Um Caso Clínico de Lepra Multibacilar com Vários Surtos de Eritema Nodoso Leproso

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RESUMO – A lepra é uma doença granulomatosa crónica com longo período de incubação causada pelo bacilo *Mycobacte-rium leprae* que afeta principalmente a pele, mucosas e sistema nervoso periférico. Tem risco de sequelas permanentes e impacto significativo na qualidade de vida do paciente. É clinicamente heterogénea com possíveis apresentações atípicas. Descrevemos o caso de uma mulher de 31 anos, fototipo V, com lepra multibacilar caracterizada por múltiplos surtos de eritema nodoso leproso como manifestação inaugural. A doença foi adquirida num grupo de crianças e adolescentes de uma região endémica de África, evoluiu sem tratamento durante 3 anos, e manifestou-se com algumas características clínicas incomuns e notável envolvimento linfático. Destacamos a importância da colaboração entre centros especializados e parcerias institucionais, a fim de fornecer os recursos de diagnósti-co e os cuidados adequados às populações afetadas.
PALAVRAS-CHAVE – Eritema Nodoso; Lepra Lepromatosa; Lepra Multibacilar.

A Case Report of Multibacillary Leprosy Presenting with Multiple Outbreaks of Erythema Nodosum Leprosum

ABSTRACT – *Leprosy is a chronic granulomatous disease with a long incubation period caused by Mycobacterium leprae that mainly affects the skin, mucous membranes and the peripheral nervous system. It carries the risk of per-manent sequels with a significant impact on the patient's quality of life. It has a considerable clinically diver-sity and possible atypical presentations. We present a case of a 31-year-old, skin phototype V woman with multibacillary leprosy characterized by multiple outbreaks of erythema nodosum leprosum, as an inaugural manifestation of the disease. The disease was acquired within a group of children and adolescents from an endemic region of Africa, evolved untreated for 3 years, and presented with unusual features and remarkable lymphatic involvement. We highlight the importance of building and maintaining collaboration between expert centers and institutional partnerships in order to provide the adequate diagnostic resources and appropriate care to the affected populations.*
KEYWORDS – *Erythema Nodosum; Leprosy, Lepromatous; Leprosy, Multibacillary.*

INTRODUCTION

Leprosy is a chronic granulomatous disease with a long incubation period caused by *Mycobacterium leprae* that mainly affects the skin, mucous membranes and the peripheral nervous system.[1-3] It is transmitted from person--to-person via inhalation of infectious droplets and has a long incubation period.[2] Ridley and Jopling leprosy classification (1966) is based on clinical and histological

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criteria with two polar forms, from tuberculoid to lepromatous, depending upon the cellular immune system of the host.[4] The operational classification created by the World Health Organization (WHO) in order to facilitate the choice of treatment regimens, clas-sifies leprosy as paucibacillary (characterized by a limited number of skin lesions: maximum five) or multi-bacillary (with symmetric skin lesions, nodules, plaques and thickened dermis).[5,6] We will refer to WHO clas-sification throughout the article. Leprosy is a serious disease with risk of permanent sequels and a significant impact on the patient's quality of life when not promptly treated.[3,7-9] It remains one of the leading causes of physical disability from an infectious disease in developing countries with 1 to 2 million individual disabled because of leprosy worldwide.[2,10]

We present a patient with multibacillary leprosy acquired within a group of children and adolescents from an endemic area of Africa that evolved untreated for 3 years and presented with multiple outbreaks of *erythema nodosum leprosum* (ENL).

CASE REPORT

A 31-year-old female patient, Fitzpatrick skin type V, missionary, working in Luanda was admitted to our hospital with a 3-year history of disseminated skin lesions, fever, malaise, anorexia and weight loss (12% of body weight in six months). There was no relevant past medical history. The patient had first noticed red patches over her feet, 3 years before, and these progressively spread to her legs, thighs, arms and abdomen. She complained of intermittent pruritus, pain and burning sensation on the skin lesions. The symptoms had a chronic relapsing-remitting course with multiple outbreaks lasting approximately 2 to 3 months.

Physical examination revealed symmetrically distributed red-brown plaques and nodules predominantly on the lower extremities (Fig. 1) but also involving the upper extremities (Fig. 2) and lower abdomen. A painless left axillary lymph node with approximately 2 cm was detected as well as non-tender bilateral enlarged and hard inguinal lymph nodes (> 2 cm). On the dorsal hands, some of the nodules suppurated spontaneously. The neurological examination was unremarkable. Motor evaluation revealed normal muscle bulk and tone and strength was normal and symmetric. There was no evidence of peripheral sensory loss since light touch, pin-prick, position sense, and vibration sense were intact in fingers and toes. Reflexes were symmetric (2+) at the biceps, triceps, knees, and ankles. No enlarged peripheral nerves were palpable.

Laboratory testing revealed microcytic hypochromic anemia. Serological tests for HCV, HBV, HTLV and HIV types 1 and 2 were negative. Blood and urine cultures were also negative. QuantiFERON testing was positive but the chest X-ray did not reveal any stigmata of latent or active tuberculosis. A full body computed tomography scan disclosed lymph node enlargement in both axillary, inguinal, external iliacus and internal obturator areas, and homogeneous

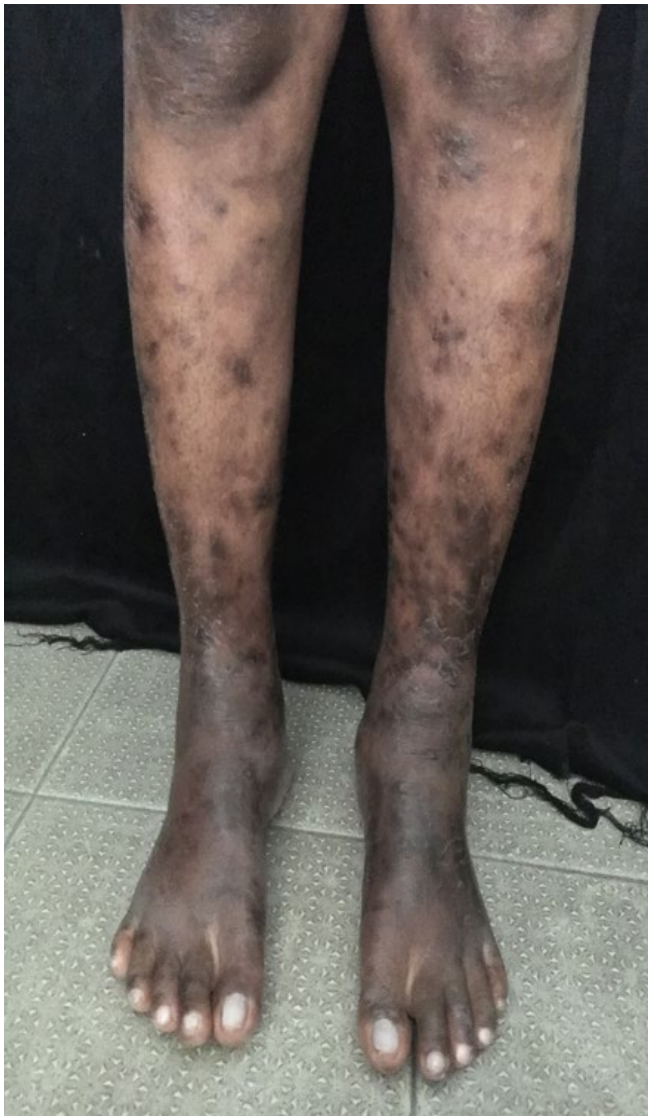

Figura 1 - Multibacillary leprosy, clinical picture: Symmetrically distributed painful, red to brown nodules and diffusely infiltrated plaques.

hepatosplenomegaly, with no focal lesions. Histopathological findings on two skin biopsies taken from the most active edge of the plaques (from the arm and thigh) were consistent with leprosy (Fig. 3) revealing perivascular lymphohistiocytic aggregates in the dermis. Both isolated bacilli and globi (clumps of bacilli) were seen on Ziehl-Neelsen (ZN) staining. The aspirate from an inguinal lymph node stained with ZN revealed multiple acid-fast bacilli (AFB). Samples for bacilloscopy were obtained from the earlobes which allowed AFB identification. We were also able to find the bacilli on nasal secretions upon mucosal smear examination. A positive identification for *M. leprae* was made by nested PCR for the detection of RLEP repetitive sequences in a lymph node sample. The molecular detection of drug resistance associated mutations in *rpoB*, *folC* and *gyrA* genes was assessed using the GenoType LepraeDR and no mutation was found.

Figura 2 - Multibacillary leprosy, clinical picture: Bilateral hand edema with infiltrated skin lesions.

A diagnosis of multibacillary leprosy was made with skin, lymph node and spleen involvement. A multi-drug therapy with dapsone (100 mg per day), clofazimine (50 mg per day and 300 mg once a month) and ri-fampicin (600 mg per month) for 24 months was proposed. To address the associated ENL cochicine (starting with a dose of 0.6 mg twice daily) and pentoxifylline (400 mg every 8 hours) were initially considered (the patient referred a history of prednisone allergy). Unfortunately, due to social and economic constraints, the patient went back to her home country. We were able to contact the patient who let us know that she was on the third month of treatment, with clinical improvement.

DISCUSSION

Diagnosis of leprosy is based on different clinical parameters, mainly on dermatological and neurological examination. Since *M. leprae* cannot be grown in vitro, a reliable

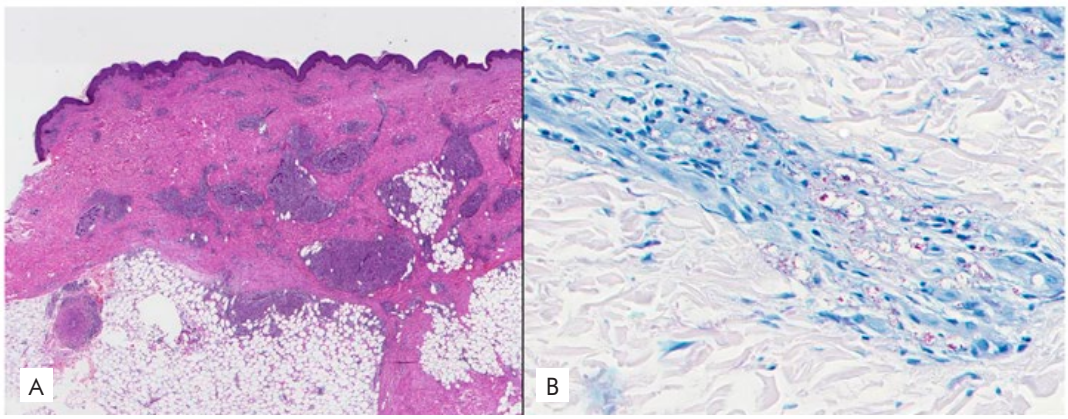

Figura 3 - Multibacillary leprosy, histopathological findings: **(A)** Perivascular lymphohistiocytic aggregates in the dermis (H&E, x 40). **(B)** Sheets of foamy histiocytes with clumps (globi) of intracellular AFB were identified on Ziehl-Neelsen staining (x100).

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and definitive diagnosis is obtained by histopathological diagnosis and demonstration of AFB in skin biopsies, lymph nodes, nasal secretions or skin samples for bacilloscopy which are usually collected from the earlobes.[1,2] A definitive diagnosis on histo-pathological grounds is not always possible. PCR amplification of *M. leprae*-specific sequences allows a definitive diagnosis and can be particularly useful in cases of paucibacillary leprosy.[11-13] In this case, the patient had positive skin smears from the earlobes and nasal secretions and multiple AFB on the aspirate from an involved lymph, consistent with a case of multibacillary leprosy hence, molecular techniques were not essen-tial for the diagnosis. However, given the unusual presentation with notable lymphatic involvement and ab-sence of clinical neurological involvement, PCR positivity of RLEP confirmed the presence of *M. leprae*. Beyond routine diagnostic tests, sequencing of resistance genes allowed the exclusion of strains resistant to rifampicin and dapsone based on the most characteristic gene mutations.

Although clinical manifestations of leprosy are largely confined to skin and peripheral nervous system, there are a few case reports of lepra presenting with lymphadenopathy, as in this case.[14-16] In fact, leprosy has propensity to involve lymph node, spleen, bone marrow, eyes and testes. Singh *et al*. highlight the utility of fine needle aspiration cytology (FNAC) in these cases. FNAC of one of the involved lymph nodes yields adequate material for cytologic studies.[15] Several other studies and case reports stress out the utility of FNAC as an alternative to slit skin smears and skin biopsy for diagnosis of all cases of leprosy.[17-19] It can be easily per-formed directly from the skin lesions or ear lobes. Studies evaluating the cytomorphology of leprosy lesions in FNAC found a histopathological correlation rate of 77% - 78%.[17,19] It may be especially useful in endemic areas where histopathological services are not routinely available.

In this case, skin biopsies revealed aggregates of lymphocytes and macrophages containing abundant foamy cytoplasm. Numerous AFB were seen with ZN staining. These features are consistent with a borderline lepromatous leprosy, according to Ridley and Jopling classification, which correlates well with the clinical picture. In order to achieve maximum correlation between clinical and histopathological findings, the selection of the site for biopsy is very important since clinically dissimilar lesions from the same patient may show different types of histopathology.[7,20] A study from Kumar *et al*. showed that maximum correlation is seen with lepromatous leprosy.[7] We must keep in mind that histological findings should always be interpreted in correlation with clinical findings.[20]

This case shows the diversity and possible unusual presentations of leprosy, with a complete picture of multibacillary leprosy but no clinical signs of peripheral nerve involvement which cannot be totally excluded since an electroneuromyography was not performed. The clinical evolution is consistent with multiple out-breaks of ENL as a manifestation of a non-treated multibacillary lepromatous patient. ENL is a type 2 reaction characterized by acute inflammation that appears suddenly consisting of an acute eruption of symmetrical distributed papules and nodules, usually in repeated episodes, lasting several days (usually 1 to 2 weeks). Patients may exhibit signs of systemic involvement such as fever, lymphadenopathy, limb edema, hepatosple-nomegaly, leukocytosis, arthritis, iridocyclitis, orchitis, nephritis and painful nerve enlargement, among others.[1,21-23] It occurs due to the immunological complications of multibacillary leprosy and it is a systemic inflammatory reaction probably associated with bacterial destruction and the release of antigens that leads to antibody production and consequent immune-complex formation.[21,22] Most cases are treated with anti-inflammatory drugs such as acetylsalicylic acid, indomethacin, chloroquine and colchicine. Thalidomide has a rapid action, controlling symptoms within 24-48 hours. Because of its teratogenicity it should not be used as first-line therapy for women in childbearing age. Clofazimine, which is included in lepra treatment regimen, is effective on chronic ENL. Pentoxifylline is another viable option, with a variety of anti-inflammatory effects, but a slow action period. Prednisone acts rapidly on the control of acute inflammation, but this patient referred an history of prednisone allergy.[22]

Multidrug therapy is warranted to prevent or slow the development of resistance. The World Health Organization standardized regimen is a three first-line drug combination, namely, dapsone, rifampicin and clo-fazimine for all leprosy patients, with a duration of treatment of 6 months for paucibacillary leprosy and of 12 months for multibacillary leprosy.[6] However, treatment is difficult since it must be continued for a long period with potential adverse effects from the several drugs used and with a high cost, particularly for less developed countries.[9] Treatment tendency is towards shorter and uniform drug treatments.[6,24] However, in this case, a treatment duration of 24 months was proposed because some studies show an increase in severity of ENL when one-year is compared to two-year regimen.[25,26]

Despite effective treatments the prevalence and incidence of leprosy have plateaued since 2005 and the number of new cases diagnosed with permanent disability remains unchanged since 2010 reflecting that transmission has not stopped.[1,10] Therefore, collaboration between expert centers and institutional partnerships is vital in order to provide the adequate diagnostic resources and appropriate care to the affected populations.[9]

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REFERENCES

1. Cruz RCdS, Bührer-Sékula S, Penna MLF, Penna GO, Talhari S. Leprosy: current situation, clinical and laboratory aspects, treatment history and perspective of the uniform multidrug therapy for all patients. Ana Bras Dermatol. 2017;92:761-73. doi: 10.1590/abd1806-4841.20176724.
2. Forbes BA, Hall GS, Miller MB, Novak SM, Rowlinson MC, Salfinger M, et al. Practice guidelines for clinical microbiology laboratories: mycobacteria. Clin Microbiol Rev. 2018;31:e00038-17. doi: 10.1128/CMR.00038-17.
3. Sarkar R, Pradhan S. Leprosy and women. Int J Womens Dermatol. 2016;2:117-21.
4. Ridley D, Jopling W. Classification of leprosy according to immunity. A five-group system. Int J Lepr. 1966;34:255-73.
5. World Health Organization. WHO expert committee on leprosy. Geneva: WHO expert committee on leprosy; 1998.
6. World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. Geneva: WHO; 2018.
7. Kumar SA, Ranjana S, Savitri S, Sanjiv G. How accurately do clinical diagnosis correlate with biopsy findings in leprosy? J Pak Assoc Dermatol. 2017;27):23-9.
8. de Sousa JR, Sotto MN, Simões Quaresma JA. Leprosy as a complex infection: breakdown of the Th1 and Th2 immune paradigm in the immunopathogenesis of the disease. Front Immunol. 2017;8:1635. doi: 10.3389/fimmu.2017.01635.
9. Smith CS, Aerts A, Saunderson P, Kawuma J, Kita E, Virmond M. Multidrug therapy for leprosy: a game changer on the path to elimination. Lancet Infec Dis. 2017;17:e293-7. doi: 10.1016/S1473-3099(17)30418-8.
10. Chaptini C, Marshman G. Leprosy: a review on elimination, reducing the disease burden, and future research. Lepr Rev. 2015;86:307-15.
11. Martinez AN, Talhari C, Moraes MO, Talhari S. PCR-based techniques for leprosy diagnosis: from the laboratory to the clinic. PLoS Negl Trop Dis. 2014;8:e2655. doi: 10.1371/journal.pntd.0002655.
12. Chaitanya V, Cuello L, Das M, Sudharsan A, Ganesan P, Kanmani K, et al. Analysis of a novel multiplex polymerase chain reaction assay as a sensitive tool for the diagnosis of indeterminate and tuberculoid forms of leprosy. Int J Mycobacteriol. 2017;6:1-8. doi: 10.4103/2212-5531.201885.
13. Franco-Paredes C, Marcos LA, Henao-Martínez AF, Rodríguez-Morales AJ, Villamil-Gómez WE, Gotuzzo E, et al. Cutaneous mycobacterial infections. Clin Microbiol Rev. 2019;32:e00069-18. doi: 10.1128/CMR.00069-18.
14. Chowdhury AR, Bandyopadhyay G, Bhattacharyya P, Chakraborty S. An unusual presentation of leprosy: Lepromatous lymphadenitis. Int J Med Public Health. 2015;5:381-3. doi: 10.1159/000462959.
15. Singh P, Mushtaq D, Bala J, Kapur K, Rana A. Lepropmatous lymphadenitis mimicking non hodgkins lymphoma: A case diagnosed by fine needle aspiration cytology. J Clin Diagn Res. 2011;5:869-71. doi: 10.1080/10428190410001655166.
16. Yang SY, Leong WM, Kasunuran CM, Huang JX, Ho SJ, Aw CW, et al. Extensive Lepromatous lymphadenitis preceding lesions on the face and earlobes: an unusual presentation of leprosy in Singapore. Case Rep Dermatol. 2018;10:35-40. doi: 10.1159/000462959.
17. Nigam P, Kumar P, Pathak N, Mittal S. Fine needle aspiration cytology in reactional and non-reactional leprosy. Indian J Dermatol Venereol Leprol. 2007;73:247.
18. Rajesh NG, Siddaraju N, Muthalagan E, Jain D, Kumari R, Balasubramanian P. Report of a case emphasizing the clinical utility of fine needle aspiration cytology in the diagnosis of histoid leprosy. Cytopathology. 2015;26:132-3. doi: 10.1111/cyt.12144.
19. Ray R, Mondal RK, Pathak S. Benefits and limitations of fine needle aspiration cytology in the diagnosis and classification of leprosy in primary and secondary healthcare settings. Cytopathology. 2015;26:238-43. doi: 10.1111/cyt.12179.
20. Semwal S, Joshi D, Goel G, Asati D, Kapoor N. Clinico-histological correlation in Hansen's disease: three-year experience at a newly established tertiary care center in Central India. Indian J Dermatol. 2018;63:465-8. doi: 10.4103/ijd.IJD_525_17.

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21. Suryawati N, Saputra H. Erythema nodosum leprosum presenting as sweet's syndrome-like reaction in a borderline lepromatous leprosy patient. Int J Mycobacteriol. 2018;7:191-4. doi: 10.4103/ijmy.ijmy_49_18.
22. Costa PdSS, Fraga LR, Kowalski TW, Daxbacher ELR, Schuler-Faccini L, Vianna FSL. Erythema nodosum leprosum: Update and challenges on the treatment of a neglected condition. Acta Trop. 2018;183:134-41. doi: 10.1111/ddg.13301.
23. Fischer M. Leprosy–an overview of clinical features, diagnosis, and treatment. J Dtsch Dermatol Ges. 2017;15:801-27.
24. Saunderson PR. Uniform multidrug therapy for leprosy – time for a rethink? Indian J Med Res. 2016;144:499-501. doi: 10.4103/0971-5916.200884.
25. Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O, Suneetha S, et al. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. Am J Trop Med Hyg. 2006;74:868-79.
26. Balagon M, Saunderson PR, Gelber RH. Does clofazimine prevent erythema nodosum leprosum (ENL) in leprosy? A retrospective study, comparing the experience of multibacillary patients receiving either 12 or 24 months WHO-MDT. Lepr Rev. 2011;82:213-22.