Am. J. Trop. Med. Hyg., 109(1), 2023, pp. 53–56
doi:10.4269/ajtmh.22-0701

Case Report: Necrotizing Erythema Nodosum as a Manifestation of Lepromatous Leprosy Relapse 50 Years after the Initial Infection

Juan Galeano,[1] Alejandra Contreras,[2] Lorena Pabón,[2] Ana C. Ruiz,[3] Héctor Serrano-Coll,[4] and Margarita Arboleda[4]*

[1]*University Hospital of Münster, Münster, Germany;* [2]*Rosario University, Bogotá, Colombia;* [3]*CES University, Medellín, Colombia;* [4]*Colombian Institute of Tropical Medicine ICMT-CES, Apartadó, Colombia*

Abstract. Leprosy is a chronic infection caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis* that preferentially compromises peripheral nerve, skin, and mucous membranes. Colombia achieved the goal of leprosy elimination in 1997. However, in Urabá (Colombia), there has been an increase in leprosy cases beginning in 2020. This case report shows a leprosy relapse 5 decades after the initial infection debuted as a necrotizing erythema nodosum leprosum. Therefore, long-term follow-up of patients with risk factors for relapse is emphasized, especially those treated before the standard of multidrug therapy (dapsone, clofazimine, and rifampin). This case report stresses the importance the importance of clinical follow-up and surveillance of patients with these events of interest for the public health.

INTRODUCTION

Leprosy is a chronic infection caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*.[1] This disease predominantly affects peripheral nerves, skin, eyes, and mucous membranes.[2] This disease is a neglected and public health issue mainly in vulnerable populations with limited healthcare access. Currently, the WHO's efforts to eliminate the spread of this infection are focused on early detection and management with multidrug therapy (MDT) for leprosy.[3]

In 2020, the WHO reported 127,558 new cases of leprosy in 139 countries,[4] and in 2021, Colombia registered 307 new cases of this disease. Remarkably, Colombia reached the goal of eliminating the disease in 1997,[5] and its leprosy control program has helped reduce leprosy cases in the past 5 years.[6] However, since 2020, Urabá, a Colombian region with high economic inequality located in the northwest of the country, has observed an increase in leprosy cases according to active surveillance of household contacts in leprosy patients.

Furthermore, the clinical leprosy spectrum is broad and directly related to the host's immune response. It is described by the Ridley–Jopling classification, which includes five categories based on immunological approach: tuberculoid, borderline tuberculoid, borderline lepromatous, and lepromatous.[2] This classification is helpful in recognizing patients at risk of presenting leprosy reactions secondary to hypersensitivity reactions of type III and IV, which increase morbidity and disability.[6] There are three types of leprosy reactions: type 1 or reversal reaction is related to borderline forms, type 2 or erythema nodosum leprosum (ENL) is associated with lepromatous forms, and Lucio's phenomenon (type 3) is exclusively documented in diffuse lepromatous leprosy patients, mainly in Mexico.[1] Lucio's phenomenon and the vasculonecrotic forms of ENL have similarities and are difficult to clinically differentiate.[7–9] It is important to note that reversal reactions and ENL can occur before, during, or after MDT, even after achieving microbiological recovery,[10] whereas Lucio's phenomenon appears before MDT.[7–9]

This article describes a leprosy relapse with a type 2 leprosy reaction 50 years after the primoinfection, in Apartadó, Urabá region, Colombia.

CASE DESCRIPTION

A 73-year-old male patient from Chigorodó, Antioquia (Urabá), diagnosed with leprosy in 1970, received therapy for 5 years. In 1980, the patient required a new 3-year cycle of treatment due to relapse. An unknown pharmacological regimen was used on both 3, and the patient was considered cured.

In December 2021, the patient presented with unquantified intermittent fever; chills; lower limb pain; and erythematous, tender nodules on his chest, right arm, and back. Physical examination showed madarosis, hyperpigmented lesions with alterations of sensitivity (thorax, abdomen, extremities), and painful subcutaneous erythematous nodules in the deltoid region of the right arm, upper thorax, epigastrium, and back (Figure 1). The patient was diagnosed with type 2 leprosy and received treatment with prednisolone (1 mg/kg/day) and follow-up after 72 hours.

Subsequently, the patient returned to clinical evaluation with fever and increased erythema and lesion size (left upper thorax and interscapular region), which gained an impetiginized appearance. Given the risk of complications such as bacterial infection, the patient was hospitalized. The admission's blood tests showed leukocytosis with neutrophilia, mild anemia, a slight increase in creatinine, and elevation of C-reactive protein (Table 1). The patient was managed with cefazolin, methylprednisolone, and thalidomide.

The histopathological analysis showed septal and lobular panniculitis without vasculitis, with numerous acid-fast bacilli in the modified Ziehl Neelsen stain forming globi (Figure 1). Additionally, a conventional polymerase chain reaction tissue study confirmed the presence of *M. leprae*. The high bacillary load visualized was considered indicative of active disease. However, the patient's household contacts did not show skin or neural involvement related to leprosy. Subsequently, according to WHO guidelines, the patient was diagnosed with leprosy relapse and started on multibacillary MDT.

Approximately 30 days after starting MDT therapy and discontinuing thalidomide, the patient presented a reappearance of fever and worsening nodular lesions with necrotic areas (Figure 1). Rehospitalization was necessary due to

*Address correspondence to Margarita Arboleda, Colombian Institute of Tropical Medicine ICMT-CES, Carrera 98 #106-176, Apartadó, Colombia. E-mail: marboleda@ces.edu.co

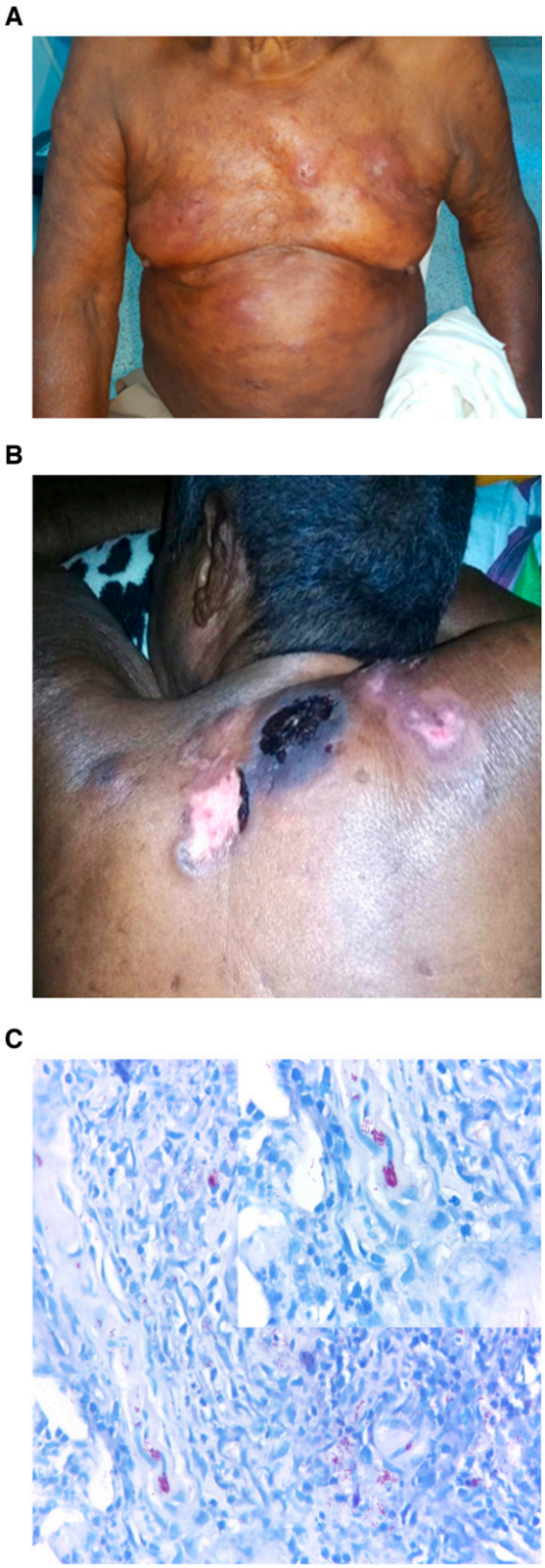

FIGURE 1. Skin lesions and histopathological findings. **(A)** Nodular (panniculitis) and hiperpigmented lesions with sensitivity alterations in the thorax, abdomen, and extremities. **(B)** Necrotic cutaneous areas on the old lesions simulating a Lucio phenomenon. **(C)** Numerous acid-fast bacilli in modified Ziehl Nielsen stain.

TABLE 1
Paraclinical evaluation

Parameter	Value (leprosy patient)	Normal value
Hemoglobin (g/dL)	10.6	14–17.5
Hematocrit (%)	31.2	40–52
Leukocytes (per mm^3)	15.71×10^3	$4.8–11 \times 10^3$
Neutrophils (per mm^3)	11.48×10^3	$2–7.4 \times 10^3$
Lymphocytes (per mm^3)	2.58×10^3	$0.7–4.5 \times 10^3$
Plaquettes (per mm^3)	319×10^3	$150–500 \times 10^3$
C reactive protein (mg/dL)	15.26	0–5
AST (U/L)	15.7	5–40
ALT (U/L)	12.9	5–41
Serum creatinine (mg/dL)	1.24	0.67–1.19
Ureic nitrogen (mg/dL)	19	4.8-5.9
Glycosylated hemoglobin (%)	5.6%	4.8–5.9

ALT = alanine transaminase; AST = aspartate transaminase.

suspected necrotic erythema nodosum leprosum and possible bacterial infection. Broad-spectrum antimicrobial therapy was administered, and a skin biopsy was performed. It showed fibrin exudate, multiple polymorphonuclear cell accumulations, and acute septal and lobular panniculitis with liquefactive necrosis but no vasculitis. Steroid therapy was initiated, with a transition to thalidomide after clinical improvement. Subsequently, the patient was discharged for outpatient monitoring.

DISCUSSION

This case is the first report of leprosy relapse occurring 5 decades after receiving antibacillary treatment. The main mechanisms involved in reoccurrences were as follows: 1) insufficient therapy—inappropriate clinical classification (bacillary persistence), nonadherence, or resistance; and 2) reinfection mainly in elderly people treated with dapsone monotherapy.[11] Analyzing the clinical characteristics, previous treatment, timing of skin manifestations, and evaluating the possibility of new exposures can help to establish the etiology.

Relapses are common in older people and male patients.[12] A leprosy relapse is clinically characterized by signs of activity in previously resolved skin or nerve lesions or by new cutaneous or neural manifestations. One of these manifestations is the Type-2 leprosy reaction. In individuals who finished full treatment more than 5 years ago, however, the bacillary burden should be negative, and the development of the immune complexes and clinical appearance of type 2 leprosy reactions should be impossible.[10] This leprosy reaction usually appears in patients with lepromatous forms, associated with a high bacillary index and the presence of coinfection, mood disorders (stress), pregnancy, or any clinical situation that alters the immune response.[13] These risk factors increase humoral activity in the host, causing immune complexes to deposit in the tissue and inducing complement activation through the classical pathway. Furthermore, there is platelet aggregation and increased recruitment of proinflammatory cells (neutrophils, macrophages), which could generate panniculitis, multiorgan inflammatory manifestations, and, in severe cases, the appearance of necrotic erythema nodosum.[10,14,15] Notably, in this case, the patient's clinical and histopathological findings suggest the overlap of relapse and type 2 leprosy reaction, a coexistence that has already been reported in a case series of patients with rare ENL.[16]

Although this patient's treatment during the primary infection and the first relapse is unknown, the patient likely received monotherapy with dapsone. This was the leprosy treatment in Colombia from 1942[17] to 1985 when MDT was introduced,[18] 3 years after the WHO established it.[16]

Notoriously, dapsone monotherapy is one of the main risk factors for relapse due to the development of resistance.[12,13,19,20] Approximately 55% to 57% of cases occur between 3 and 6 years after treatment.[21] For instance, Gonçalves et al. conducted a study with patients from the Brazilian Amazon, observing a median time to relapse of 12.8 years in those who received dapsone monotherapy and a maximum of 29 years in those who received polychemotherapy for less than 9 months.[11] However, this case in Urabá is the first time an outpatient presented with relapse after 50 years.

Clinically, relapses and reinfections are indistinguishable, especially in endemic areas.[12,13] Laboratory confirmation is made by demonstrating the existence of two strains by genomic analysis. In this case, the patient's household contacts were evaluated without identifying skin or neural symptoms, and it was impossible to establish the presence of other confirmed cases of leprosy in this community.

The diagnosis of relapse is made considering clinical, bacteriological, therapeutic, histopathological, and serological criteria.[13] In this case, the diagnosis was made using clinical and histological criteria and the molecular confirmation of *M. leprae*.

The treatment of relapses is standard MDT according to the WHO recommendations; if resistance to rifampicin occurs, the second-line drugs are quinolones, clarithromycin, and minocycline.[22] Conversely, type 2 leprosy reactions, a type III hypersensitivity reaction, require immunomodulatory therapy as the treatment aims to control inflammation and pain while reducing the recruitment of inflammatory cells.[10] High-dose steroids also provide rapid improvement. However, thalidomide is the primary therapy to avoid prolonged use of steroids; its main anti-inflammatory effect is mediated by its action anti–tumor necrosis factor.[14] Other drugs such as azathioprine, methotrexate, cyclosporin A, dapsone, clofazimine, and minocycline have also been used in steroid-dependent patients.[23]

Finally, we emphasize that the presence of *M. lepromatosis*, the causal agent of type 3 leprosy reactions (Lucio's phenomenon, characterized by necrotic lesions and vasculitis), was recently documented in Colombia.[21] This initially simulated the clinical presentation of this case.

However, the immune and histopathological differentiation between necrotic erythema nodosum and Lucio's phenomenon is complex because both present as leukocytoclastic vasculitis and cause ulcerative lesions on the skin. Further research is necessary to gain a better understanding of these two events of immunological hypersensitivity in leprosy and is also relevant to perform genomic studies focus on finding new biomarkers for leprosy reactions detection.

CONCLUSION

This case report shows the importance of long-term clinical follow-up of leprosy patients with risk factors for relapse, especially those treated before the standardization of MMT as the first line for leprosy. In addition, it is essential to take a detailed clinical history in leprosy patients with new skin and nerve involvement or leprosy reactions several years after finishing treatment with MDT, highlighting the importance of clinical follow-up and surveillance of patients with these events of interest for the public health. Finally, genomic surveillance is important in communities with a high burden of leprosy to identify circulating strains and differentiate between relapse and reinfection by *M. leprae* in individuals with new clinical manifestations of leprosy.

Received November 10, 2022. Accepted for publication December 26, 2022.

Published online May 30, 2023.

Acknowledgments: We thank the patient who voluntarily participated in this case report and Karen María Rivas Hincapié, a nursing assistant at the Tuberculosis and Leprosy Program—Bolivarian Clinic, who provided clinical information on the patient and photos during his hospitalization at the Bolivarian Clinic. In addition, we thank the Colombian Institute of Tropical Medicine and the Research and Innovation Department at CES University for collaboration in developing this case report.

Data availability: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

Authors' addresses: Juan Galeano, University Hospital of Münster, Münster, Germany, E-mail: juank996@gmail.com. Alejandra Contreras and Lorena Pabón, Rosario University, Bogotá, Colombia, E-mails: alma_c8@hotmail.com and lore-110@hotmail.com. Ana C. Ruiz, CES University, Medellín, Colombia, E-mail: acruiz@ces.edu.co. Héctor Serrano-Coll and Margarita Arboleda, Colombian Institute of Tropical Medicine ICMT-CES, Apartadó, Colombia, E-mails: hserrano@ces.edu.co and marboleda@ces.edu.co.

REFERENCES

1. Alemu Belachew W, Naafs B, 2019. Position statement: leprosy: diagnosis, treatment and follow-up. *J Eur Acad Dermatol Venereol 33:* 1205–1213.
2. White C, Franco-Paredes C, 2015. Leprosy in the 21st century. *Clin Microbiol Rev 28:* 80–94.
3. Feasey N, Wansbrough-Jones M, Mabey DC, Solomon AW, 2010. Neglected tropical diseases. *Br Med Bull 93:* 179–200.
4. Lepra, 2022. *www.who.int*. Available at: https://www.who.int/es/news-room/fact-sheets/detail/leprosy. Accessed September 20, 2022.
5. OPS/OMS/Colombia. *Día mundial de la lucha contra la lepra*. Available at: https://www3.paho.org/col/index.php?option=com_content&view=article&id=2121:dia-mundial-de-la-lucha-contra-la-lepra&Itemid=562. Accessed September 10, 2014.
6. Informe de evento, 2022. *Lepra*. Sivigila periodo epidemiológico II. Colombia: Instituto Nacional de Salud: Bogotá, Colombia. Available at: https://www.ins.gov.co/buscador-eventos/Informes deevento/LEPRA%20PE%20XIII-2021.pdf. Accessed March 15, 2023.
7. Benard G, Sakai-Valente NY, Bianconcini Trindade MA, 2009. Concomitant Lucio phenomenon and erythema nodosum in a leprosy patient: clues for their distinct pathogeneses. *Am J Dermatopathol 31:* 288–292.
8. Sharma P, Kumar A, Tuknayat A, Thami GP, Kundu R, 2019. Lucio phenomenon: a rare presentation of Hansen's disease. *J Clin Aesthet Dermatol 12:* 35–38.
9. Kamath S, Vaccaro SA, Rea TH, Ochoa MT, 2014. Recognizing and managing the immunologic reactions in leprosy. *J Am Acad Dermatol 71:* 795–803.
10. Fonseca AB, Simon MD, Cazzaniga RA, de Moura TR, de Almeida RP, Duthie MS, Reed SG, de Jesus AR, 2017. The influence of innate and adaptative immune responses on the differential clinical outcomes of leprosy. *Infect Dis Poverty 6:* 5.
11. Gonçalves FG, Belone AFF, Rosa PS, Laporta GZ, 2019. Underlying mechanisms of leprosy recurrence in the Western

Amazon: a retrospective cohort study. *BMC Infect Dis 19:* 460.
12. Kaimal S, Thappa DM, 2009. Relapse in leprosy. *Indian J Dermatol Venereol Leprol 75:* 126–135.
13. Bhat RM, Vaidya TP, 2020. What is new in the pathogenesis and management of erythema nodosum leprosum. *Indian Dermatol Online J 11:* 482–492.
14. Fonseca AB, Simon MD, Cazzaniga RA, de Moura TR, de Almeida RP, Duthie MS, Reed SG, de Jesus AR, 2017. The influence of innate and adaptative immune responses on the differential clinical outcomes of leprosy. *Infect Dis Poverty 6:* 5.
15. Serrano-Coll H, Salazar-Peláez L, Acevedo-Saenz L, Cardona-Castro N, 2018. *Mycobacterium* leprae-induced nerve damage: direct and indirect mechanisms. *Pathog Dis 76*, doi: 10.1093/femspd/fty062.
16. Wankhade VH, Debnath P, Singh RP, Sawatkar G, Bhat DM, 2019. A retrospective study of the severe and uncommon variants of erythema nodosum leprosum at a tertiary health center in central India. *Int J Mycobacteriol 8:* 29–34.
17. Botero-Jaramillo N, Padilla-Pinzón LT, Beltrán-Serrano MA, Ossa-Trujillo RH, 2017. Tratamiento de la enfermedad de Hansen en Colombia: medicalización y control de la enfermedad a lo largo del siglo XX. *Rev Fac Nac Salud Publica 35:* 358–368.
18. World Health Organization, 1982. *Chemotherapy of Leprosy for Control Programs: Report of a WHO Study Group*. World Health Organization Technical Report Series, No 675. Geneva, Switzerland: WHO.
19. Rodríguez G, Pinto R, Laverde C, Sarmiento M, Riveros A, Valderrama J, Ordóñez N, 2004. Recidivas postratamiento de la lepra multibacilar. *Biomédica 24:* 133–139.
20. Ramu G, 1995. Clinical features and diagnosis of relapses in leprosy. *Indian J Lepr 67:* 45–59.
21. World Health Organization, 2018. Guidelines for the diagnosis, treatment, and prevention of leprosy. Geneva, Switzerland: WHO.
22. Alakad R, Nofal A, Assaf M, 2021. Atypical presentations of erythema nodosum leprosum: diagnostic and therapeutic aspects. *J Dtsch Dermatol Ges 19:* 1133–1143.
23. Cardona-Castro N, Escobar-Builes M, Serrano-Coll H, Adams LB, Lahiri R, 2022. *Mycobacterium* lepromatosis as Cause of Leprosy, Colombia. *Emerg Infect Dis 28:* 1067–1068.