



ACTAS Derma-Sifiliográficas

Full English text available at
www.actasdermo.org



CASE REPORT

Erythema Nodosum Leprosum and Reversal Reaction in 2 Cases of Imported Leprosy[☆]

A. Pulido-Pérez,^{*} M.D. Mendoza-Cembranos, J.A. Avilés-Izquierdo, R. Suárez-Fernández

Servicio de Dermatología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Received 8 December 2011; accepted 8 September 2012

KEYWORDS

Leprosy;
Hansen disease;
Vasculitis;
Thalidomide;
Neuropathy

PALABRAS CLAVE

Lepra;
Enfermedad de
Hansen;
Vasculitis;
Talidomida;
Neuropatía

Abstract Leprosy reactions, which are abrupt changes in the clinical condition of patients with immunologically unstable forms of the disease, can mask the cardinal signs of leprosy, delaying both diagnosis and treatment. The main complications that arise from delayed diagnosis reflect the characteristic features of the disease, involving impaired nerve function and both local (ulcers, pyogenic infection, osteomyelitis) and systemic compromise. Thorough clinical examination, sensory testing, and, where necessary, histopathology and microbiology, are essential when leprosy is suspected. Rapid initiation of anti-inflammatory treatment reduces the risk of functional impairment, the main concern in leprosy. We describe type 1 and type 2 leprosy reactions in 2 patients who had not yet been diagnosed with the disease.

© 2011 Elsevier España, S.L. and AEDV. All rights reserved.

Eritema nudoso leproso y reacción de reversión en 2 casos de lepra importada

Resumen Las leprorreacciones suponen cambios clínicos de inicio súbito en los pacientes que presentan formas inmunológicamente inestables de la enfermedad de Hansen. Estos cuadros pueden enmascarar los signos cardinales de la misma y demorar así su diagnóstico y tratamiento. Las principales complicaciones derivadas de este retraso son las relacionadas con el compromiso neural, local (ulceraciones, piodermatitis, osteomielitis...) y/o sistémico característico de estos cuadros. Ante su sospecha debe realizarse un minucioso examen clínico, exploración de la sensibilidad y, cuando se precise, estudio histopatológico y microbiológico. La instauración inmediata de tratamiento antiinflamatorio disminuye el riesgo de secuelas funcionales, principal causa de morbilidad en la lepra. A continuación, se presentan dos casos de leprorreacciones de tipo I y II en pacientes no diagnosticados hasta ese momento de enfermedad de Hansen.

© 2011 Elsevier España, S.L. y AEDV. Todos los derechos reservados.

[☆] Please cite this article as: Pulido-Pérez A, Mendoza-Cembranos MD, Avilés-Izquierdo JA, Suárez-Fernández R. Eritema nudoso leproso y reacción de reversión en 2 casos de lepra importada. Actas Dermosifiliogr. 2013;104:915–919.

^{*} Corresponding author.

E-mail address: ana.pulido@madrimasd.net (A. Pulido-Pérez).

Introduction

Hansen disease, or leprosy, is uncommon in Spain. It is no longer considered a public health problem in our country^{1,2} and most new cases are imported from leprosy-endemic areas in Southeast Asia, South America, and Africa.³ The virtual absence of autochthonous cases and the added difficulty of evaluating dermatological conditions in patients from other racial groups complicate the early diagnosis of leprosy.

Leprosy is characterized by a wide spectrum of clinical manifestations that affect the skin, the mucosas, the eyes, the organs, and/or the nerves. On occasions, its cardinal signs or symptoms may be masked by sudden clinical changes known as leprosy reactions,⁴ which are triggered by changes in immune response.^{5,6} Multiple factors are involved in the development of leprosy reactions, but commencement of specific leprosy treatment is a factor in a considerable number of cases.

We describe 2 cases of type 1 and type 2 leprosy reactions in patients with previously undiagnosed leprosy that illustrate the diagnostic challenges in such cases.

Case Descriptions

The first patient, a 25-year-old woman from Brazil who had been living in Spain for 6 months, visited the emergency department with high fever (up to 39°C), general malaise, watery rhinorrhea, and painful, erythematous nodules located predominantly on the limbs (Fig. 1). The manifestations had started the previous week, but the patient had experienced similar lesions—which cleared spontaneously—on several occasions in the previous 3 months. Blood tests revealed a normocytic, normochromic anemia, leukocytosis with neutrophilia, mild elevation of the transaminases, and considerably increased serum levels of immunoglobulin G. The ear, nose, and throat examination confirmed mucosal edema in the paranasal sinuses. The



Figure 1 Erythematous nodules affecting both thighs of a patient with erythema nodosum leprosum (type 2 leprosy reaction).



Figure 2 Distal purpuric lesions in a patient with erythema nodosum leprosum (type 2 leprosy reaction).

skin examination revealed multiple, asymptomatic brownish papules symmetrically distributed on the legs and the arches of the soles that were clinically diagnosed as lepromas. There were also purple nonulcerated papules on the distal third of the toes (Fig. 2). The path of the right common peroneal nerve was thickened and electromyography demonstrated a severe sensory-motor neuropathy. Biopsy of a nodule showed a diffuse inflammatory infiltrate in the deep dermis and subcutaneous tissue composed of lymphocytes, neutrophils and histiocytes with vacuolated cytoplasm (Fig. 3). The neutrophils exhibited marked tropism for the walls of the small dermal vessels but there was no evidence of fibrinoid necrosis. Ziehl-Neelsen staining showed acid-alcohol-fast bacilli (AAFB) within the histiocytes. A slit-skin smear taken from the earlobe, elbow, and a brownish papule on the leg showed 10 AAFB in one 100× microscope field (bacterial index, 3+). The diagnosis was erythema nodosum leprosum in a patient with subpolar lepromatous leprosy. Multiple drug therapy (MDT) was

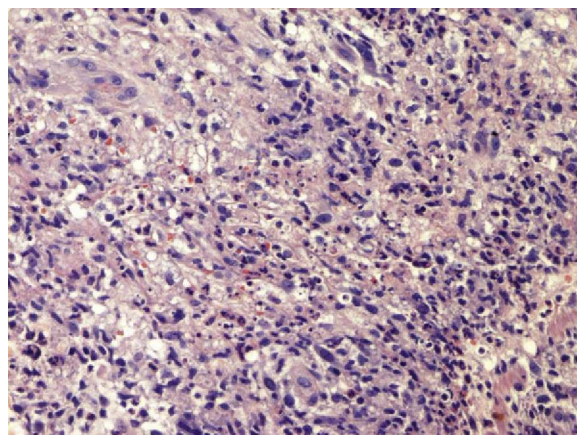


Figure 3 Lymphocytic, neutrophilic, and histiocytic infiltrate in the deep dermis in a patient with erythema nodosum leprosum (hematoxylin-eosin, original magnification ×40).



Figure 4 Erythematous, edematous facial plaques in a patient with a type 1 leprosy reaction.

initiated following the regimen recommended by the World Health Organization for patients with multibacillary leprosy (rifampicin, clofazimine, and dapsone) in combination with oral corticosteroids (prednisone, 1 mg/kg/d). The nodules, fever, and general malaise all resolved. However, when the corticosteroid dose was reduced to 0.5 mg/kg/d, the patient experienced a new episode of nodules and fever that required treatment with thalidomide (150 mg/d). The response was complete.

The second patient was a 38-year-old man, born in the Philippine Islands and resident in Spain for 4 months, who visited the emergency department following the sudden worsening of annular skin lesions that had developed initially on the face and been treated in the patient's country of origin a year earlier. There was no fever or other systemic symptoms. The patient was questioned further but could not remember what treatment he had received or for how long. Physical examination showed erythematous, edematous plaques that were neither painful nor hot and were located on the lesions initially described by the patient (Fig. 4). There was also a striking alteration of the nasal pyramid due to a road traffic accident. The neurological examination revealed moderate hypoesthesia in the area of a scaly plaque on the right leg. Two biopsies were taken: one from an erythematous, edematous plaque on the face and the other from the scaly plaque on the right leg. Multiple noncaseating granulomas surrounded by a crown of lymphocytes and located mainly around the nerves and the skin appendages were visible in both lesions, together with edema of the superficial and deep dermis. Skin-smear examination of a facial plaque showed a low bacillary load (2+) of AAFB. The diagnosis was a type 1 reaction in a patient with borderline leprosy. We initiated treatment with corticosteroids (prednisone, 0.5 mg/kg/d), which led to a gradual improvement, plus MDT (rifampicin, clofazimine, and dapsone) for 12 months in view of the little information available on previous treatments.

Discussion

Leprosy reactions are sudden changes in the clinical condition of patients diagnosed with leprosy.⁴ They typically occur in patients with immunologically unstable forms of leprosy, but no clinical predictors have been identified to date. These clinical conditions, which are defined according to the Ridley-Jopling classification,⁷ fall within the spectrum of clinical, microbiologic, histologic, and immunologic manifestations that occur between the 2 extremes, or poles, of leprosy: at one end, tuberculoid or paucibacillary leprosy and at the other, lepromatous or multibacillary leprosy (Table 1).

The factors involved in the development of these states disrupt the balance between the mycobacteria and the host's immune system. Examples of triggers that alter the immune state are adrenal gland insufficiency, stress, intercurrent infections, pregnancy, and, in particular, specific leprosy treatment.⁸

Classically, there are 2 types of type 1 leprosy reactions: an upgrading, or reversal, reaction and a downgrading reaction.⁹ Downgrading reactions are assumed to represent a shift towards the lepromatous (multibacillary) pole of the disease and are correlated with a decrease in cellular immune response. Reversal reactions, by contrast, are seen in patients who have received treatment and experience an increase in immune response. Type 1 reversal reactions are considered to be a delayed hypersensitivity reaction (or type IV reaction according to the Gell and Coombs classification), involving augmented type 1 helper T-cell response.^{9,10} Clinically, pre-existing lesions become inflamed and there is considerable exacerbation of neurological manifestations (polyneuritis with marked inflammation of the nerves). Patients may sometimes develop new lesions and general malaise, usually due to the sudden neurological deterioration. Treatment includes rest and systemic corticosteroids.

Type 2 leprosy reactions are essentially due to a type III hypersensitivity reaction, mediated by circulating immune complexes formed by antibodies binding to antigens. These complexes cannot be cleared by the kidneys or phagocytized by macrophages and therefore deposit on the vessel walls.¹¹ The release of inflammatory cytokines and the subsequent recruitment of neutrophils contribute to the development of characteristic clinical manifestations that vary according to the organ involved. When the skin is affected patients develop painful inflammatory nodules (a condition known as erythema nodosum leprosum as it is not an inflammatory process occurring within the septa of the subcutaneous tissue), necrotic areas (Lucio phenomenon), or plaques resembling erythema multiforme. Patients may also develop neuritis, with palpable, painful enlargement of the affected nerves.¹² Treatment includes rest, acetylsalicylic acid, pentoxifylline, systemic corticosteroids, and clofazimine. However, thalidomide (100-300 mg/d) remains the treatment of choice in recurrent cases because it is well tolerated and maintains prolonged remission.^{13,14} Women of childbearing age receiving this drug must be warned to use effective contraception.

Early diagnosis of leprosy reactions is very important. While these reactions are uncommon in our setting, a late

Table 1 Characteristics of Type 1 and 2 Leprosy^{15–17} Reactions.

	Type 1 Reactions	Type 2 Reactions
Immune response	Type 1 helper cells	Type 2 helper cells
Pathogenesis	Type IV (delayed cell-mediated) hypersensitivity reaction	Type III hypersensitivity reaction (immune complex formation and deposition)
Clinical subtypes	TT _s , BT, BB	BL, LL _s
Host	Previous treatment (except in downgrading reactions)	Previous treatment or not
Types	Reversal reaction Downgrading reaction	Erythema nodosum leprosum Lucio phenomenon Erythema multiforme-like reaction
Cutaneous manifestations	Edema of previous lesions Increase in distal scaling Nerve involvement	Nodules Necrotic areas Polymorphous erythematous plaques Nerve involvement
Histopathology (changes with respect to conventional histologic findings)	Tuberculoid granulomas Dermal edema	Neutrophilic infiltrate in the mid and deep dermis and subcutaneous cellular tissue Leukocytoclastic vasculitis of the small and medium vessels
Treatment	Rest NSAIDs Systemic corticosteroids	Rest Acetylsalicylic acid, pentoxifylline Systemic corticosteroids Clofazimine Thalidomide

Abbreviations: BB, mid-borderline leprosy; BL, borderline lepromatous leprosy; LL_s, subpolar lepromatous leprosy; NSAIDs, nonsteroidal anti-inflammatory drugs; TT_s, subpolar tuberculoid leprosy.

diagnosis can lead to irreversible nerve damage and severe functional impairment.

Ethical Disclosures

Protection of humans and animals. The authors declare that no tests were carried out in humans or animals for the purpose of this study.

Confidentiality of data. The authors declare that no private patient data appear in this article.

Right to privacy and informed consent. The authors declare that no private patient data appear in this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- De las Aguas JT. Historia de la lepra en España. *Piel*. 2005;20:485–97.
- Alfonso JL, Vich FA, Vilata JJ, de las Aguas JT. Factors contributing to the decline of leprosy in Spain in the second half of the twentieth century. *Int J Lepr Other Mycobact Dis*. 2005;73:258–68.
- Rodríguez E, Díaz O, Hernández G. Vigilancia de la lepra. Situación en el mundo y en España. *Bol Epidemiol Semanal*. 2010;18:201–12.
- Lázaro-Ochaita P. Infecciones cutáneas por micobacterias. In: Lázaro-Ochaita P, editor. *Dermatología: texto y atlas*. Madrid: Meditecnica; 2003. p. 177–98.
- Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. *Clin Microbiol Rev*. 2006;19:338–81.
- Goulart IM, Penna GO, Cunha G. Imunopatologia da hanseníase: a complexidade dos mecanismos da resposta imune do hospedeiro ao *Mycobacterium leprae*. *Rev Soc Bras Med Trop*. 2002;35:365–75.
- Kundu SK. Features of the Ridley-Jopling classification and its application in the clinical field. *Int J Lepr Other Mycobact Dis*. 1979;47:64–5.
- Brito MF, Ximenes RA, Gallo ME, Bühler-Sékula S. Association between leprosy reactions after treatment and bacterial load evaluated using anti PGL-I serology and bacilloscopy. *Rev Soc Bras Med Trop*. 2008;41:67–72.
- Walker SL, Lockwood DN. Leprosy type 1 (reversal) reactions and their management. *Lepr Rev*. 2008;79:372–86.
- Scollard DM, Joyce MP, Gillis TP. Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. *Clin Infect Dis*. 2006;43:e19–22.
- Cuevas J, Rodríguez-Peralto JL, Carrillo R, Contreras F. Erythema nodosum leprosum: reactional leprosy. *Semin Cutan Med Surg*. 2007;26:126–30.
- 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.
- Van Veen NH, Lockwood DN, Van Brakel WH, Ramirez Jr J, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane review. *Lepr Rev*. 2009;80:355–72.
- Nash J, editor. ILEP technical bulletin: Management of erythema nodosum leprosum. 18th Meeting of the ILEP Technical Commission; 2011, October 11; London: International Federation of Anti-Leprosy Associations; 2011.

15. Azadeh B, Dabiri S. Langerhans cells in skin lesions of leprosy. *Iran J Med Sci.* 2004;29:51–5.
16. Cuevas-Santos J, Contreras F, McNutt S. Multibacillary leprosy: lesions with macrophages positive for S100 protein and dendritic cells positive for Factor 13^a. *J Cutan Pathol.* 1998;25:530–7.
17. Lockwood DN, Lucas SB, Desikan KV, Ebenezer G, Suneetha S, Nicholls P. The histological diagnosis of leprosy type 1 reactions: identification of key variables and an analysis of the process of histological diagnosis. *J Clin Pathol.* 2008;61:595–600.