Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2012;21:39-41
doi: 10.2478/v10162-012-0011-6

Erythema nodosum leprosum associated with minocycline

Ana Rita Travassos[1] ✉, Joana Antunes[1], David Pacheco[1], Luís Soares Almeida[1], Paulo Filipe[1], Manuel Sacramento Marques[1]

Abstract

Erythema nodosum leprosum is defined by the appearance of tender skin nodules, which can be accompanied by fever, joint pain, neuritis, edema, malaise and/or lymphadenopathy. The authors describe the case of a 19-year-old Angolan black woman, resident in Portugal for the last 10 years, diagnosed with Hansen's disease at the age of 12, irregular with follow-up and non-compliant with treatment. She was referred to our clinic with painful nodules and pustules on the upper limbs, diffuse facial infiltration with pustules and fever, after initiating minocycline with the intention of treating acne. Diagnosis of erythema nodosum leprosum was confirmed by the presence of acid-fast bacilli in the skin smear and also in skin biopsy. Minocycline was suspended and the patient was treated with systemic steroids, with prompt clinical improvement. Our case is reported to alert clinicians to this unusual presentation of erythema nodosum leprosum in a patient treated with highly bactericidal drugs that were not intended to treat Hansen's disease.

Received: 28 February 2012 | **Returned for modification:** 11 March 2012 | **Accepted:** 22 March 2012

Introduction

Reactional states of leprosy are expressions of immunological disturbance and are generally divided into two variants: type 1 (Jopling's type I or reversal reaction) and type 2 (Jopling's type II reaction), which relates to erythema nodosum leprosum (ENL) (1). Lucio's phenomenon may be considered a type 2 or 3 reaction, according to different authors (2, 3).

Erythema nodosum leprosum is defined by the appearance of tender skin nodules that can be accompanied by fever, joint pain, bone tenderness, neuritis, edema, malaise, anorexia, and/or lymphadenopathy (4).

Erythema nodosum leprosum has been described as a helper T cell type I (Th1) response to Mycobacteria leprae, characterized by the consistent presence of tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) and also by the predominance of CD4+ over CD8+ T-cells (5). The pathological alterations in ENL include: inflammatory infiltrate of neutrophils with vasculitis and/or panniculitis and deposition of immune complexes and complement together with Mycobacterium leprae antigens in the skin (5, 6).

Case report

We report the case of a 19-year-old Angolan woman living in Portugal for the last decade, with Hansen's disease diagnosed at age 12. The patient was irregularly followed up and was not compliant with treatment. Six weeks before referral, she initiated minocycline with the intention to treat acne. The patient was referred to our outpatient dermatology clinic due to the appearance of painful subcutaneous erythematous nodules and pustules on the upper limbs, diffuse facial infiltration with pustules (Fig. 1), and fever.

Laboratory examinations showed leukocytosis with neutrophilia (white blood cell differential count: 24.45 × 109/L leukocytes with 92% neutrophils, 4.7% lymphocytes, 2.3% monocytes, 0.2% eosinophils, and 0.1% basophils); elevation of C-reactive protein (CRP) 21.7 mg/dL (normal < 0.5 mg/dL); and erythrocyte sedimentation rate (ESR) 120 mm/h (normal < 12 mm/h). Serological tests for human immunodeficiency virus, hepatitis C virus, hepatitis B virus, and syphilis were all negative. Other investigations including liver and renal function tests, serum electrolytes, chest X-ray, and ECG were within normal limits, without sensitive alterations or other systemic abnormalities.

Skin smears obtained from arm and facial lesions were stained using the Ziehl–Neelsen method and were positive for acid-fast bacilli (AFB), with a bacteriological index (BI) of 3+ (range from 0 to 6+). The skin biopsy showed a perivascular and perineural granulomatous infiltrate at the full thickness of the dermis, extending to the panniculus adiposus, with the presence of foamy histiocytes, lymphocytes, neutrophils, and fragmented AFB (Fig. 2), supporting the diagnosis of ENL.

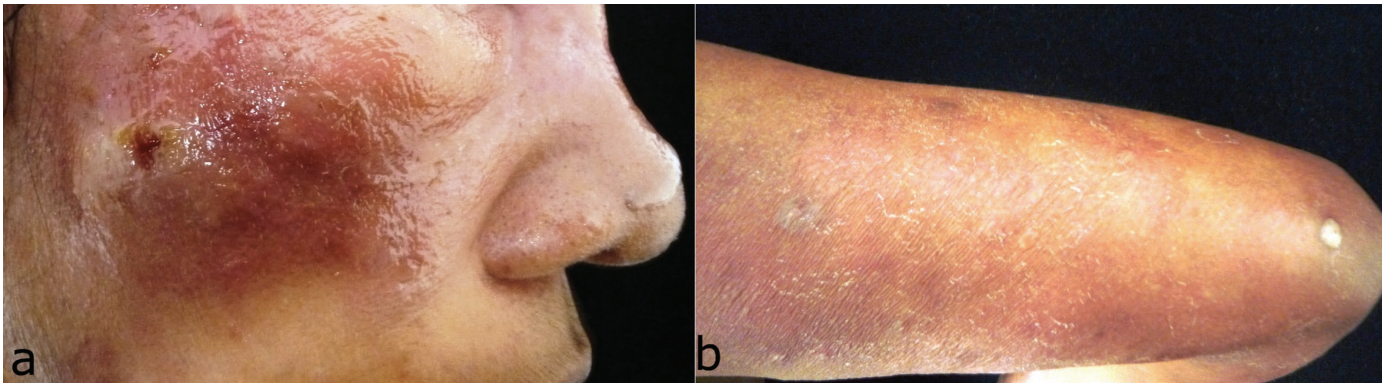

Figure 1 | **a.** Diffuse facial infiltration with pustules. **b.** Erythematous subcutaneous nodules and pustules on the right arm.

[1]Clínica Universitária de Dermatologia, Hospital de Santa Maria (CHLN), Avenida Prof. Egas Moniz, 1649-035 Lisboa, Portugal. ✉**Corresponding author:** ritatravassos@gmail.com

Minocycline was suspended and the patient treated with prednisolone (0.5 mg/kg/day), with prompt clinical improvement and normalization of laboratory parameters. Systemic steroid therapy was maintained for 2 months and multidrug therapy for multibacillary leprosy initiated, (MB-MDT): rifampicin, clofazimine, and dapsone. The patient was advised to continue the medication for 12 months.

Discussion

ENL is a type 2 leprosy reaction and occurs mainly in patients on MDT, often during the first 6 months of therapy, although some develop it after completion of treatment (7). A number of factors have been implicated in precipitating ENL, such as conditions leading to physiological or mental stress, pregnancy, trauma, intercurrent illness, vaccination, and a variety of drugs including anti-leprosy medications and common antibiotics taken for other illnesses, which are also anti-leprotic (e.g., doxycycline; ofloxacin), dapsone, iodides, and bromides (3, 7, 8).
The high release of bacterial antigen load from dying bacilli, leading to immune-complex formation and TNF-α secretion, has been suggested as the main pathogenic mechanism in ENL reactions (7, 8).

Although ENL usually occurs a few years after starting MDT or even in untreated patients (9), our patient had been irregularly treated with MDT previously and ENL occurred 6 weeks after the use of minocycline, with clinical improvement after suspension of the drug.

Although minocycline is mainly used to treat acne, it also has been reported to have bacteriostatic activity against Mycobacteria leprae. Interestingly, in the ENL cases published in the literature, minocycline is specifically described as a replacement therapy in ENL, rather than as a trigger for it (8). According to the Naranjo et al. adverse drug reaction probability scale (10), minocycline-induced ENL was probable. Furthermore, the possibility of other types of drug reaction to minocycline was ruled out because AFB were identified in the skin smear and skin biopsy and also by the absence of eosinophils, along with the presence of a characteristic pandermal, perivascular, and perineural granulomatous infiltrate in the skin biopsy.

In relation to ENL therapy, although there is some evidence in the literature that thalidomide is particularly beneficial, as well as clofazimine (1, 11, 12), we chose to avoid thalidomide because our patient was a young woman of childbearing age with poor compliance with medical advice. Instead, we opted for treatment with prednisolone (with prompt clinical response and without major adverse effects), followed by MB-MDT (a clofazimine-containing regimen), which is described in the literature as being effective in longstanding prevention of ENL during treatment for leprosy, as well as in the reduction of steroids (4).

The clinical diagnosis of ENL was unexpected, but the patient's provenance from a leprosy-endemic region was of relevance to consider this diagnosis. The differential diagnosis includes other types of panniculitis such as erythema nodosum, which may be associated with sarcoidosis, tuberculosis, and other infections. Nevertheless, lesions in ENL are widespread, may appear in clusters, and do not last as long as the lesions of the classical erythema nodosum, which are longer-lived and favor the lower extremities (13). The presence of a granulomatous septal panniculitis, with perivascular and perineural lymphohistiocytic infiltrate and fragmented AFB in affected skin, was in accordance with the diagnosis of ENL.

Clinicians should be aware of this unusual presentation of ENL in a patient treated with highly bactericidal drugs that were not intended to treat Hansen's disease. This is particularly important in geographical areas where this disease is still rare and therefore not very frequently suspected when making a diagnosis.

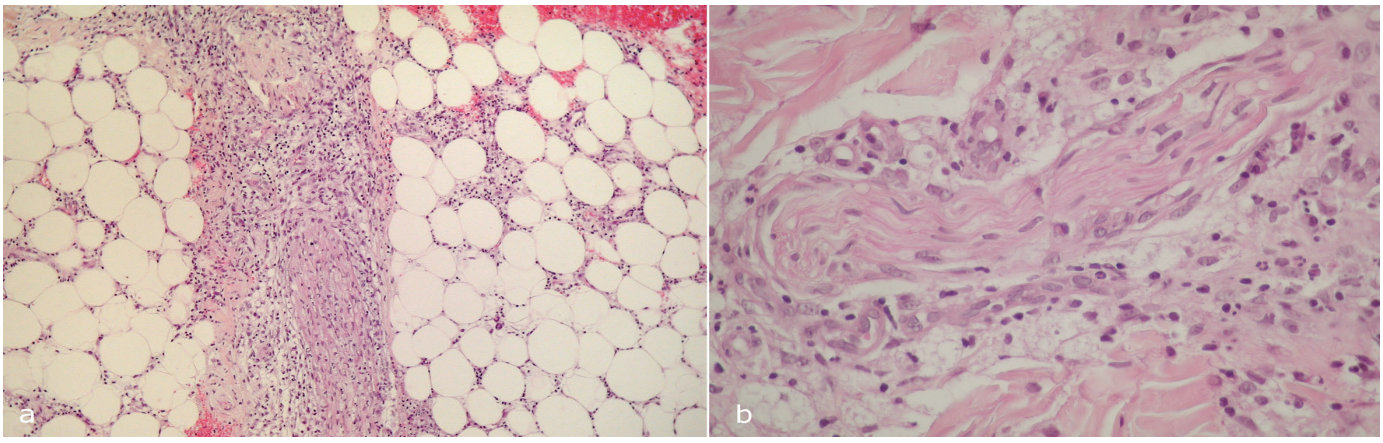

Figure 2 | Skin biopsy of erythema nodosum leprosum. **a.** Predominantly granulomatous septal panniculitis (H&E: 100×). **b.** Large histiocytic foam cells around a nerve, speckled with neutrophils (H&E: 400×).

References

1. Wolff K, Goldsmith L, Katz S, Gilchrest B, Paller A, Leffell D. Fitzpatrick´s dermatology in general medicine. 7th ed. New York (NY): McGraw-Hill; c2008. Chapter 186, Leprosy; p. 1787-96.
2. Weedon D. Weedon´s pathology. 3rd edition. Philadelphia (PA): Churchill Livingstone; c2010. Chapter 23, Bacterial and rickettsial infections: Leprosy; p. 562-6.
3. Cuevas J, Rodríguez-Peralto JL, Carrillo R, Contreras F. Erythema nodosum leprosum: reactional leprosy. Semin Cutan Med Surg. 2007;26:126-30.
4. 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.
5. Kahawita IP, Lockwood DN. Towards understanding the pathology of erythema nodosum leprosum. Trans R Soc Trop Med Hyg. 2008;102:329-37.
6. Gupta L, Singal A, Pandhi D, Sharma S. Co-existent acquired perforating collagenosis and lepromatous leprosy with erythema nodosum leprosum: Response to treatment. Indian J Dermatol Venereol Leprol. 2011;77:520-2.
7. Ramesh V, Pahwa M. Some unusual type 2 reactions in leprosy. Int J Dermatol. 2010;49:172-5.
8. Dave S, Thappa DM, Nori AV, Jayanthi S. A rare variant of erythema nodosum leprosum: a case report. Dermatol Online J. 2003;9:11.
9. Hastings RC. Leprosy. Singapore (RS): Churchill Livingstone; 1994.

10. Naranjo CA, Busto U, Sellers EM, Sandor O, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.
11. Van Veen NH, Lockwood DN, Van Brakel WH, Ramirez J Jr, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane review. Lepr Rev. 2009; 80: 355-72.
12. Araújo MG. Leprosy in Brazil. Rev Soc Bras Med Trop. 2003;36:373-82.
13. Bolognia JL, Jorizzo JJ, Rapini RP. Dermatology. 2nd ed. St. Louis: Mosby Elsevier; c2008. Chapter 74, Mycobacterial infections: Leprosy. p. 1107-14.