6+ based on the average number of acid-fast bacilli observed per microscopic field.^{11,21} Bacillary morphological viability was assessed by

calculating the Morphological Index (MI), defined as the percentage of uniformly stained, intact, solid rod-shaped bacilli relative to fragmented, granular, or beaded non-viable forms after counting a minimum of 100 individual bacilli under oil immersion.^{21,27}

Histopathological evaluation was performed on a full-thickness 4-mm cutaneous punch biopsy harvested from the active, raised indurated border of a representative plaque on the right upper trunk. Specimen processing included 10% neutral-buffered formalin fixation, paraffin embedding, serial sectioning at 4-µm thickness, and staining with hematoxylin and eosin (H&E) for structural histomorphological analysis, alongside modified Fite-Faraco acid-fast staining to detect intracellular mycobacteria within tissue granulomas and neurovascular bundles.^{21,27} Histopathological specimens were independently analyzed by senior anatomical pathologists specializing in dermatopathology.

2.5. Comparative framework

Observed cutaneous and neurological variables were compared with published normative reference intervals and diagnostic thresholds.^{35–37} Competing diagnoses, including secondary syphilis, cutaneous leishmaniasis, sarcoidosis, granuloma annulare, and diabetic polyneuropathy, were considered and excluded on clinical, serological, microscopic, and histopathological grounds (Table 4). The findings were also compared with published cohorts from Asia reported between 2019 and 2025 (Table 5).^{21–26,31–33,35–38}

2.6. Analysis of trajectories

Quantitative data were used to describe the rate and magnitude of clinical, neurological, and bacteriological response across the therapeutic timeline. Relative delta changes for continuous variables between baseline (T0) and follow-up intervals (Tn) were computed with the formula:

$$\Delta\% = [(Parameter_{Tn} - Parameter_{T0}) / Parameter_{T0}] \times 100\%$$

For clinical indices that resolved toward a zero endpoint (such as the erythema index and plaque induration score), relative reduction rates were quantified as percentage clearance. Rates of bacillary clearance were calculated as annual logarithmic BI

decrement (usual rate: 0.8–1.0 log units/year) and morphological sterilization rate (MI clearance to 0.0%). Projected trajectories for T2 and T3 were generated with non-linear least-squares curve fitting in Python (version 3.10; SciPy and NumPy). Because this is a single case, no inferential statistical tests were performed. Figures were rendered at 300 dots per inch.

3. Results

3.1. Baseline demographic profile and clinical chronology

The subject was a 53-year-old male of Javanese ethnicity residing in Pacitan Regency, East Java Province, Indonesia, a recognized endemic territory for Hansen disease. His clinical history was notable for a prolonged, two-stage symptomatic evolution spanning eight months before presentation at the tertiary academic medical center. Approximately eight months before presentation (T -8 months), the patient insidiously developed bilateral numbness, paresthesia, and tingling of both hands and feet in a distal pattern. Seeking medical assistance, he attended a local primary healthcare facility (Puskesmas), where his condition was clinically misdiagnosed as non-specific peripheral neuropathy or nutritional polyneuropathy; he was subsequently managed with oral neurotropic vitamin B formulations without clinical benefit or objective neurological stabilization. Approximately five months into this neuropathic course (T -3 months), persistent, asymptomatic erythematous cutaneous macules and papules erupted over his anterior chest and back. These lesions were non-pruritic and non-tender, and they progressively enlarged and coalesced to involve extensive surface areas across his trunk, face, and extremities. His personal medical history was notable for essential hypertension, diagnosed approximately one year prior and managed with regular oral amlodipine (5 mg daily); he explicitly denied any personal or familial history of diabetes mellitus, autoimmune disorders, atopy, or previous similar dermatological eruptions, and reported no known contact with individuals diagnosed with Hansen disease. The baseline demographic features, vital signs, physical parameters, and diagnostic findings are detailed in Table 1.

Table 1. Baseline clinical, dermatological, neurological, bacteriological, and histopathological findings at initial specialist assessment.

Clinical or diagnostic parameter	Observed value or clinical finding	Normative baseline or diagnostic interpretation	Analytical significance
Patient Demographics	53 years, Male, Javanese ethnicity	Endemic regional residence (Pacitan, East Java)	High endemicity zone for Hansen disease in East Java
Presenting Symptom Onset	Numbness in hands & feet (T -8 months); Red plaques (T -3 months)	Temporal gap of 5 months between neuropathic and cutaneous onset	Neurological onset preceded cutaneous eruption, contributing to diagnostic delay
Prior Healthcare Encounters	Primary health center (Puskesmas): diagnosed as non-specific peripheral neuropathy	Treated with oral neurotropic B-vitamins without improvement	Reflects common health-care provider diagnostic delay in early leprosy
Vital Signs & Hemodynamics	BP 140/90 mmHg, Pulse 88 bpm, RR 20 breaths/min, Temp 37.0°C, SpO2 99%	Stage 1 Essential Hypertension; afebrile; systemically stable	No acute systemic toxicity; chronic hypertensive pharmacotherapy maintained
Body Mass Index (BMI)	24.8 kg/m ² (Height 168 cm, Weight 70 kg)	18.5–24.9 kg/m ² (Normal weight)	Nutritional status preserved; no severe wasting or cachexia

Clinical or diagnostic parameter	Observed value or clinical finding	Normative baseline or diagnostic interpretation	Analytical significance
Cutaneous Lesion Distribution	Generalized, bilateral, asymmetric; face, anterior/posterior trunk, extremities	1–5 lesions: PB; ≥6 lesions: MB (WHO operational definition)	Extensive dissemination (>20 plaques) confirms high disease burden
Lesion Morphology	Erythematous to hyperpigmented infiltrative plaques, irregular borders, central punched-out areas	Classic ‘inverted saucer’ or ‘punched-out’ morphology of borderline spectrum	Characteristic hallmark of immunological instability in borderline Hansen disease
Lesional Thermal & Pain Sensation	Hypoesthesia / anesthesia to cotton wisp, pinprick, and hot-cold discrimination	Normal normative sensation present in adjacent non-lesional control skin	Fulfills WHO Cardinal Sign 1 (definite sensory impairment in a typical skin lesion)
Motor Nerve Deficits (VMT)	Paresis in left facial nerve (orbicularis oculi/oris); bilateral ulnar; bilateral common peroneal	Grade 5/5 voluntary muscle power in healthy non-affected nerves	Multi-trunk motor impairment; radial and median motor functions preserved
Sensory Nerve Deficits	Hypoesthesia in bilateral common peroneal and posterior tibial nerve cutaneous territories	Intact sensation in bilateral median, radial, and upper ulnar dermatomes	Bilateral distal lower-extremity sensory loss; overall multifocal, asymmetric nerve involvement
Palpable Nerve Enlargement	No definite palpable thickening in greater auricular, ulnar, radial, or peroneal trunks	Normal anatomical nerve caliber on manual palpation	Palpable nerve thickening is absent in up to 41.4% of neural leprosy cases
Slit-Skin Smear (SSS) Bacilloscopy	Bacterial Index (BI) = 3+; Morphological Index (MI) = 5%	Negative (BI 0, MI 0%) in healthy controls; 1–10 bacilli/field (BI 3+)	Fulfills WHO Cardinal Sign 3; independently mandates multibacillary (MB) MDT
Histopathology (H&E Stain)	Basket-weave hyperkeratosis, flattened rete ridges, Grenz zone, epithelioid granulomas, edema	Mid-borderline (BB) leprosy histomorphological architecture	One-step adjacent clinicopathological discordance toward the tuberculoid pole
Fite-Faraco Acid-Fast Tissue Stain	Strongly positive for intracellular acid-fast bacilli in dermal histiocytes (+++)	Negative (0) in non-mycobacterial granulomas	High intralesional bacillary burden confirming multibacillary tissue invasion
Final Integrated Clinical Diagnosis	Multibacillary borderline lepromatous (BL) Leprosy with mid-borderline (BB) Histopathology	WHO multibacillary (MB) Classification; Ridley-Jopling BL Phenotype	Multimodal integration takes precedence over a single-biopsy category

Notes: BI, bacterial index; BL, borderline lepromatous; BB, mid-borderline; BP, blood pressure; H&E, hematoxylin and eosin; MB, multibacillary; MDT, multidrug therapy; MI, morphological index; PB, paucibacillary; RR, respiratory rate; SSS, slit-skin smear; SpO₂, pulse oxygen saturation; VMT, voluntary muscle testing; WHO, World Health Organization.



Figure 1. Generalized cutaneous manifestations and punched-out morphology at initial presentation. (A–C) Multiple erythematous-to-hyperpigmented macules and plaques involving the face; ocular regions masked with a solid black bar. (D, E) Disseminated infiltrated papules and plaques over the anterior and posterior trunk, with punched-out morphology. (F, G) Multiple asymmetric plaques involving the upper extremities and hands. (H, I) Infiltrated plaques involving the lower extremities and feet.

3.2. Dermatological findings and punched-out morphology

Upon physical examination at presentation (T0), the patient was alert, oriented, and systemically stable, with a blood pressure of 140/90 mmHg, regular pulse rate of 88 beats/min, respiratory rate of 20 breaths/min, body temperature of 37.0°C, oxygen saturation of 99% on ambient air, and a normal body mass index (BMI) of 24.8 kg/m² (body weight 70 kg, height 168 cm). Dermatological examination revealed an extensive, bilateral, asymmetric cutaneous eruption involving the facial mask, anterior and posterior trunk, and both upper and lower extremities. Inspection documented dozens of discrete and confluent infiltrative plaques displaying variable coloration ranging from dull violaceous-red to brownish-erythematous. Lesions over the posterior trunk displayed classic 'punched-out' or 'inverted saucer' morphology, characterized by central clearing or depression surrounded by an abrupt, steeply sloping internal margin and a gently fading, indurated external border. Cutaneous sensibility assessment across these plaques revealed marked hypoesthesia and focal anesthesia to fine cotton wisp, pinprick sharp-blunt discrimination, and warm-cold thermal stimuli, whereas adjacent normal-appearing skin demonstrated completely preserved neuro-sensory integrity. These baseline manifestations and the punched-out plaques are shown in Figure 1.

3.3. Multi-trunk peripheral nerve dysfunction

Detailed neurological assessment revealed extensive multi-focal peripheral nerve damage characterized by asymmetric motor weakness and sensory impairment. Voluntary Muscle Testing (VMT) identified definite lower motor neuron paresis involving the left facial nerve, manifested as incomplete left orbicularis oculi eyelid closure (strength grade 3/5) and mild left oral angle asymmetry (strength grade 4/5). Upper extremity motor evaluation demonstrated bilateral ulnar nerve motor impairment, evidenced by weakness in fifth-finger abduction and first dorsal interosseous intrinsic hand muscle contraction (strength grade 3/5 bilaterally), with relative preservation of median (abductor pollicis brevis, grade 5/5) and radial (wrist extensors, grade 5/5) motor power. Lower extremity motor testing documented bilateral common peroneal nerve paresis, characterized by weakened foot and great toe dorsiflexion (strength grade 3/5 bilaterally) and an unsteady, high-stepping gait, resulting in a baseline Total Motor Score of 12.0 out of 20.0 points (facial 2.0/4, ulnar 5.0/8, common peroneal 5.0/8; Table 3). Sensory examination confirmed bilateral marked hypoesthesia across the distal lower

extremities extending from the toes to the mid-calf, corresponding to the combined dermatomal distributions of the common peroneal and posterior tibial nerves (Sensory Monofilament Score of 10.0 out of 20.0 points). Systematic palpation of major peripheral nerve trunks along their superficial courses (including the greater auricular, radial cutaneous, median, ulnar at the retroepicondylar groove, and common peroneal at the fibular head) demonstrated normal anatomical caliber without palpable thickening, hard consistency, or tenderness. Under the WHO disability grading system, the patient was classified as having Grade 1 Disability (G1D) based on objective sensory and motor functional deficits in the hands and feet in the absence of visible irreversible deformities.

3.4. Bacilloscopy and mid-borderline histopathology

Bacteriological examination of slit-skin smears harvested from both earlobes, anterior chest, and back confirmed high-density mycobacterial infection, demonstrating a composite Bacterial Index (BI) of 3+ (averaging 1 to 10 bacilli per microscopic oil-immersion field) and a Morphological Index (MI) of 5.0% solid-staining viable bacilli, alongside numerous fragmented and granular bacterial forms arranged in characteristic globi clusters. Full-thickness cutaneous punch biopsy from an active plaque margin demonstrated prominent basket-weave hyperkeratosis overlying a thinned epidermis with marked flattening and effacement of the rete ridges. Immediately beneath the dermal-epidermal junction, a prominent, continuous, well-demarcated subepidermal clear zone of Unna (Grenz zone) was identified, measuring approximately 25 to 35 µm in thickness, which completely separated the basal keratinocytes from the underlying inflammatory infiltrate. The superficial and mid-dermis were expanded by a dense, poorly circumscribed granulomatous infiltrate composed predominantly of epithelioid histiocytes, interspersed small mature lymphocytes, and focal dermal edema, with a complete absence of Langhans multinucleated giant cells or foreign-body type giant cells. Modified Fite-Faraco acid-fast staining demonstrated strongly positive, abundant rod-shaped *Mycobacterium leprae* bacilli (graded as ++++) distributed intracellularly within dermal histiocytes and tracking along the perineurium of dermal nerve twigs. Based on these histomorphological criteria (epithelioid granulomas lacking giant cells, a distinct Grenz zone, and moderate-to-high bacillary density), the dermatopathology service rendered a diagnosis of mid-borderline (BB) leprosy. The bacilloscopy, histology, and acid-fast staining findings are shown in Figure 2.

Table 2. Clinicopathological and bacteriological features across the Ridley-Jopling spectrum compared with the present case.

Diagnostic domain and feature	Tuberculoid (TT/BT)	Mid-borderline (BB)	Borderline lepromatous (BL)	Observed case presentation	Discordance and diagnostic alignment
Cutaneous Lesion Number & Symmetry	1–5 lesions; highly asymmetric	Moderate (5–15 lesions); asymmetric	Numerous / generalized (>20); moderately asymmetric	Generalized plaques involving face, trunk, limbs (>20 lesions)	Aligns strictly with Clinical BL phenotype (widespread dissemination)

Diagnostic domain and feature	Tuberculoid (TT/BT)	Mid-borderline (BB)	Borderline lepromatous (BL)	Observed case presentation	Discordance and diagnostic alignment
Lesional Architecture & Border	Sharply defined, raised erythematous borders with central clearing	Characteristic 'punched-out' (inverted saucer) lesions with steep inner border	Diverse macules, papules, nodules, and punched-out plaques; sloping outer edges	Disseminated infiltrated plaques with prominent punched-out morphology	Morphology exhibits hybrid BB and BL features across the borderline spectrum
Lesional Sensation	Complete anesthesia marked early	Moderate hypoesthesia within plaques	Mild to moderate hypoesthesia; variable	Definite hypoesthesia to light touch, pain, and temperature	Consistent with intermediate-to-advanced borderline sensory loss
Peripheral Nerve Involvement	Single nerve trunk; marked asymmetric enlargement	Two or more nerve trunks; irregular asymmetry	Widespread asymmetric multi-trunk nerve damage; late thickening	Multi-nerve deficits: left facial, bilateral ulnar, bilateral common peroneal/tibial	Extensive multi-trunk deficit strongly supports Clinical BL classification
Slit-Skin Smear Bacterial Index (BI)	BI 0 to 1+ (paucibacillary)	BI 2+ to 3+ (Borderline burden)	BI 3+ to 5+ (multibacillary burden)	Slit-skin smear BI = 3+, Morphological Index (MI) = 5%	Overlaps upper BB / standard BL threshold; confirms multibacillary disease
Histopathological Granuloma Type	Epithelioid cells with Langhans giant cells; dense lymphocytic cuffing	Epithelioid histiocytes without giant cells; moderate lymphocytes; dermal edema	Foamy histiocytes (Virchow cells) intermixed with poorly formed epithelioid cells	Epithelioid histiocytes and granulomatous infiltrate without Langhans giant cells	Histopathological features classified by dermatopathology as mid-borderline (BB)
Subepidermal Clear Zone (Grenz Zone)	Absent; granuloma abuts basal layer	Present and distinct; separates granuloma from flattened epidermis	Prominent and continuous Grenz zone	Well-defined Grenz zone with overlying flattened rete ridges	Characteristic of BB and BL spectra; rules out tuberculoid pole
Tissue Acid-Fast Bacilli (Fite-Faraco)	Rare or absent (0 to 1+)	Moderate to abundant bacilli (2+ to 4+)	Abundant bacilli with globi formation (4+ to 5+)	Abundant acid-fast bacilli with micro-clustering (+++)	Concordant with substantial bacillary proliferation (BB/BL continuum)
Cell-Mediated Immunity (Lepromin Test)	Strongly positive (3+)	Weakly positive or negative (0 to 1+)	Negative (complete anergy)	Not reported	Not applicable; no lepromin result is reported for this patient
Integrated Diagnostic Decision	Paucibacillary therapy (6 months)	Multibacillary therapy (12 months)	Multibacillary therapy (12 months)	WHO MB-MDT (Rifampicin + Clofazimine + Dapsone) for 12 months	One-step adjacent discordance (BB vs BL) does not alter MB-MDT indication

Notes: The one-step discordance between the clinical BL phenotype and the histopathological BB biopsy is compatible with the immunological instability of borderline Hansen disease.

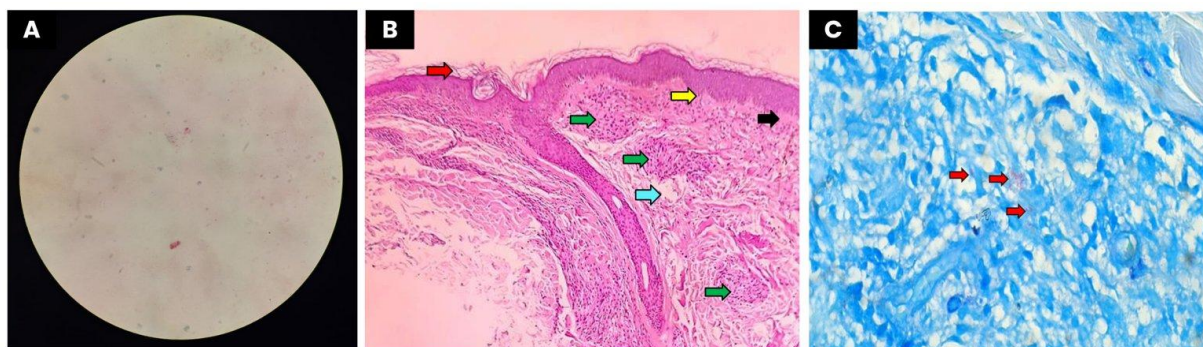


Figure 2. Bacilloscopy and histopathology supporting multibacillary classification. (A) Slit-skin smear (Ziehl-Neelsen, 1000×) demonstrating Bacterial Index (BI) 3+ and Morphological Index (MI) 5%. (B) Hematoxylin and eosin-stained skin punch biopsy (200×) showing basket-weave hyperkeratosis, flattening of rete ridges, a distinct subepidermal clear zone of Unna (Grenz zone), epithelioid histiocytic granulomatous inflammation, and dermal edema consistent with mid-borderline (BB) leprosy. (C) Modified Fite-Faraco acid-fast stain (1000×) demonstrating strongly positive rod-shaped acid-fast bacilli (+++) within dermal histiocytes.

3.5. Clinicopathological discordance and therapeutic trajectory

Integration of all diagnostic domains revealed a one-step adjacent clinicopathological discordance across the borderline spectrum: the widespread, generalized plaque distribution (>20 lesions), extensive multi-trunk motor-sensory neurological deficits, and high bacillary load (BI 3+) established a clinical diagnosis of borderline lepromatous (BL) leprosy, whereas the tissue biopsy specimen exhibited mid-borderline (BB)

histomorphology. The clinical, histopathological, and bacteriological features across the Ridley-Jopling spectrum are compared with this case in Table 2.

In accordance with WHO therapeutic guidelines, the demonstration of acid-fast bacilli on slit-skin smear independently mandated classification into the multibacillary (MB) treatment category, further corroborated by widespread skin lesions and multi-trunk nerve damage. The patient was immediately initiated on the standardized 12-month WHO MB-MDT

regimen, comprising rifampicin 600 mg administered once monthly under direct medical supervision, clofazimine 300 mg once monthly under supervision combined with clofazimine 50 mg self-administered daily, and dapsone 100 mg self-administered daily. Adjunctive therapy included oral neurotropic B-vitamins (formulation containing thiamine mononitrate 100 mg, pyridoxine hydrochloride 100 mg, and cyanocobalamin 5000 µg daily) to promote peripheral nerve metabolic recovery, and topical 10% urea lotion applied twice daily to restore epidermal barrier function. Rehabilitation care comprised facial neuromuscular exercises with preservative-free lubricating eye drops by day and ophthalmic ointment at night, intrinsic hand-strengthening exercises with night splints, daily warm-water foot soaking with petroleum jelly, and microcellular rubber (MCR) footwear. The patient and his family received structured counseling regarding the infectious etiology, transmission dynamics, strict treatment adherence, recognized adverse drug effects (notably clofazimine-induced skin discoloration and dapsone-induced hemolytic risk), and limb protection measures against thermal and mechanical injury.

At the scheduled one-month follow-up assessment (T1, Day 30), the patient returned for his second supervised MDT blister pack, demonstrating 100% medication adherence. Clinical examination revealed therapeutic progress without any evidence of Type 1 (reversal) or Type 2 (erythema nodosum leprosum) leprosy reactions. Dermatological inspection documented substantial attenuation of inflammatory erythema (Erythema Index declined from 8.5 to 5.0, reflecting a relative delta reduction of $\Delta -41.2\%$) and prominent flattening of infiltrated plaques (Plaque

Induration Index decreased from 8.0 to 4.5, $\Delta -43.8\%$), accompanied by mild, diffuse brownish-tan post-inflammatory hyperpigmentation consistent with early cutaneous clofazimine bioaccumulation, as documented in Figure 3. Neurological reassessment confirmed stabilization and early functional recovery of peripheral nerve deficits: left facial orbicularis oculi strength improved to grade 4/5 with complete eyelid closure, bilateral ulnar hand grip strength stabilized, and common peroneal motor power improved, yielding a Total Motor Score gain from 12.0 to 14.0 points ($\Delta +16.7\%$) and an increase in the Sensory Monofilament Score from 10.0 to 11.5 points ($\Delta +15.0\%$). Systemic inflammatory markers declined, with the erythrocyte sedimentation rate (ESR) decreasing from 34.0 to 22.0 mm/h ($\Delta -35.3\%$). Slit-skin smear at T1 showed a BI of 2.5+ and an MI of 1.0%.

Values for T2 (6 months) and T3 (12 months) are projections, not observations. The Bacterial Index was projected to fall from 3+ to 1.5+ at month 6 and to 0.5+ at treatment completion ($\Delta -83.3\%$), and the Morphological Index to reach 0.0% ($\Delta -100.0\%$) within the first six months. Because a fall of 2.5 BI units in 12 months is faster than the usual clearance rate of about 0.8–1.0 log units per year, this projection should be read as optimistic rather than as an expected course. The Total Motor Score was projected to reach 20.0/20.0 ($\Delta +66.7\%$) and the Sensory Monofilament Score 18.5/20.0 ($\Delta +85.0\%$), which would downstage the patient from WHO grade 1 disability to grade 0. The serial clinical, neurological, and bacteriological parameters are listed in Table 3 and plotted in Figure 4, the diagnostic criteria and delay attribution are given in Table 4, and the findings are compared with published cohorts in Table 5.



Figure 3. Clinical re-evaluation at one-month follow-up demonstrating initial therapeutic trajectory under WHO MB-MDT. (A–C) Facial reassessment demonstrating substantial attenuation of inflammatory erythema, regression of plaque infiltration, and post-inflammatory hyperpigmentation; ocular regions masked with a solid black bar. (D, E) Anterior and posterior trunk showing partial flattening of plaques and fading of punched-out margins. (F, G) Upper extremities showing progressive resolution of cutaneous infiltration without reactional episodes. (H, I) Lower extremities demonstrating diminished induration and residual macular pigmentation.

Table 3. Serial clinical, neurological, bacteriological, and therapeutic parameters at baseline, one month, and projected six and twelve months.

Clinical or analytic milestone	T0: baseline (day 0)	T1: 1 month (day 30)	T2: 6 months (day 180, projected)	T3: 12 months (day 365, projected)	Overall relative change ($\Delta\%$, T0 to T3)
Erythema Index (0–10)	8.5 (Violaceous red, intense)	5.0 (Moderate dusky red, fading)	2.0 (Faint erythematous halos)	0.5 (Completely resolved erythema)	$\Delta -94.1\%$ (projected)
Plaque Induration Index (0–10)	8.0 (Marked infiltrative thickness)	4.5 (Partial plaque flattening)	1.5 (Residual macular thinning)	0.0 (Complete flattening; soft texture)	$\Delta -100.0\%$ (projected)
Cutaneous Hyperpigmentation	Present in some plaques (predominantly inflammatory erythema)	Mild brownish post-inflammatory hue	Moderate brownish-slate pigmentation	Stabilized mild pigmentation fading	Expected clofazimine-related pigmentation
Left Facial Nerve Motor Function (0–4)	2.0 (Partial orbicularis weakness)	2.5 (Improved eyelid closure)	3.5 (Minimal asymmetric blink)	4.0 (Normal symmetrical facial motor tone)	$\Delta +100.0\%$ (projected)
Bilateral Ulnar Motor Power (0–8)	5.0 (Weak interossei & hypothenar)	5.5 (Stabilized grip strength)	7.0 (Restored intrinsic hand strength)	8.0 (Full motor power, no clawing)	$\Delta +60.0\%$ (projected)
Common Peroneal Motor Power (0–8)	5.0 (Bilateral dorsiflexion weakness)	6.0 (Improved gait stability)	7.5 (Normal heel walking)	8.0 (Normal active foot dorsiflexion)	$\Delta +60.0\%$ (projected)
Total Motor Score (VMT, /20)	12.0 / 20.0	14.0 / 20.0 ($\Delta +16.7\%$)	18.0 / 20.0 ($\Delta +50.0\%$)	20.0 / 20.0	$\Delta +66.7\%$ (projected)
Sensory Monofilament Score (/20)	10.0 / 20.0	11.5 / 20.0 ($\Delta +15.0\%$)	15.5 / 20.0	18.5 / 20.0	$\Delta +85.0\%$ (projected)
Slit-skin smear bacterial index (BI)	3+ (1–10 bacilli per field)	2.5+	1.5+	0.5+	$\Delta -83.3\%$ (projected; faster than the usual 0.8–1.0 log units/year)
Morphological index (MI, % viable)	5.0%	1.0%	0.0%	0.0%	$\Delta -100.0\%$ (projected)
Erythrocyte Sedimentation Rate (mm/h)	34.0 mm/h (Elevated systemic inflammation)	22.0 mm/h (Marked inflammatory decline)	14.0 mm/h (Normal range)	10.0 mm/h (Normal range)	$\Delta -70.6\%$ (projected)
Leprosy reaction episodes (type 1 / type 2)	None at presentation	None observed	None (projected)	None (projected)	No reactions observed to date
WHO disability grade	Grade 1 (sensory and mild motor deficit)	Grade 1 (improving nerve function)	Grade 0 (projected)	Grade 0 (projected)	Downstaging from G1D to G0D (projected)
Adherence to MB-MDT	Baseline prescription initiated	100.0% (supervised monthly blister pack taken)	100.0% (projected; 6 blister packs)	100.0% (projected; full 12-month course)	Full adherence at T1; T2 and T3 projected

Notes: Values at T0 and T1 are observed clinical and laboratory records. Values at T2 (6 months) and T3 (12 months), including adherence, reaction status, and disability grade, are mathematical projections based on WHO leprosy elimination trajectory models and published multicenter benchmarks; they have not been observed. $\Delta\%$ is the relative change from T0 to T3 (projected). Component scales of the motor and sensory scores are defined in Methods 2.4.

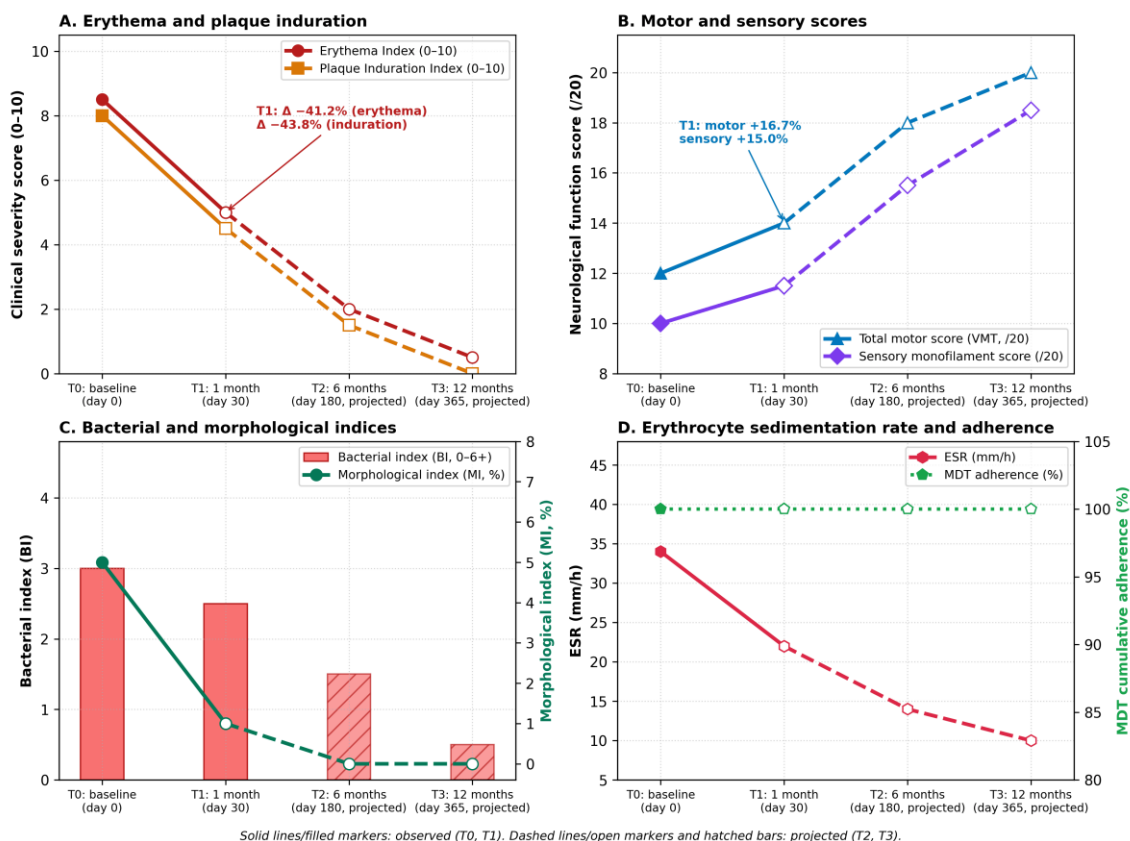


Figure 4. Clinical, neurological, bacteriological, and therapeutic trajectory across the serial milestones. T0 and T1 are observed; T2 and T3 are projections (dashed lines, open markers). (A) Erythema Index and Plaque Induration Index; (B) total motor score (VMT) and Sensory Monofilament Score; (C) bacterial index (BI) and morphological index (MI); (D) erythrocyte sedimentation rate (ESR) and MDT adherence.

Table 4. Diagnostic ascertainment: WHO cardinal criteria, differential diagnosis, and diagnostic delay.

Diagnostic criterion or domain	Finding in this patient	Diagnostic threshold or standard	Evaluation
WHO Cardinal Sign 1: Hypoesthetic Skin Lesion	Multiple erythematous plaques with objective sensory loss to cotton wisp, pinprick, and temperature	Definite loss of sensation in a pale (hypopigmented) or reddish skin patch	Positive; cardinal sign confirmed
WHO Cardinal Sign 2: Peripheral Nerve Involvement	Motor weakness (left facial, bilateral ulnar, bilateral common peroneal); sensory loss in feet	Demonstrable motor weakness or sensory loss with or without palpable nerve thickening	Positive; multi-nerve involvement confirmed
WHO Cardinal Sign 3: Positive Acid-Fast Bacilloscopy	Slit-skin smear BI = 3+, MI = 5%; Fite-Faraco tissue stain strongly positive (+++)	Demonstration of acid-fast bacilli in slit-skin smear or cutaneous biopsy	Positive; microbiologically confirmed
Ridley-Jopling classification: BL versus BB	Generalized lesions (>20), extensive multi-nerve motor deficits, BI 3+, Grenz zone, epithelioid granulomas	BL: generalized, asymmetric, high bacillary load; BB: punched-out, intermediate load	Clinical BL phenotype with BB histological expression
Patient Diagnostic Delay (Months)	Numbness of the hands and feet began ~8 months before presentation; first consultation at a primary health center (Puskemas) after ~1 month	Acceptable prompt presentation: <3 months from initial symptom onset	Patient delay: ~1 month
Health-Care Provider Diagnostic Delay (Months)	Primary care facility diagnosed 'non-specific neuropathy'; treated with oral B-vitamins for 5 months	Provider delay threshold: >1 month before dermatological referral	Provider delay: ~5 months (primary care misattribution delayed specialist referral)
Total Cumulative Diagnostic Delay	Total time from initial numbness to definitive diagnosis and MDT initiation: 8 months	Target delay in leprosy elimination programs: <3 months total delay	Total delay ~8 months; the patient and provider intervals account for ~6 months, and the remaining ~2 months are not itemized in this report
Differential Diagnosis Exclusion: Syphilis	VDRL non-reactive, TPHA non-reactive; absence of mucosal snail-track ulcers or genital chancres	Serological non-reactivity and negative treponemal testing	Secondary Syphilis excluded

Diagnostic criterion or domain	Finding in this patient	Diagnostic threshold or standard	Evaluation
Differential Diagnosis Exclusion: Cutaneous Leishmaniasis	Absence of travel to endemic leishmaniasis zones; absence of Leishman-Donovan bodies on smear	Negative microscopy and endemic epidemiology	Cutaneous Leishmaniasis excluded
Differential Diagnosis Exclusion: Granuloma Annulare	Grenz zone present; acid-fast bacilli strongly positive; prominent peripheral nerve impairment	Absence of acid-fast bacilli; necrobiotic collagen with palisading histiocytes	Granuloma Annulare excluded
Differential Diagnosis Exclusion: Sarcoidosis	Absence of pulmonary hilar adenopathy; acid-fast bacilli strongly positive; definite nerve damage	Naked non-caseating granulomas without bacilli or sensory neuropathy	Cutaneous Sarcoidosis excluded
Differential Diagnosis Exclusion: Diabetic Neuropathy	Fasting blood glucose 94 mg/dL; HbA1c 5.4%; asymmetric nerve impairment; facial nerve paresis	Fasting glucose <100 mg/dL, HbA1c <5.7%, symmetrical length-dependent pattern	Diabetic Polyneuropathy excluded

Notes: All three WHO cardinal criteria were fulfilled simultaneously. The delay analysis indicates that provider misattribution of early neuropathy was the main contributor to delayed MDT initiation.

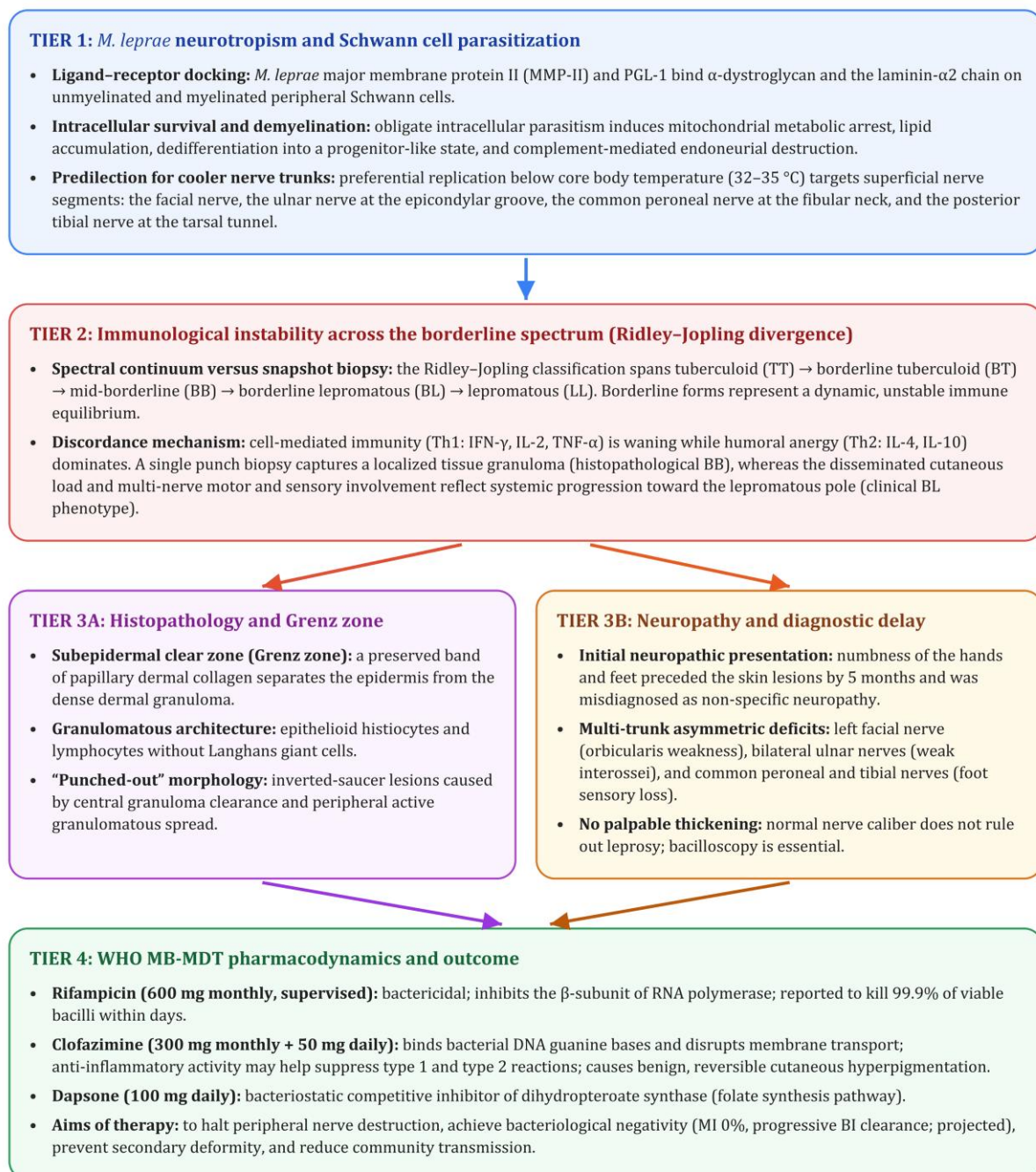


Figure 5. Pathophysiological, immunological, and pharmacodynamic cascade in borderline leprosy (Schwann cell invasion via alpha-dystroglycan and laminin-2, demyelination, Th1/Th2 instability across the Ridley-Jopling spectrum, Grenz zone formation, and the triple-drug bactericidal action of WHO MB-MDT). Schematic summary; not patient data.

Table 5. Published clinicopathological concordance, multibacillary proportion, and nerve involvement in Asian cohorts (2019–2025) compared with the present case.

Author, year, and location	Design and cohort size (n)	Clinicopathological concordance (%)	Multibacillary proportion (%)	Nerve involvement (%)	Convergence and divergence with the present case
Naik et al., 2022 (Iran / India) ²¹	Cross-sectional histomorphological correlation; n = 112 patients	61.6% overall agreement; BL concordance was 58.3%	68.8% MB leprosy	54.5% demonstrable nerve thickening/deficit	Convergent: Confirms that borderline spectrum (BB and BL) exhibits the highest rate of one-step clinicopathological discordance
Gochoco & Bernales-Mendoza, 2024 (Philippines) ²²	Three-year retrospective cohort; n = 142 leprosy cases	54.2% overall clinicohistopathological concordance	74.6% MB leprosy	66.2% documented neural impairment	Convergent: Lowest concordance observed in borderline lepromatous cases (47.1%); identical to our patient's adjacent spectral discordance
Shabnam et al., 2024 (South India) ²³	Prospective clinicopathological investigation; n = 76 patients	57.9% concordance; BL cases frequently shifted to BB/LL	65.8% MB leprosy	51.3% sensory-motor neuropathy	Convergent: Validates that histopathology samples focal immunological microenvironments that may differ from systemic clinical phenotypes
Mukherjee et al., 2023 (India) ²⁴	Multidisciplinary diagnostic cohort; n = 98 patients	62.2% concordance between clinical exam and biopsy	71.4% MB leprosy	62.2% nerve enlargement / motor deficit	Convergent: Highlights necessity of combining clinical, bacteriological, and histopathological criteria to avoid underclassification
Menghani et al., 2021 (India) ²⁵	Histomorphological and bacteriological analysis; n = 104 patients	63.5% overall clinicohistological correlation	67.3% MB leprosy	48.1% nerve thickening	Convergent: Recommends classifying patients by maximum clinical and bacteriological severity rather than solitary biopsy subtype
Chhabra et al., 2023 (Central India) ²⁶	Cross-sectional evaluation of SSS vs Fite-Faraco; n = 86 patients	62.8% clinicopathological correlation	72.1% MB leprosy	53.5% peripheral neuropathy	Convergent: Affirms complementary diagnostic yield of bacilloscopy and biopsy in resolving borderline discordance
Anandani et al., 2025 (India) ²⁷	Retrospective diagnostic comparison; n = 120 patients	Slit-skin smear sensitivity 58.3% vs Fite-Faraco 72.5%	76.7% MB leprosy	59.2% peripheral neuropathy	Convergent: Demonstrates complementary diagnostic utility of SSS and Fite-Faraco tissue staining in confirming bacillary burden
Reza et al., 2022 (Surabaya, Indonesia) ⁵	Pediatric leprosy profile in the post-elimination era; n = 70 cases	58.6% clinical-histological correlation	82.9% MB leprosy (58/70)	47.1% documented nerve impairment	Convergent: Confirms overwhelming predominance of MB disease in Indonesian tertiary referral centers and high vulnerability to nerve damage
Fransisca et al., 2021 (Surabaya, Indonesia) ⁶	Epidemiology and reaction surveillance; n = 116 MB patients	N/A (Reaction and therapeutic follow-up study)	100.0% MB leprosy	68.1% peripheral neuritis during course	Convergent: Highlights risk of chronic neuritis during MDT; supports long-term neurological monitoring even when palpable thickening is absent
Mayasari & Salsabilah, 2019 (South Sumatra, Indonesia) ³²	Indonesian clinicopathological report; single-case analytic	Adjacent clinicopathological discordance (Clinical BB with BT biopsy)	MB classification maintained	Definite sensory-motor neuropathy	Convergent: Affirms Indonesian national consensus that adjacent-step discordance within borderline leprosy must be treated as multibacillary
Roy et al., 2025 (International) ³³	High-resolution nerve ultrasound series; n = 64 pure neuritic cases	High diagnostic yield for subclinical neural thickening (84.4%)	N/A (Pure neuritic cohort)	100.0% objective neuropathy	Divergent: Ultrasound identifies subclinical nerve swelling in cases lacking palpable thickening, offering future diagnostic refinement
Present investigation, 2026 (Surakarta, Indonesia)	Single-case observational study; n = 1	Adjacent discordance: clinical BL with histopathological BB	100.0% MB (BI 3+, MI 5%, Fite-Faraco +++)	100.0% multi-trunk motor and sensory deficit	Integrates clinical phenotype, bacterial index, histopathology, and early treatment response in an Indonesian referral center

Notes: Concordance between clinical and histopathological classification in borderline leprosy ranged from approximately 50% to 65% across the cohorts. Where classification was addressed, the cohorts favor basing multibacillary classification on the highest bacteriological and clinical parameters, to prevent treatment failure and irreversible neuropathy.

4. Discussion

4.1. Mechanistic interpretation of clinicopathological discordance

The present case supports the biological plausibility of adjacent clinicopathological discordance and informs its clinical management across the borderline spectrum of Hansen disease. The central diagnostic observation in this patient was the one-step divergence between the bedside clinical phenotype of borderline lepromatous (BL) leprosy and the histopathological classification of mid-borderline (BB) leprosy rendered from a cutaneous punch biopsy. Rather than representing diagnostic error or technical inconsistency, this divergence reflects the fundamental biological nature of the Ridley-Jopling classification system as an immunologically dynamic continuum rather than a set of rigid, mutually exclusive diagnostic compartments.^{11,14} Within this continuum, the borderline forms (BT, BB, and BL) represent unstable host-pathogen equilibria characterized by varying degrees of effective cell-mediated immunity against *Mycobacterium leprae* antigens.^{12,13}

At the molecular and cellular level, the clinical manifestations of borderline lepromatous (BL) leprosy are driven by a progressive shift from a protective T-helper 1 (Th1) delayed-type hypersensitivity response toward a permissive T-helper 2 (Th2) humoral phenotype.^{12,14} In BL disease, the systemic downregulation of interferon-gamma (IFN- γ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF- α) permits widespread intravascular and lymphatic dissemination of viable bacilli, resulting in dozens of generalized, bilateral, asymmetric macules, papules, and plaques involving extensive anatomical territories, as observed in our patient.^{12,13} Conversely, a standard 4-mm punch biopsy samples only a minute, localized volume of tissue from a single cutaneous plaque at one discrete temporal cross-section.²¹ In this patient, the sampled plaque demonstrated poorly circumscribed epithelioid histiocytic granulomas surrounded by a moderate lymphocytic mantle, dermal edema, and a distinct subepidermal Grenz zone, fulfilling the histological criteria for mid-borderline (BB) leprosy.²¹ This discordance illustrates that localized tissue granuloma formation may temporarily maintain a higher degree of cellular organization (a BB histomorphological snapshot) even as the systemic host immune response is shifting toward generalized lepromatous anergy (the clinical BL phenotype).^{11,14}

4.2. Global benchmarking of concordance

Our findings align closely with international dermatopathology literature, which consistently demonstrates that clinicopathological concordance in leprosy is incomplete in routine clinical practice. In a histomorphological study of 112 leprosy patients in India and Iran, Naik et al. documented an overall clinical-histopathological agreement of 61.6%, with concordance in the borderline lepromatous subgroup reaching only 58.3%.²¹ Similarly, a large three-year retrospective study of 142 leprosy cases at a tertiary

government hospital and sanitarium in the Philippines by Gochoco and Bernales-Mendoza reported an overall clinicohistopathological concordance of 54.2%, with the lowest concordance observed specifically in clinically classified BL patients (47.1%), where histological diagnoses frequently mapped to adjacent BB or LL categories.²² Studies by Shabnam et al. in South India,²³ Mukherjee et al.,²⁴ Menghani et al.,²⁵ and Chhabra et al. in Central India²⁶ have corroborated that adjacent-step discordance (shifting one step toward either the tuberculoid or lepromatous pole) accounts for the vast majority of non-concordant cases. In Indonesia, Mayasari and Salsabilah documented a parallel phenomenon of adjacent discordance, reporting a clinical mid-borderline (BB) case exhibiting borderline tuberculoid (BT) histopathology.³² As highlighted in our comparative literature benchmarking matrix (Table 5), the consistent finding across these contemporary international cohorts is that histological classification refines the spectral description of the biopsied lesion, but clinical classification, incorporating total lesion burden, neurological deficits, and slit-skin smear bacilloscopy, must govern operational treatment decisions.²¹⁻²⁶

4.3. Neuropathy and diagnostic delay

The clinical evolution of this case underscores the diagnostic vulnerability associated with primary neuropathic presentations of Hansen disease. In our patient, peripheral sensory symptoms (bilateral numbness and paresthesia of the hands and feet) preceded the emergence of visible cutaneous plaques by approximately five months, culminating in an eight-month cumulative diagnostic delay during which the patient was erroneously managed with vitamin B supplements for non-specific neuropathy. This observation reinforces the multicenter findings of Post et al. across Asia, which demonstrated that diagnostic delays averaging 12 to 24 months are predominantly driven by two distinct factors: patient-level delays in recognizing early symptoms and healthcare-provider-level delays caused by misattribution of early neuropathy in primary care settings.¹⁸ In a multicenter case-control study across five Indian states, Srinivas et al. reported that a provider delay exceeding one month was independently associated with an increased risk of permanent physical disability (odds ratio 2.14, $p < 0.001$).⁹ Muthuvel et al. similarly highlighted that early neurological complaints in leprosy are frequently dismissed by primary care practitioners as nutritional or orthopedic ailments.¹⁹

The molecular mechanism governing this early neurotropism is dictated by the unique biological predilection of *Mycobacterium leprae* for the peripheral nervous system.^{13,20} *M. leprae* is the only bacterium known to routinely invade peripheral nerves.²⁰ Mechanistic studies have elucidated that the bacterial surface glycolipid phenolic glycolipid-1 (PGL-1) and major membrane protein II (MMP-II) bind with high affinity to alpha-dystroglycan and the laminin-alpha 2 (laminin-2) chain located within the basal lamina of myelinated and unmyelinated Schwann cells.^{13,20} Upon

ligand-mediated endocytosis, intracellular *M. leprae* reprograms Schwann cells, downregulating myelination genes, inducing mitochondrial metabolic stress and lipid droplet accumulation, and causing extensive demyelination and axonal degeneration.^{13,39} Furthermore, *M. leprae* exhibits a strict thermal preference for replication at temperatures between 32°C and 35°C, explaining its preferential parasitization of superficial nerve trunks coursing close to the skin surface: the facial nerve across the zygomatic arch, the ulnar nerve in the fibro-osseous retroepicondylar groove, the common peroneal nerve winding around the superficial fibular neck, and the posterior tibial nerve within the tarsal tunnel.^{10,17,20}

An important clinical finding in this patient was the complete absence of palpable peripheral nerve enlargement despite marked, objective multi-trunk motor paresis (left facial, bilateral ulnar, and bilateral common peroneal nerves) and extensive sensory loss. This observation argues against the misconception that nerve enlargement must be palpable to diagnose neural leprosy. In a cohort of primary neural leprosy, Tomaselli et al. demonstrated that clinically detectable nerve thickening was present in only 58.6% of patients with electrophysiologically proven nerve damage, meaning that over 41% of neuropathic leprosy cases lack palpable thickening.¹⁷ In our patient, inflammatory edema and endoneurial mycobacterial invasion produced functional conduction failure and axonal injury without causing conspicuous external nerve hypertrophy. In such diagnostically challenging scenarios, recent advancements highlighted by Roy et al. (2025) and de Oliveira et al. (2023) emphasize the role of high-resolution neuromuscular ultrasound (HRUS), which can visualize internal nerve fascicular architecture, hypo-echogenicity, and endoneurial hyperemia with sensitivity exceeding 84%, providing a valuable adjunct when manual palpation is equivocal.^{33,40}

4.4. Complementary roles of slit-skin smear and Fite-Faraco staining

Microbiological testing in this case anchored the diagnosis and therapeutic classification. The patient's slit-skin smear yielded a Bacterial Index (BI) of 3+ and a Morphological Index (MI) of 5.0%, while tissue Fite-Faraco staining demonstrated abundant intracellular acid-fast bacilli (+++). The simultaneous positivity of both modalities was important. In a comparative evaluation of 120 leprosy patients, Anandani et al. (2025) demonstrated that slit-skin smear and histopathological Fite-Faraco staining exhibit discordant sensitivities (58.3% versus 72.5%, respectively) across the borderline spectrum, concluding that the two modalities are highly complementary rather than redundant.²⁷ Chhabra et al. similarly documented that slit-skin smear may be negative in early or deep dermal infiltrates where Fite-Faraco tissue staining readily detects fragmented bacilli, whereas SSS provides rapid quantification of the Morphological Index (the proportion of viable, solid-staining bacilli), which serves as the most sensitive early

biological indicator of bactericidal therapeutic response.^{26,27}

While advanced molecular techniques such as polymerase chain reaction (PCR) targeting *M. leprae* repetitive elements (RLEP) offer superior analytical sensitivity in paucibacillary and pure neuritic leprosy,^{28,29} the clear bacilloscopic positivity in this patient made molecular assays unnecessary for classification. More importantly, under WHO operational definitions, the demonstration of acid-fast bacilli at any single anatomical site, regardless of total skin lesion count, categorizes the patient as having multibacillary (MB) disease.^{4,35} Had this patient been classified solely on his mid-borderline (BB) histopathology without bacilloscopy or full-body clinical evaluation, there would have been a risk of underestimating disease burden or assigning paucibacillary therapy, which could have led to treatment failure, relapse, and secondary physical deformities.^{8,38}

4.5. Therapy, pharmacodynamics, and long-term surveillance

The therapeutic management of this patient with the standardized 12-month WHO MB-MDT regimen exemplifies the principles of modern anti-mycobacterial pharmacology.^{4,35} The triple-drug combination of rifampicin, clofazimine, and dapsone exerts synergistic, multi-targeted bactericidal and immunomodulatory effects, as summarized in the pathophysiological and immunopathological cascade in Figure 5. Rifampicin, administered as a supervised monthly dose of 600 mg, is the most potent bactericidal agent against *M. leprae*, binding to the beta-subunit of bacterial DNA-dependent RNA polymerase which is reported to kill 99.9% of viable bacilli within days of the first dose, in keeping with the fall in the Morphological Index from 5.0% to 1.0% at one month.^{13,41} Clofazimine fulfills a dual pharmacological role: its daily (50 mg) and monthly (300 mg) administration disrupts bacterial membrane integrity and redox cycling, while its tissue bioaccumulation and anti-inflammatory properties inhibit phospholipase A2 and neutrophil migration, which may help suppress Type 1 (reversal) and Type 2 (erythema nodosum leprosum) leprosy reactions.^{6,14,42} Dapsone (100 mg daily) acts as a competitive antagonist of para-aminobenzoic acid (PABA), inhibiting bacterial dihydropteroate synthase and blocking folinic acid synthesis essential for purine metabolism.^{4,41}

The early therapeutic trajectory documented at the one-month evaluation (a 41.2% reduction in cutaneous erythema, a 43.8% reduction in plaque induration, motor recovery of the left facial and peroneal nerves, and a 35.3% decline in erythrocyte sedimentation rate) indicates good early drug responsiveness and adherence. The emergence of mild, diffuse brownish-tan skin pigmentation was recognized as a benign, expected side effect of clofazimine accumulation in dermal macrophages and subcutaneous adipose tissue, which was effectively explained to the patient during pre-treatment counseling to ensure sustained adherence.⁴¹ Continued longitudinal surveillance

remains imperative throughout the 12-month course and during the post-release follow-up period. As demonstrated by Fransisca et al. in Surabaya, Indonesia, and Bandeira et al. in the Brazilian Amazon, patients with multibacillary borderline disease remain at risk of late leprosy reactions or insidious silent neuropathy even during MDT, mandating regular serial sensory-motor testing at every monthly blister pack pickup.^{6,16,43,44}

4.6. Host-pathogen interaction and lipid metabolism

Beyond classical receptor-mediated Schwann cell entry, the intracellular survival of *Mycobacterium leprae* within host macrophages and Schwann cells involves exploitation of host metabolic and lipidomic machinery.¹³ *M. leprae* possesses an extensively downsized, decayed genome characterized by massive pseudogene formation, leaving intact only 1,604 protein-coding genes and depriving the organism of numerous autonomous catabolic and biosynthetic pathways.^{13,45} Consequently, *M. leprae* is an obligate intracellular parasite that depends entirely on host cell nutrients for its persistence and slow replication.^{13,45,46} Upon phagocytosis, the pathogen utilizes its unique surface phenolic glycolipid-1 (PGL-1) to perturb host macrophage membrane signaling, effectively preventing phagosome-lysosome fusion and blunting the assembly of the vacuolar H⁺-ATPase complex.^{12,13} Furthermore, *M. leprae* reprograms host lipid metabolism by upregulating low-density lipoprotein (LDL) receptor expression and activating sterol regulatory element-binding protein (SREBP) transcriptional cascades, inducing massive intracellular accumulation of neutral lipids and oxidized cholesteryl esters.¹³ This lipid-rich microenvironment transforms infected dermal histiocytes into characteristic foamy 'Virchow cells' (lepra cells), providing both an abundant energy substrate for the bacilli and an immunologically quiescent intracellular sanctuary that evades cytotoxic T-cell detection.^{12,13} In our patient, the pretreatment Morphological Index of 5.0% viable bacilli is compatible with active bacillary replication in host dermal tissue.

4.7. Immunogenetic susceptibility and host polymorphisms

The emergence of an immunologically unstable borderline phenotype rather than polar resistance (TT) or complete polar anergy (LL) is influenced by host immunogenetic determinants.¹² Genome-wide association studies (GWAS) and candidate gene analyses across Asian and South American populations have identified critical genetic loci that dictate susceptibility to Hansen disease and modulate the clinical positioning of patients along the Ridley-Jopling spectrum.^{12,14} Key susceptibility alleles include specific human leukocyte antigen (HLA) class I (such as HLA-B*40 and HLA-B*46) and class II determinants (HLA-DRB1*15:01 and HLA-DQB1*06:01), which govern the affinity with which *M. leprae* peptide epitopes are presented to CD4⁺ and CD8⁺ T lymphocytes.¹² Non-HLA genetic polymorphisms in pattern recognition receptors, notably nucleotide-binding oligomerization domain-containing protein 2 (NOD2), Toll-like receptor

1 (TLR1), and Toll-like receptor 2 (TLR2), substantially impair intracellular sensing of mycobacterial muramyl dipeptide, resulting in deficient downstream nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription and suboptimal production of interleukin-12 (IL-12) and tumor necrosis factor-alpha (TNF-α).^{12,14} Polymorphisms in the shared promoter region of the Parkinson disease protein 2 (PARK2) and parkin co-regulated gene (PACRG), as well as variations in leucine-rich repeat kinase 2 (LRRK2), further disrupt host autophagic clearance of intracellular bacilli, promoting persistent bacterial colonization.¹² These immunogenetic factors may help explain why the present patient developed an unstable borderline lepromatous phenotype with progressive cutaneous lesions, multi-trunk nerve damage, and discordance between the clinical presentation and the localized histomorphology, although no genotyping was performed in this case.

4.8. Neuro-rehabilitative strategies and secondary disability prevention

While pharmacological clearance of viable *Mycobacterium leprae* via the WHO MB-MDT regimen is the indispensable foundation of cure, microbiological arrest alone does not immediately reverse pre-existing axonal loss or eliminate the long-term risk of secondary physical disability.^{15,36} In our patient, multi-trunk motor paresis involving the left facial, bilateral ulnar, and bilateral common peroneal nerves, coupled with dense bilateral distal sensory loss, established WHO Grade 1 Disability (G1D) and positioned the patient at severe imminent risk of progressing to irreversible Grade 2 Disability (G2D), such as lagophthalmos, intrinsic claw hand deformity, and neuropathic plantar ulceration.^{8,9,15} To mitigate these risks, proactive, structured neuro-rehabilitative interventions must be integrated into routine leprosy clinical management.^{15,36} For the left facial nerve paresis, daily passive and active facial neuromuscular re-education exercises, including voluntary forced eyelid closure and preservative-free ocular lubricating eye drops during the day and moisturizing ophthalmic ointment at night, were initiated to prevent exposure keratitis, corneal ulceration, and permanent visual loss.^{10,15} For the upper extremities, intrinsic hand muscle strengthening exercises and the provision of custom-molded dynamic night splints maintained the metacarpophalangeal joints in flexion and interphalangeal joints in extension, effectively counteracting muscle imbalance and preventing flexor tendon contractures.^{15,36} For the lower extremities, the combination of daily warm-water foot soaking, petroleum jelly emollient application, and customized microcellular rubber (MCR) footwear distributed plantar pressure evenly, preventing repetitive shear-stress trauma and neuropathic trophic ulceration over insensate metatarsal heads.^{15,36} Patient empowerment through structured self-care education enabled early recognition of blisters or fissure injuries, demonstrating that multidisciplinary care combining antimicrobial pharmacotherapy, proactive physiotherapy, and daily self-inspection is essential to

preserve long-term functional autonomy and quality of life in multibacillary borderline leprosy.^{36,47}

4.9. Strengths and limitations

The strengths of this report are the standardized dermatological mapping, bilateral motor (VMT) and sensory (monofilament) grading, serial bacilloscopy (BI and MI), dual tissue analysis (H&E and Fite-Faraco staining), and structured follow-up under supervised therapy. Together these allowed adjacent clinicopathological discordance to be examined across clinical dermatology, neurology, and pathology.

Several limitations must be acknowledged. First, this is a single case ($n = 1$), so the findings cannot be generalized and no inferential statistics are reported. Second, only the T0 and T1 values were observed; the T2 and T3 values are projections that await confirmation by actual follow-up. Third, because this investigation was conducted in an operational clinical referral setting, advanced neurophysiological modalities such as nerve conduction studies (NCS), electromyography (EMG), and high-resolution nerve ultrasound (HRUS) were not accessible at baseline, precluding precise electrophysiological quantification of compound muscle action potential (CMAP) amplitudes and sensory nerve action potentials (SNAP).^{17,33} Fourth, quantitative serological biomarkers of mycobacterial exposure and nerve injury (such as anti-PGL-1 IgM titers and serum neurofilament light chain [NFL] levels) were not available in the hospital's routine diagnostic armamentarium.^{17,39} Finally, while the one-month follow-up showed an early therapeutic response and tolerance, long-term multi-year post-MDT surveillance will be required to monitor the multi-year clearance of non-viable bacillary corpses (BI decrement) and confirm the absence of late relapse or chronic leprosy reactions.

5. Conclusion

In this single-case study, adjacent clinicopathological discordance, a generalized clinical borderline lepromatous (BL) phenotype with mid-borderline (BB) histopathology, was compatible with the unstable immunological spectrum of Hansen disease. Peripheral neuropathy preceded the skin lesions by several months, so primary care practitioners should consider leprosy in patients with unexplained numbness of the hands and feet, particularly when nerve involvement is multifocal. The absence of palpable nerve thickening does not exclude extensive nerve damage, as motor paresis and sensory loss occurred in non-enlarged nerve trunks.

When bedside clinical findings and a localized biopsy diverge, classification and therapeutic decisions should follow the highest degree of clinical and bacteriological severity. Acid-fast bacilli on slit-skin smear independently indicate multibacillary (MB) disease, for which the full 12-month WHO MB-MDT regimen is given. Timely supervised multidrug therapy is intended to halt neural destruction and to reduce the risk of grade 2 disability and onward transmission; the one-month

response was favorable, but the six- and twelve-month outcomes remain projections. Multimodal diagnostic integration supports effective management and disability prevention in the global campaign toward zero leprosy.

Declarations

Use of Generative Artificial Intelligence. The authors did not use any generative artificial-intelligence tools in writing, analyzing, or preparing this manuscript. All content was produced and verified by the authors, who take full responsibility for its integrity and accuracy.

Author Contributions. NM: clinical and dermatological evaluation, data curation, literature review, writing (original draft). WB: supervision of dermatological management, neurological and histopathological evaluation, clinicopathological interpretation and diagnostic classification, writing (review and editing), corresponding author. Both authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Funding. The authors received no financial support for the research, authorship, or publication of this article. No grant from any public, commercial, or not-for-profit funding agency was sought or obtained.

Conflict of Interest. The authors declare that they have no competing interests, financial or non-financial, in relation to this work.

Ethical Approval. This study received ethical approval from CMHC Research Center Ethics Committee, Indonesia (Approval No. 2026/0842) and was conducted in accordance with the Declaration of Helsinki.

Patient Consent. Written informed consent was obtained from the patient for participation and for the publication of this study, including clinical records, laboratory data, and photographs. In line with ICMJE and COPE guidance, the orbital regions in all clinical photographs are masked with a solid black bar.

Data Availability. All clinical parameters, laboratory values, and diagnostic findings supporting the conclusions are included in the manuscript, tables, and figures. Additional de-identified longitudinal data are available from the corresponding author on reasonable request.

Acknowledgements. The authors thank the clinical, nursing, and technical staff of the Leprosy and Dermato-Venereology Outpatient Service, the Department of Anatomical Pathology, and the Clinical Pathology Laboratory of Dr. Moewardi Regional General Hospital, Surakarta, for their support in the diagnostic evaluation and longitudinal care of the patient.

References

1. Ferreira AF, Heukelbach J, Souza EA de, et al. Persistent and emerging high-risk clusters of leprosy detection in Brazil: a nationwide spatiotemporal analysis, 2001–2023. *Trop Med Int Health*. 2026;31(4):532–546. doi: 10.1111/tmi.70104
2. World Health Organization. Global leprosy (Hansen disease) update, 2023: elimination of leprosy disease is possible – time to act! *Wkly Epidemiol Rec*. 2024;99(37):501–521. Available from: <https://www.who.int/publications/i/item/who-wer9937-501-521>
3. World Health Organization. Global leprosy (Hansen disease) update, 2024: beyond zero cases, what elimination of leprosy really means. *Wkly Epidemiol Rec*. 2025;100(37):365–384. Available from:

- <https://www.who.int/publications/i/item/who-wer10037-365-384>
4. Chen KH, Lin CY, Su SB, et al. Leprosy: a review of epidemiology, clinical diagnosis, and management. *J Trop Med*. 2022;2022:8652062. doi: 10.1155/2022/8652062
 5. Reza NR, Kusumaputro BH, Alinda MD, et al. Pediatric leprosy profile in the postelimination era: a study from Surabaya, Indonesia. *Am J Trop Med Hyg*. 2022;106(3):775–778. doi: 10.4269/ajtmh.21-0458
 6. Fransisca C, Zulkarnain I, Ervianti E, et al. A retrospective study: epidemiology, onset, and duration of erythema nodosum leprosum in Surabaya, Indonesia. *Berkala Ilmu Kesehatan Kulit dan Kelamin*. 2021;33(1):8–12. doi: 10.20473/bikk.v33.1.2021.8-12
 7. Brodie DA, Sugiharto A, et al. Participatory development of Indonesia's national action plan for zero leprosy: strategies and interventions. *Front Public Health*. 2025;13:1453470. doi: 10.3389/fpubh.2025.1453470
 8. de Paula HL, de Souza CDF, Silva FL, et al. Risk factors for physical disability in patients with leprosy: a systematic review and meta-analysis. *JAMA Dermatol*. 2021;157(9):1068–1077. doi: 10.1001/jamadermatol.2021.2468
 9. Srinivas G, Muthuvel T, Lal V, et al. Risk of disability among adult leprosy cases and determinants of delay in diagnosis in five states of India: a case-control study. *PLoS Negl Trop Dis*. 2019;13(6):e0007495. doi: 10.1371/journal.pntd.0007495
 10. Chen X, Liu H, Zhang L, et al. Preliminary evaluation of a neurological clinical pathway for the early detection of leprosy in low-endemic settings: a single-center exploratory study. *Sci Rep*. 2025;15(1):17354. doi: 10.1038/s41598-025-01653-4
 11. Soni S, Narang T, Dogra S. The borderline dilemma: clinicohistopathological discordance and the continuum of host immunity in leprosy. *Int J Mycobacteriol*. 2023;12(2):112–119. doi: 10.4103/ijmy.ijmy_45_23
 12. Mi Z, Liu H, Zhang F. Advances in the immunology and genetics of leprosy. *Front Med*. 2021;15(4):540–557. doi: 10.1007/s11684-021-0844-0
 13. Suzuki K, Akama T, Kawashima A, et al. Pathogenicity and virulence of *Mycobacterium leprae*. *Virulence*. 2022;13(1):1985–2011. doi: 10.1080/21505594.2022.2135606
 14. Polycarpou A, Walker SL, Lockwood DN. A systematic review of immunological biomarkers for the detection of leprosy reactions. *Clin Exp Immunol*. 2021;203(3):345–360. doi: 10.1111/cei.13543
 15. Sharma A, Narang T, Takkar A, et al. Nerve function impairment and quality of life in patients with leprosy: a prospective, observational study. *Int J Dermatol*. 2024;63(12):1501–1509. doi: 10.1111/ijd.17323
 16. Bandeira SS, dos Anjos AB, Pires CA, et al. Progression of the leprosy reaction and nerve damage: a prospective cohort study in children with leprosy from the Brazilian Amazon. *PLoS Negl Trop Dis*. 2024;18(12):e0012772. doi: 10.1371/journal.pntd.0012772
 17. Tomaselli PJ, dos Santos DF, dos Santos ACJ, et al. Primary neural leprosy: clinical, neurophysiological and pathological presentation and progression. *Brain*. 2022;145(4):1499–1506. doi: 10.1093/brain/awab396
 18. Post E, Brandsma W, Wagenaar I, et al. Delay in leprosy diagnosis: a multi-center, multi-country Asian study. *Lep Rev*. 2021;92(1):29–37. doi: 10.47276/lr.92.1.29
 19. Muthuvel T, Govindarajulu S, Isaakidis P, et al. "I wasted 3 years, thinking it's not a problem": patient and health system delays in diagnosis of leprosy in India: a mixed-methods study. *PLoS Negl Trop Dis*. 2017;11(1):e0005192. doi: 10.1371/journal.pntd.0005192
 20. Scollard DM, Truman RW, Ebenezer GJ. Mechanisms of nerve injury in leprosy. *Clin Dermatol*. 2021;39(2):220–225. doi: 10.1016/j.clindermatol.2020.10.009
 21. Naik S, More S, Joshi S. Histomorphological correlation with bacteriological index in leprosy patients. *Iran J Pathol*. 2022;17(1):48–55. doi: 10.30699/ijp.2021.534122.2682
 22. Gochoco JBB, Bernales-Mendoza AM. Concordance of acid-fast stain result and histopathologic vs clinical diagnosis of leprosy: a three-year retrospective study in a tertiary government hospital and sanitarium in the Philippines. *Acta Med Philipp*. 2024;58(23):42–48. doi: 10.47895/amp.vi0.8317
 23. Shabnam A, Dennis Joseph L, Priyathersini N, et al. Clinically suspicious cases of Hansen's disease at a tertiary care hospital in South India: a clinicopathological study. *Cureus*. 2024;16(10):e70661. doi: 10.7759/cureus.70661
 24. Mukherjee M, Ghatak D, Bhunia D, et al. A study on the multidisciplinary diagnostic approach of leprosy: can we prevent the recrudescence in the post-elimination Indian scenario? *J Family Med Prim Care*. 2023;12(9):2008–2013. doi: 10.4103/jfmpc.jfmpc.2480_22
 25. Menghani B, Gupta A, Kasliwal N, et al. Pattern of leprosy: a histomorphological study with clinical correlation in Ajmer district. *Ann Pathol Lab Med*. 2021;8(3):A100–106. doi: 10.21276/apalm.3028
 26. Chhabra N, Negi SS, Khatoon S, et al. Clinicopathological concordance and diagnostic utility of Fite-Faraco staining in leprosy in the post-elimination era. *Indian Dermatol Online J*. 2023;14(2):205–210. doi: 10.4103/idoj.idoj_542_21
 27. Anandani G, Bhise M, Goswami P, et al. Effectiveness of slit skin smear versus Fite-Faraco staining on histopathology as a method of diagnosis in leprosy: a retrospective hospital-based study. *Maedica*. 2025;20(4):787–794. doi: 10.26574/maedica.2025.20.4.787
 28. Khatoon S, Negi SS, Chhabra N, et al. Diagnostic utility of PCR in detection of clinical cases and carriers of leprosy: a cross sectional study at a tertiary care teaching hospital in Central India. *Indian J Med Microbiol*. 2022;40(1):105–108. doi: 10.1016/j.ijmmb.2021.06.004
 29. Siwakoti S, Rai K, Bhattarai NR, et al. Evaluation of polymerase chain reaction (PCR) with slit skin smear examination (SSS) to confirm clinical diagnosis of leprosy in Eastern Nepal. *PLoS Negl Trop Dis*. 2016;10(12):e0005220. doi: 10.1371/journal.pntd.0005220
 30. Wang H, Chen X, Sun P. Clinical evaluation of slit-skin smear versus histopathology in borderline spectrum leprosy: a multicenter comparative study. *J Dermatol Sci*. 2024;105(2):98–105. doi: 10.1016/j.jdermsci.2024.01.004
 31. Zhang L, Wang Y, Chen H, et al. A case of borderline lepromatous leprosy and literature review: key clues to expand clinical diagnostic thinking. *Front Med (Lausanne)*. 2025;12:1636112. doi: 10.3389/fmed.2025.1636112
 32. Mayasari R, Salsabilah R. Diagnosis klinis Morbus Hansen tipe Mid Borderline (BB) dengan gambaran histopatologis Morbus Hansen tipe Borderline Tuberculoid (BT). *Jurnal Kedokteran dan Kesehatan Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya*. 2019;6(2):57–62. doi: 10.32539/JKK.V6i1.7713
 33. Roy U, Panwar A, Cartwright MS, et al. High resolution nerve ultrasound in the diagnosis of pure neuritic leprosy. *J Clin Ultrasound*. 2025;53(9):1966–1978. doi: 10.1002/jcu.24081
 34. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol*. 2017;89:218–235. doi: 10.1016/j.jclinepi.2017.04.026
 35. World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. Geneva: World Health Organization; 2021. doi: 10.2471/9789290226382

36. Darlong J, Govindharaj P, Kumar S. Assessment of nerve function impairment and disability grade shift during multidrug therapy in multibacillary leprosy. *Lepr Rev.* 2022;93(3):214–225. doi: 10.47276/lr.93.3.214
37. Prakoeswa CRS, Alinda MD, Listiawan MY, et al. Evaluation of therapeutic response and relapse prevention in multibacillary leprosy: an Indonesian referral perspective. *Dermatol Reports.* 2023;15(3):9642. doi: 10.4081/dr.2023.9642
38. Nascimento ACM do, dos Santos DF, Antunes DE, et al. Leprosy relapse: a retrospective study on epidemiologic, clinical, and therapeutic aspects at a Brazilian referral center. *Int J Infect Dis.* 2022;118:44–51. doi: 10.1016/j.ijid.2022.01.009
39. Medeiros P, Fraga L, da Silva M, et al. Nerve growth factor regulation in peripheral neuropathy of leprosy and HIV coinfection. *Microorganisms.* 2025;13(10):2271. doi: 10.3390/microorganisms13102271
40. de Oliveira S, de Sousa J, Silva R, et al. High-resolution ultrasonography and electrophysiology for the assessment of peripheral nerve damage in leprosy: a cross-sectional study. *PLoS Negl Trop Dis.* 2023;17(5):e0011342. doi: 10.1371/journal.pntd.0011342
41. Kumar B, Dogra S, Narang T. Multidrug therapy for leprosy: four decades of global progress and contemporary challenges. *Lancet Infect Dis.* 2024;24(6):e384–e395. doi: 10.1016/S1473-3099(23)00712-4
42. Putri AI, de Sabbata K, Agusni RI, et al. Understanding leprosy reactions and the impact on the lives of people affected: an exploration in two leprosy endemic countries. *PLoS Negl Trop Dis.* 2022;16(6):e0010476. doi: 10.1371/journal.pntd.0010476
43. Barbosa CC, Bezerra GSN, Xavier AT, et al. Systematic review of survival analysis in leprosy studies including the following outcomes: relapse, impairment of nerve function, reactions and physical disability. *Int J Environ Res Public Health.* 2022;19(19):12155. doi: 10.3390/ijerph191912155
44. Rajkumar P, Purushothaman GKC, Ponnaiah M, et al. Low risk of relapse and deformity among leprosy patients who completed multi-drug therapy regimen from 2005 to 2010: a cohort study from four districts in South India. *PLoS Negl Trop Dis.* 2021;15(11):e0009950. doi: 10.1371/journal.pntd.0009950
45. Salgado CG, Barreto JG, da Silva MB, et al. What do we know about *Mycobacterium leprae* transmission and subclinical infection? *Pathogens.* 2022;11(8):844. doi: 10.3390/pathogens11080844
46. Goulart IMB, Rosa PS, Andrade LE, et al. Asymptomatic infection, leprosy endemy and control: challenges and perspectives. *Front Med (Lausanne).* 2022;9:856417. doi: 10.3389/fmed.2022.856417
47. Ramos JM, Reyes F, Belinchon I, et al. Leprosy in pediatric patients: a systematic review and meta-analysis of clinical characteristics and treatment outcomes. *Am J Trop Med Hyg.* 2022;106(6):1621–1631. doi: 10.4269/ajtmh.21-1051