Case Report

# Multibacillary leprosy relapse presenting as hypopigmented patches and concurrent erythema nodosum leprosum after initial multidrug therapy

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## Abstract

Leprosy is a chronic granulomatous disease of the skin, peripheral nerves, and mucosal membranes caused by *Mycobacterium leprae*. Although curable with multidrug therapy (MDT), relapse, reinfection, or immunologic reactions can occur. Leprosy reactions are abnormal immune responses ranging from type IV hypersensitivity to immune-complex–mediated phenomena, such as erythema nodosum leprosum (ENL). We report a 23-year-old man who completed MDT for multibacillary leprosy 1 year prior and presented with a 2-week history of tender, erythematous subcutaneous nodules, systemic symptoms, and pre-existing hypopigmented patches. Imaging revealed lymphadenopathy and splenomegaly, suggesting systemic inflammation. Biopsies showed granulomatous collections of epithelioid to foamy histiocytes centered on dermal nerve bundles and adnexal structures, with focal early vasculitic changes and scattered neutrophils. Fite-Faraco staining demonstrated numerous weakly acid-fast bacilli. These findings were consistent with leprosy relapse and concurrent ENL. Treatment was initiated with monthly rifampin, moxifloxacin, and minocycline (RMM), alongside methotrexate and prednisone. This case highlights an unusual presentation of leprosy relapse with concurrent ENL following completion of MDT. Ongoing surveillance and follow-up are essential to monitor for relapse, reinfection, and reactions, particularly in high-risk patients.

## Introduction

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae* and, less commonly, *Mycobacterium lepromatosis*. Globally, leprosy affects approximately 250 000 individuals annually, with up to 225 cases reported in the United States each year.[1] In the United States, 75% of cases occur in immigrants from endemic regions. Leprosy primarily involves the skin and peripheral nerves but can also affect mucous membranes, eyes, and bones.[2]

Leprosy classification reflects the host immune response to *M. leprae*.[3] In tuberculoid (paucibacillary [PB]) leprosy, strong cell-mediated immunity limits skin lesions, whereas lepromatous (multibacillary [MB]) leprosy is associated with widespread lesions and a high bacterial load owing to poor immunity. Intermediate forms represent a continuum between these poles. Accurate clinicopathological correlation is essential for diagnosis.

Leprosy is curable with 6 to 12 months of multidrug therapy (MDT), consisting of dapsone and rifampin for PB disease and the addition of clofazimine for MB leprosy.[3] Despite effective treatment, relapse and immunologic reactions may occur, which—if untreated—can result in significant morbidity and disability. We present a challenging case of post-MDT relapsed leprosy manifesting as erythema nodosum leprosum (ENL), a type 2 leprosy reaction (T2LR).

## Case Synopsis

A 23-year-old man presented to the emergency department with a 2-week history of painful, erythematous nodules on the bilateral upper and lower extremities. The patient, who immigrated from Vietnam 6 months prior, had been diagnosed with MB leprosy 5 years earlier and completed a 12-month course of MDT (rifampin, dapsone,

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and clofazimine) 1 year prior. Post-treatment, he developed persistent hypopigmented patches on the extremities. Previous treatments for the nodular rash, including methylprednisolone, cephalexin, and ciprofloxacin, provided minimal improvement. Review of systems was notable for fevers, abdominal pain, nausea, and non-bloody, non-bilious vomiting. He denied sexual activity or sick contacts and had no history of immunosuppression or current medications.

Examination revealed tender, erythematous subcutaneous nodules admixed with hypopigmented patches on the arms, forearms, and legs (**Figure 1**). Sensory and motor function were intact. Laboratory studies showed leukocytosis and microcytic anemia; blood cultures and serologies for hepatitis, human immunodeficiency virus, and syphilis were negative. QuantiFERON-TB Gold was indeterminate. Chest radiograph was unremarkable, while computed tomography of the chest, abdomen, and pelvis demonstrated axillary and inguinal lymphadenopathy with splenomegaly.

Punch biopsies of a hypopigmented patch and an erythematous nodule revealed granulomatous collections of epithelioid to foamy histiocytes centered on dermal nerve bundles and adnexal structures (**Figure 2A**). The erythematous nodule also showed early vasculitic changes with scattered neutrophils (**Figure 2B**), consistent with ENL. Fite-Faraco staining highlighted numerous weakly acid-fast bacilli (**Figure 2C**). Grocott's methenamine silver and Gram stains were negative.

The patient was diagnosed with MB leprosy relapse and ENL. After consultation with the National Hansen Disease Program, the patient was started on monthly RMM for MB leprosy, along with methotrexate, thalidomide, and prednisone for ENL; thalidomide was unavailable owing to insurance limitations. At 2 months, symptoms had improved, though new ENL lesions persisted. At 7 months, he remained on RMM without reported adverse effects.

## Case Discussion

Diagnosing leprosy relapse in a previously treated patient is challenging, particularly when accompanied by ENL. New or recurrent skin lesions, neuropathy, and systemic symptoms should raise clinical suspicion, even after successful treatment.[4] Bacteriological assessments can detect relapse in MB leprosy but are less reliable in PB cases owing to low bacterial load. Histopathology demonstrating granuloma formation, nerve involvement, inflammation, and bacilli is valuable, though findings may be subtle in PB disease. Polymerase chain reaction detection of *M. leprae* DNA is diagnostic when other methods are inconclusive.[4] In the present case, relapse was suspected clinically and confirmed histologically.

Distinguishing relapse from reinfection is important. Relapse represents recurrence of the original infection, typically months to years after treatment, whereas reinfection depends on ongoing exposure and can occur at any time.[4] Given the patient's timing and recent immigration to a non-endemic area, relapse was the most likely etiology.

Factors contributing to relapse include bacillary persistence, drug resistance from prior monotherapy, and inadequate treatment.[4] MB patients, such as the present case, are at higher risk. Relapse increases the likelihood of transmission, reactional states, worsening disease, and decreased quality of life, and it strains healthcare resources. In the present case, lack of post-MDT follow-up leaves the exact cause unclear, though bacillary persistence or incomplete therapy are plausible.

Immunologic reactions complicate management, requiring additional therapy and supportive care.[5] Type 1 leprosy reaction (T1LR), a type IV hypersensitivity reaction, typically occurs within 2 years of MDT,[5] but was excluded here based on clinical and histopathological features. Type 3 leprosy reaction (Lucio phenomenon), a rare vasculitis of untreated or inadequately treated leprosy,[6] was also excluded owing to the absence of purpura, bullae, or ulceration.

ENL, a T2LR, is an immune complex–mediated process characterized by subcutaneous erythematous nodules with fever and systemic inflammation.[5] ENL can occur before, during, or after treatment for MB leprosy,[7-10] but its presentation as a manifestation of post-MDT relapse is rare, previously reported only following dapsone monotherapy.[11] Relapsed patients are at increased risk for both T1LR and T2LR owing to *M. leprae* reactivation and heightened immune responses, which likely contributed to ENL in the present case.[12]

## Conclusion

Leprosy remains a global public health concern. This case underscores the importance of regular monitoring and follow-up during and after therapy, particularly in patients at higher risk for relapse or reinfection. Ongoing surveillance supports adherence to multidrug therapy, guides consideration of extended treatment in complex cases, and mitigates the broader public health impact of the disease.

### Potential conflicts of interest

The authors declare no conflicts of interest.

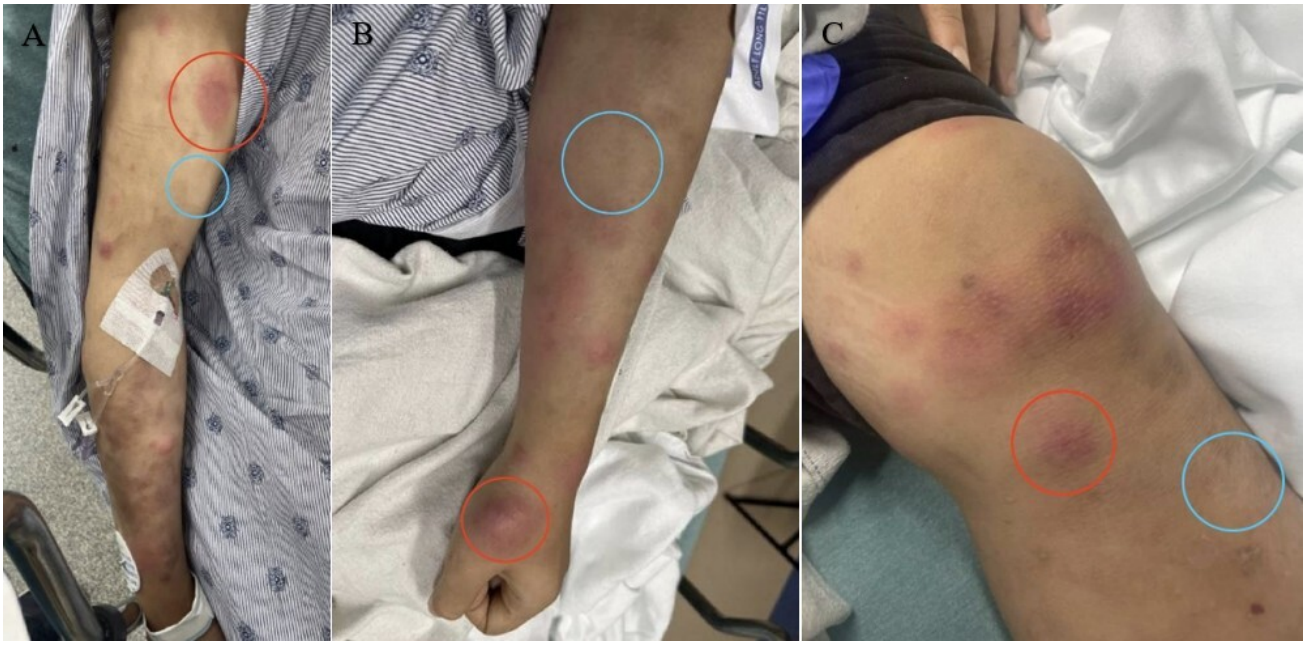


**Figure 1.** *Erythematous, subcutaneous nodules (red circles) intermixed with hypopigmented patches (blue circles) on the **(A)** right arm, **(B)** left forearm and hand, and **(C)** left knee.*

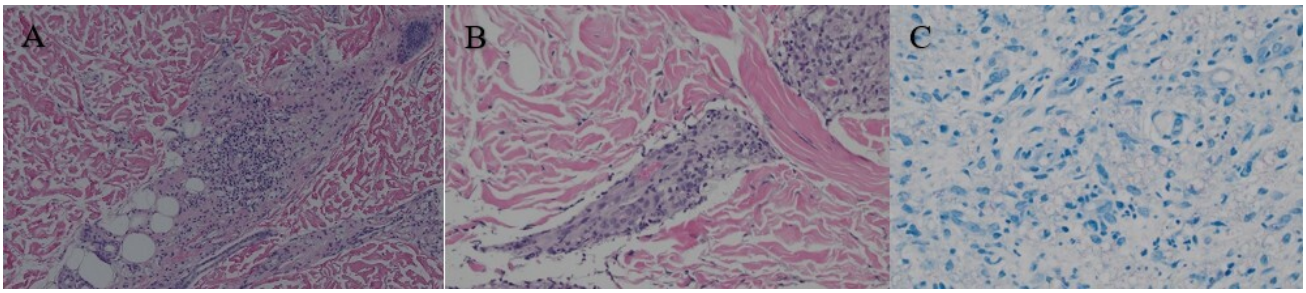


**Figure 2.** *Histopathology of leprosy lesions. **(A)** Granulomatous collections of epithelioid to foamy histiocytes centered on dermal nerve bundles and adnexal structures (hematoxylin-eosin, original magnification ×20; hypopigmented patch). **(B)** Focal early vasculitic changes with scattered neutrophils (hematoxylin-eosin, original magnification ×20; erythematous nodule), consistent with erythema nodosum leprosum. **(C)** Scattered weakly acid-fast bacilli within macrophages (Fite-Faraco, original magnification ×40; erythematous nodule).*

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