ISSN: 2687-8410
Archives of
Clinical Case Studies
DOI: 10.33552/ACCS.2026.04.000600
Iris Publishers

Case Report

Bullous Erythema Nodosum Leprosum Occurring with Severe Vasculonecrotic Reaction as the First Sign of Multibacillary Leprosy: A Rare Phenomenon

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Received Date: February 05, 2026

Published Date: February 11, 2026

Abstract

The clinical spectrum of leprosy is wide and is directly affected by the host's immune response. Reactions in leprosy, caused by hypersensitivity types III and IV, increase morbidity and disability. They are classified into three types: type 1, or the reversal reaction, which occurs in borderline forms; type 2, or erythema nodosum leprosum, associated with lepromatous forms; and Lucio's phenomenon, or type 3, seen only in patients with diffuse lepromatous leprosy. Erythema nodosum leprosum can rarely occur before treatment in patients with multibacillary leprosy. Atypical presentations are recognized and may be misleading clinically. The vasculonecrotic form of erythema nodosum leprosum is a rare presentation and can be difficult to distinguish clinically from a type 3 reaction. It indicates a severe reaction and may resemble other skin conditions, such as vasculitis. This case report describes an initial leprosy infection presenting as necrotizing erythema nodosum leprosum without obvious skin features of leprosy. It aims to highlight a challenging case of necrotic erythema nodosum leprosum that was misdiagnosed and underscores the importance of ongoing clinical follow-up and monitoring for patients experiencing these events.

Keywords: Vasculonecrotic reaction; bullous erythema nodosum leprosum

Introduction

Leprosy is a persistent infection caused by Mycobacterium leprae and Mycobacterium lepromatosis, mainly affecting the peripheral nerves, skin, and mucous membranes [1]. Leprosy reactions are sudden immune responses that can occur before, during, or after multidrug therapy, potentially leading to significant disability. They can affect nearly half of all leprosy patients at some point. There are two main types: reversal reactions (RRs), also called type 1 reactions (T1R), and erythema nodosum leprosum (ENL), or type 2 reactions (T2R). T1R occurs in up to one-third of patients within the borderline spectrum of leprosy, caused by Type IV hypersensitivity, which results from increased cell-mediated immunity against M. leprae. T2R occurs in approximately half of patients with lepromatous leprosy (LL) and in 10% of borderline lepromatous (BL) cases. These reactions involve immune complex deposition, neutrophil infiltration, and elevated circulating tumour necrosis factor-alpha (TNF-α). Although sometimes classified as a type III reaction, the Lucio phenomenon is generally regarded as a T2R [2]. T2R, which typically occurs during or after leprosy treatment, can sometimes be the first sign of the disease, making the diagnosis more difficult.

Symptoms such as ulceration, skin necrosis, and systemic signs indicate necrotic ENL, which is often misdiagnosed because it overlaps with conditions including cutaneous vasculitis, systemic juvenile idiopathic arthritis, and Sweet's syndrome. ENL results from type III hypersensitivity reactions. Its primary symptom is the formation of painful subcutaneous nodules, often accompanied by systemic symptoms such as fever, malaise, arthralgia, myalgia, neuritis, uveitis, orchitis, or other organ involvement. ENL is a painful, multi-systemic, recurrent condition that significantly affects patient health, raising the risk of nerve damage and deformities. Variable atypical patterns have been identified, including pustular, bullous, ulcerative, necrotic, and Sweet's syndrome-like ENL. It usually appears during or after leprosy treatment, but it can also be the first manifestation of the disease, making diagnosis more challenging. Necrotic ENL is an infrequent yet grave complication associated with lepromatous leprosy. It typically heals with fibrotic, hypertrophic, or extending scars. Necrotic ENL is characterized by systemic symptoms with constitutional features, visceral damage, and neuritis, which set it apart from other types.

In addition to the classic lesions, ENL's rarer but more severe variants include vesicobullous, pustular, and necrotic types, with necrotic ENL often resembling cutaneous vasculitis. Atypical skin presentations include pustular, hemorrhagic, erythema multiforme-like lesions, and severe forms like necrotic ulcers or ENL necroticans [3]. These signs can be challenging to diagnose and treat, especially when they are the first indicators of leprosy. ENL necroticans (ENN) is a rare, severe variant accounting for approximately 8% of ENL cases, characterized by vesicular, bullous, or pustular lesions that necrotize and form ulcers [4]. Proper management of the reaction is essential to prevent lasting disabilities. Recognizing the wide range of ENL symptoms is crucial to avoiding misdiagnosis and treatment delays. This case concerns a type 2 complication of leprosy, which occurs in fewer than 8% of cases and poses a diagnostic challenge. This publication aims to raise awareness of this rare but possible complication.

Case Presentation

A 40-year-old man with no significant medical history, with approximately one year of progression. The patient initially presented with left-sided peripheral facial paralysis. Subsequently, he consulted a neurologist, a maxillofacial surgeon, and an otolaryngologist; however, a definitive diagnosis was not established. One month later, the patient experienced irregular, spontaneous epistaxis, prompting another medical consultation, during which he was referred to the Rheumatology department. Imaging studies were conducted, leading to the diagnosis of small- and medium-vessel vasculitis. Treatment was initiated with corticosteroids, administered intravenously and subsequently orally at 1.5 mg/kg body weight. Additionally, a steroid-sparing immunosuppressant was added: cyclophosphamide 2 mg/kg/day administered orally. Over the course of three months, the patient showed improvement, with resolution of facial paralysis and a decrease in the frequency of epistaxis. Therefore, the steroid dose was reduced to 0.75 mg/kg body weight, and a tapering schedule was followed until discontinuation. One week later, the patient developed deep, erythematous, inflamed nodules that initially appeared abscess-like.

The lesions first appeared on the lower extremities and then spread to the abdomen and trunk. Subsequently, the nodules evolved into painful, ulcerated lesions with necrotic borders. At the same time, the patient experienced fever spikes and night sweats. One of the lesions was drained for microbiological and histopathological analysis. Suspecting a mycobacterial infection due to immunosuppression from vasculitis treatment, a PCR panel was performed to identify atypical mycobacteriosis, but all results were negative, laboratory studies were performed with no relevant alterations Table 1. The lesions progressed to form large, painful ulcers that impair function. Empirical tuberculosis treatment was initiated, but the lesions continued to increase in number and size. The pain became severe, leading to consultations with palliative and pain specialists, until the Dermatology department reviewed the case. Dermatological examination revealed widespread involvement of the body (Figure 1A), characterized by multiple polymorphic ulcers with thick, adherent, yellow-to-black necrotic crusts, along with some scarring (Figure 1B). Severe neuritis and lymphadenopathy were detected. The patient showed no motor neurological deficits or deformities (Table 1) (Figure 1).

Table 1: The patient showed no motor neurological deficits or deformities.

Paraclinical Evaluation	Value (patient)	Normal Value
Hemoglobin (g/dL)		
Glucose	101.2 mg/dL	73 – 110 mg/dL
Urea	24.5 mg/dL	12.9 – 42.9 mg/dL
Blood Urea Nitrogen	11.4 mg/dL	6 – 31 mg/dL
(BUN)		
Creatinine	1.01 mg/dL	0.6 – 1.3 mg/dL
Uric Acid	5.2 mg/dL	3.5 – 7.2 mg/dL
Total Cholesterol	143.6 mg/dL	0 – 200 mg/dL
Triglycerides	75.7 mg/dL	50 – 150 mg/dL
Total Bilirubin	0.30 mg/dL	0.30 – 1.20 mg/dL
Direct Bilirubin	0.16 mg/dL	0 – 0.50 mg/dL
Indirect Bilirubin	0.14 mg/dL	0 – 1.00 mg/dL
AST (TGO)	13.6 U/L	0 – 40 U/L
ALT (TGP)	22.06 U/L	0 – 45 U/L
Lactate Dehydrogenase	99.17 U/L	125 – 220 U/L
(LDH)		
Alkaline Phosphatase	226.7 U/L	0 – 270 U/L
HDL Cholesterol	44 mg/dL	35 – 65 mg/dL
LDL Cholesterol	87 mg/dL	80 – 189 mg/dL
VLDL Cholesterol	15 mg/dL	5 – 30 mg/dL
Castelli Index (TC/HDL)	3.3	<3.4
LDL/HDL Index	2.0	1.0 – 3.5
Sodium	137 mmol/L	137 – 145 mmol/L
Potassium	4.2 mmol/L	3.5 – 5.1 mmol/L
Chloride	98 mmol/L	98 – 107 mmol/L
CPK	55 U/L	40 – 200 U/L
CK-MB	13 U/L	0 – 25 U/L
C-reactive Protein	96.0 UI/mL	≤6.0 UI/mL

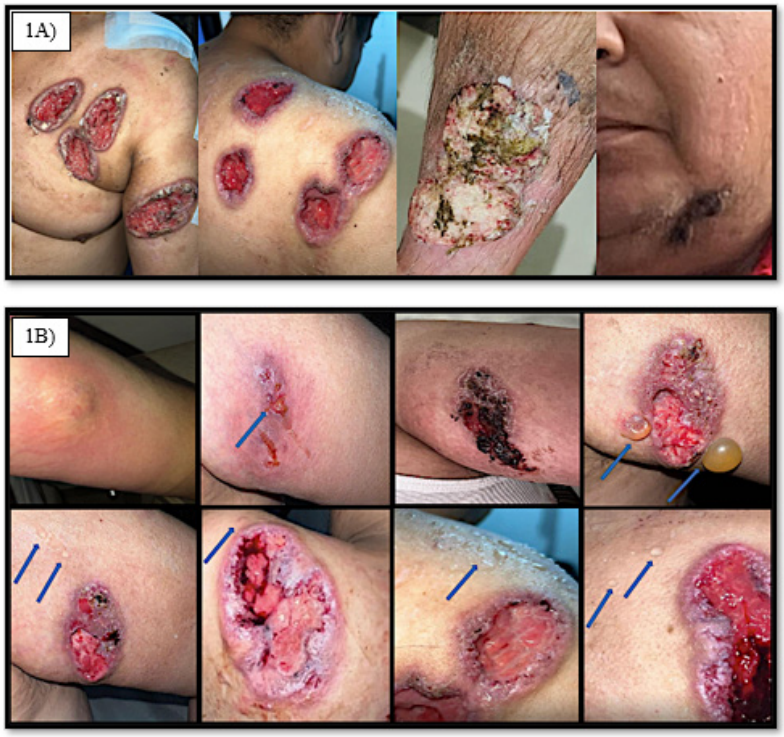

Figure 1: Clinical presentation. 1A) Widespread involvement. The dermatosis spared the palms, soles, and mucous membranes. 1B) Several clinical patterns were observed within the same patient. Due to the overlap of atypical forms, some lesions may develop into others. For example, a bulla might convert into an ulcer, followed by central necrosis. The arrows pointed to flaccid bullae with central erosion and, in some cases, crusting.

Biopsies were obtained from the posterior thorax lesions. Histopathological examination revealed the epidermis with pseudoepitheliomatous hyperplasia and focal ulceration. The papillary and reticular dermis contained a dense inflammatory infiltrate, predominantly neutrophils, which in some areas formed microabscesses, along with lymphocytes, histiocytes, foamy macrophages, and multinucleated cells. There were also dilated and congested blood vessels, extravasated erythrocytes, and thickened collagen fibres. Many neutrophils affected both superficial and deep vessels, adnexa, and small nerves. Marked enema of the upper dermis resulting in a subepidermal, cell-poor blister was observed. Numerous intact and fragmented acid-fast bacilli forming globe were observed in the modified Ziehl-Neelsen stain. The histopathological findings are consistent with a mycobacterial infection; however, the specific causative agent could not be identified to establish a definitive diagnosis. The bacilloscopy of one of the lesions located in the posterior trunk showed the presence of +++ bacilli, 50% whole, 80% normochromic, 20% hypochromic (Figure 2A).

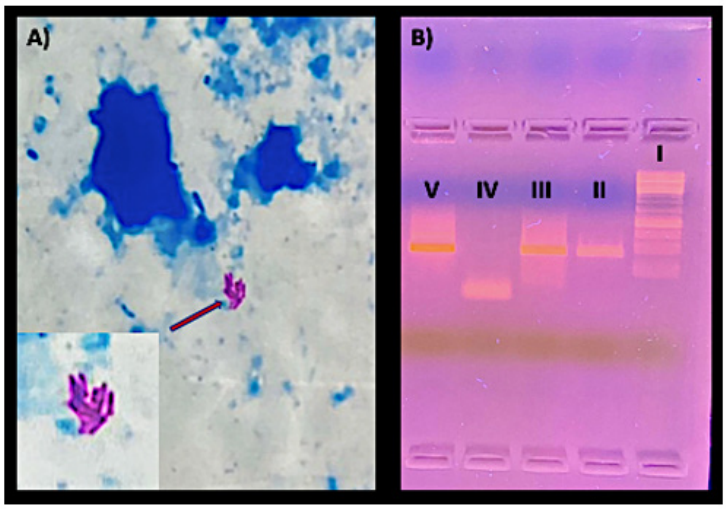

Figure 2: A) Ziehl-Neelsen stain: (+++). We observed a cluster of acid-fast bacilli at 100x magnification under the microscope. B) From right to left: I) 1,000 bp molecular weight marker. In II), our sample amplified with primers RLEP 7 and 8 (Repetitive Element of Mycobacterium leprae), a highly conserved genomic element specific to Mycobacterium leprae and not found in the genome of other mycobacterial species, making it an ideal target for the molecular diagnosis of Mycobacterium leprae. In III, we have our positive control, a sample from an armadillo previously infected with M. leprae. In IV, our negative control, molecular-grade double-distilled water, and in lane V, a sample from a patient previously diagnosed with leprosy caused by M. leprae.

A molecular study was conducted using real-time and endpoint PCR to verify the presence of *Mycobacterium lepromatosis*. Hansen's bacillus was identified (Figure 2B). Additionally, PCR-based molecular analysis did not reveal any drug resistance in M. leprae to dapsone, rifampicin, or ofloxacin (Figure 2). The patient was diagnosed with a type 2 lepromatous reaction. Treatment for the acute response was initiated alongside therapy for multibacillary lepromatous leprosy, which includes dapsone, rifampin, and clofazimine. The reaction was managed by starting Thalidomide at 400 mg daily for one week, then gradually reducing the dose by 100 mg weekly until reaching 100 mg. Prednisone was administered at 25 mg every 12 hours for one week before tapering. Pentoxifylline was prescribed at 400 mg every 12 hours for three to six months. Silver sulfadiazine was applied to the lesions, and levofloxacin was given at 750 mg daily for 14 days as antimicrobial therapy. The remarkable improvement in the lesions was visible from the first month of treatment (Figure 3).

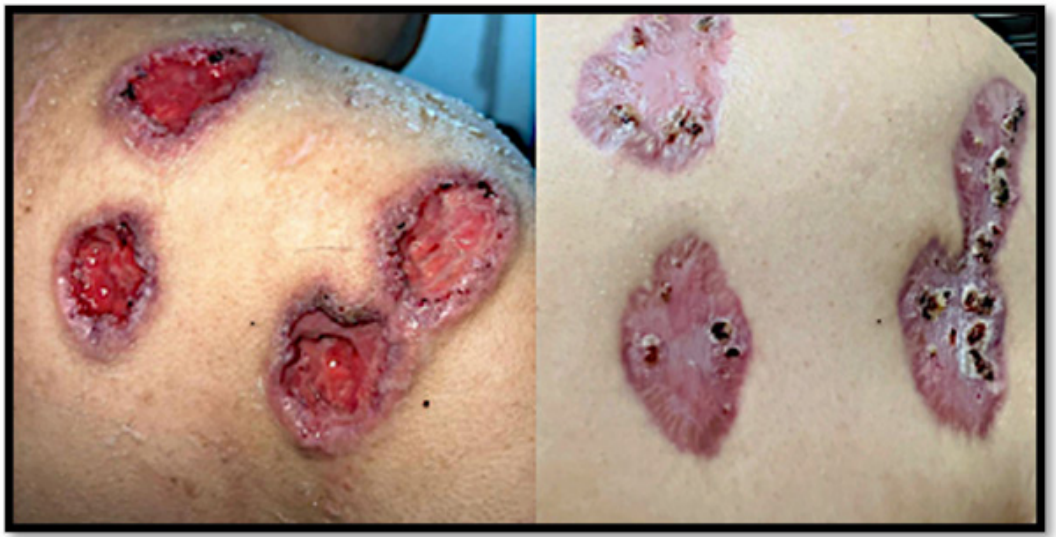

Figure 3: Significant improvement in the clinical lesions after accurate diagnosis and treatment.

Discussion

The cause of the variable presentations of ENL is uncertain, and it remains unresolved whether an immune-based explanation for this pleomorphism exists. It results from the deposition of immune complexes, which induces type III hypersensitivity reactions [5]. This manifestation signifies a more vigorous immune response and necessitates prompt intervention [6]. Due to the potential for cross-reactivity between mycobacterial antigens and human DNA, as well as polyclonal B cell activation, various autoantibodies may be detected. These include rheumatoid factor (the most common), anti-nuclear antibodies, anti-SS-A, antimitochondrial antibodies, antithyroglobulin, and p-ANCA or c-ANCA. The initial clinical presentation in our patient could be explained by leprae bacilli infecting hosts via the mucosa of the upper respiratory tract and subsequently binding to the G domain in Schwann cells. These cells can process and present the antigen to antigen-specific T lymphocytes, thereby triggering immune responses. High levels of E-selectin on vascular walls in ENL promote neutrophil migration and adhesion to endothelial cells. These neutrophils further drive inflammation by releasing cytokines, such as tumour necrosis factor (TNF)- α and interleukin (IL)-8.

Leukocytoclastic vasculitis, characterized by neutrophilic infiltration of the vessel walls, appears to be a primary pathological feature in ENL reactions. Delays in diagnosis and treatment can worsen neuronal damage and systemic involvement, leading to complications such as chronic kidney disease, which may progress to end-stage renal disease (the most common cause of death), secondary infections, and sepsis, potentially resulting in death. Necrotic ENL is often misdiagnosed because its clinical presentation closely resembles other diseases. Therefore, it is crucial to have a thorough understanding of necrotic ENL to enable early diagnosis and treatment, helping to prevent complications and improve outcomes. ENL constitutes an immune-mediated inflammatory response affecting approximately 10% of patients with borderline lepromatous leprosy and 50% of those with lepromatous leprosy, manifesting before, during, or following multidrug therapy for multibacillary leprosy (MDT-MB). Clinically, it is characterized by painful, intensely erythematous nodules or plaques. In severe instances, the presentation may resemble either lepromatous leprosy or necrotic ENL, which frequently arises during anti-leprosy treatment.

Atypical skin presentations include pustular, hemorrhagic, and erythema multiforme-like lesions, as well as severe forms such as necrotic ulcers or ENL necroticans. ENL necroticans (ENN), a rare and severe variant observed in approximately 8% of ENL cases, is characterized by vesicular, bullous, or pustular lesions that undergo necrosis and subsequently ulcerate. The presence of ulceration, skin necrosis, and constitutional and systemic symptoms indicates necrotic ENL. Erythema nodosum occurs in less than 10% of leprosy patients, making it a rare complication. However, the case described here involves the necrotizing form, which is highly uncommon, appearing in fewer than 8% of cases. In our patient, symptoms were observed before the initiation of treatment. The histopathological features of ENL show a large influx of neutrophils in the dermis, which are absorbed by clusters of vacuolated histiocytes containing bacilli. The patient received treatment after a definitive diagnosis,

utilizing a combination therapy with three medications: dapsone, rifampicin, and clofazimine.

This therapy is administered through the healthcare system and is prescribed for a duration of 12 months in cases of multibacillary leprosy. Diagnosis remains challenging due to the limited number of published instances involving this complication. Nonetheless, it is imperative to consider it, and maintaining a high index of suspicion for skin abnormalities is essential, particularly in leprosy-endemic regions such as Mexico. However, in the event of an acute reaction, as observed in this case, it is imperative to administer treatment specifically targeting the acute response, in addition to the previously specified regimen comprising dapsone, rifampin, and clofazimine. Such treatment is more vigorous and comprehensive, given that the reaction phases are associated with a high mortality rate. Corticosteroids, such as prednisolone, offer rapid control and are considered the primary treatment for ENL. They effectively decrease inflammation and quickly ease pain. Typically, they are initiated at the lowest effective dose necessary to manage ENL and then gradually tapered based on disease progression [7].

Using thalidomide in ENL offers an effective alternative to steroid treatment, providing quick anti-inflammatory results by regulating TNF, a pro-inflammatory cytokine [8]. Effective management of necrotic erythema nodosum leprosum (ENL) relies on the sustained involvement of a multidisciplinary team (MDT) and a comprehensive collaborative approach. This case demonstrates that integrating MDT efforts with corticosteroid therapy can effectively control severe symptoms. Key strategies include patient education, encouraging treatment adherence, early detection, and prompt, aggressive intervention to enhance outcomes in this challenging condition.

Conclusion

Patients with lepromatous or borderline leprosy can undergo two types of vasculonecrotic reactions: Lucio's phenomenon and ENL. These severe conditions frequently result in life-threatening infections and thrombotic complications.

Acknowledgment

We thank the patient who voluntarily participated in this case report.

Funding Statment

None declared.

Ethics and Constant

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The report was approved by the ethics committee of...

Author Contribution

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest and report no conflicts of interest for this work.

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