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ORIGINAL ARTICLE

The Current Challenge of Imported Leprosy in Spain: A Study of 7 Cases

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KEYWORDS
Leprosy;
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Abstract
Background: Although the foci of leprosy once present in Spain are now under control and almost inactive, isolated cases are still occasionally diagnosed. Meanwhile, population migration has brought about an increase in the incidence of cases corresponding to individuals from countries where leprosy is endemic, leading to changes in the epidemiology of this disease.
Objectives: The aim of this paper was to describe the clinical, epidemiologic, dermatologic, microbiologic, and therapeutic characteristics of cases of leprosy in our department in the last 5 years.
Material and methods: We report the cases of imported leprosy seen in our department between 2004 and 2009.
Results: Seven patients with leprosy (3 men and 4 women; age range, 26-80 years) were diagnosed; 2 were cases of tuberculoid leprosy, 2 borderline tuberculoid leprosy, and 3 indeterminate. All patients acquired the disease in South American or South African countries, but were residing in Spain at the time of diagnosis. One patient was a Spaniard, from Malaga, who had worked as a missionary in Venezuela for 25 years. The presence of the bacterium by either Ziehl-Neelsen stain or bacilloscopy could not be demonstrated in any of the patients.
Conclusions: We would like to draw attention to the changes we have observed in the characteristics of cases of leprosy seen in our department, the majority of which are imported. It is important to maintain a clinical suspicion of leprosy in cases of granulomatous dermatitis, particularly in patients from countries where the disease is endemic.

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PALABRAS CLAVE
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Actualidad

Lepra importada y su dificultad en el medio actual: a propósito de 7 casos

Resumen

Introducción: Aunque los focos históricos de infección leprosa en nuestro país están controlados y son prácticamente inactivos, aún se siguen diagnosticando algunos casos autóctonos aislados. La elevada movilidad poblacional actual ha traído consigo un aumento en la incidencia de casos importados de países endémicos, lo que está motivando un cambio en las características epidemiológicas del paciente afecto de lepra.
Objetivos: El propósito de este artículo es poner de manifiesto las características clínicas, epidemiológicas, dermatopatológicas, microbiológicas y terapéuticas de los pacientes diagnosticados de lepra en los últimos 5 años en nuestro Servicio.
Material y método: Presentamos los casos de lepra importada que hemos valorado en nuestro Servicio desde el año 2004 al 2009.
Resultados: Se trata de 7 casos de lepra, 3 varones y 4 mujeres, de edades comprendidas entre los 26 y los 80 años, 2 de tipo tuberculoide, 2 borderline tuberculoide y 3 de tipo indeterminada. Todos procedían de países sudamericanos o sudafricanos donde adquirieron la enfermedad, aunque residían en España en ese momento. Sólo uno de los pacientes era natural de Málaga, pero trabajó como misionero en Venezuela durante 25 años. En ningún caso se logró demostrar la existencia de bacilos mediante la técnica de Ziehl-Neelsen, siendo la baciloscopia igualmente negativa.
Conclusiones: Queremos destacar los cambios epidemiológicos que hemos observado en los casos de lepra diagnosticados en nuestro Servicio, la mayoría de los cuales son importados. Es importante seguir manteniendo la sospecha clínica de lepra ante dermatitis granulomatosas, especialmente en pacientes de países endémicos.

Introduction

Leprosy is a chronic granulomatous disease that mainly affects the skin and nerves. It is caused by *Mycobacterium leprae* or Hansen bacillus, an obligate intracellular, grampositive bacillus.[1]

Leprosy is one of the most important health problems in underdeveloped and developing countries. Although rarely fatal, it continues to be a disabling, deforming, and stigmatizing disease.[2,3] Leprosy only affects humans and requires close and prolonged contact to spread. It is associated with lower socioeconomic levels and deficient hygiene in hot climates.[4] While the route of transmission is not exactly clear, it spreads mainly via the airways and the skin. Only 3% to 6% of family members develop the disease; therefore, the patient's individual immune response plays an important role. Nevertheless, unlike tuberculosis, *M leprae* infection is no more prevalent or its clinical manifestations more severe in patients with AIDS.[5] In Spain, the prevalence of the disease is low (<1 case per 10 000 inhabitants), similar to the European average. We report 7 cases of imported leprosy diagnosed at the dermatology department of our hospital.

Materials and Methods

We reviewed all cases of imported leprosy diagnosed in the Department of Dermatology at Hospital Clínico Virgen de la Victoria in Malaga, Spain over a 5-year period (2004-2009). Our reference population comprises 457 111 inhabitants from both the city (90%) and the countryside (10%). For each patient we recorded age, sex, country of origin, length of residence in Spain, clinical manifestations, and the results of comprehensive laboratory workups (complete blood count, clotting time, biochemistry, HIV and syphilis serology testing), mucus and lymph smears, and skin biopsy, as well as treatment and outcome.

Results

Out of a total of 9 cases of leprosy diagnosed during the study period, 2 were in Spanish-born patients and 7 were imported (Table 1). Patients were aged between 26 and 80 years (3 men, 4 women) and they all had leprosy (tuberculoid in 2, borderline tuberculoid in 2, and indeterminate in 3). All the patients were from South American or Sub-Saharan countries, where the disease was acquired; however, at the time of diagnosis they were living in Spain, except for 1 patient, who was Spanish but who had worked as a missionary in Venezuela for 25 years.

The patients' skin lesions varied. The 3 patients with indeterminate leprosy had more or less extensive hypochromic/achromic lesions, mainly on the extremities (Figure 1). The trunk was also affected in 1 of these patients (Figure 2).

In patients with tuberculoid leprosy and borderline tuberculoid leprosy, most skin lesions were erythematous macules that were occasionally confluent and ran together to form large plaques (Figure 3). In a few cases these were mildly desquamative or even ring-shaped and

Table 1 Characteristics of Patients With Imported Leprosy Included in Our Study

Case	Sex Age, y	Country of Origin	Signs and Symptoms	Duration	Histopathology	Type
1[13]	F 28	Brazil	Achromic macules on the right arm	8 mo	Perineural, periadnexal, and perivascular lymphohistiocytic infiltrate	Indeterminate
2	M 33	Mali	Hypochromic macules on the upper extremities Traumatic ulcers on the fingers	8 mo	Superficial and deep perineural and perivascular lymphocytic infiltrate in the dermis	Indeterminate
3	F 32	Nigeria	Hypochromic annular lesions on the trunk	4 y	Superficial and deep mild lymphocytic infiltrate in the dermis	Indeterminate
4	F 31	Paraguay	Annular erythematous macules on the extremities	3 y	Granulomatous dermatitis with formation of granuloma	Tuberculoid
5	F 26	Brazil	Desquamative and erythematous macules on the left thigh	1 y	Granulomatous dermatitis with confluent granuloma and no necrosis	Tuberculoid
6	M 40	Colombia	Symmetrical erythematous macules on the trunk and extremities	1 y	Granulomatous dermatitis with frank granuloma formation	Borderline tuberculoid
7	M 80	Malaga (missionary in Venezuela)	Erythematous plaques and infiltrates on the trunk and extremities	6 mo	Granulomatous dermatitis with granuloma and no necrosis	Borderline tuberculoid

Abbreviations: F, female; M, male.

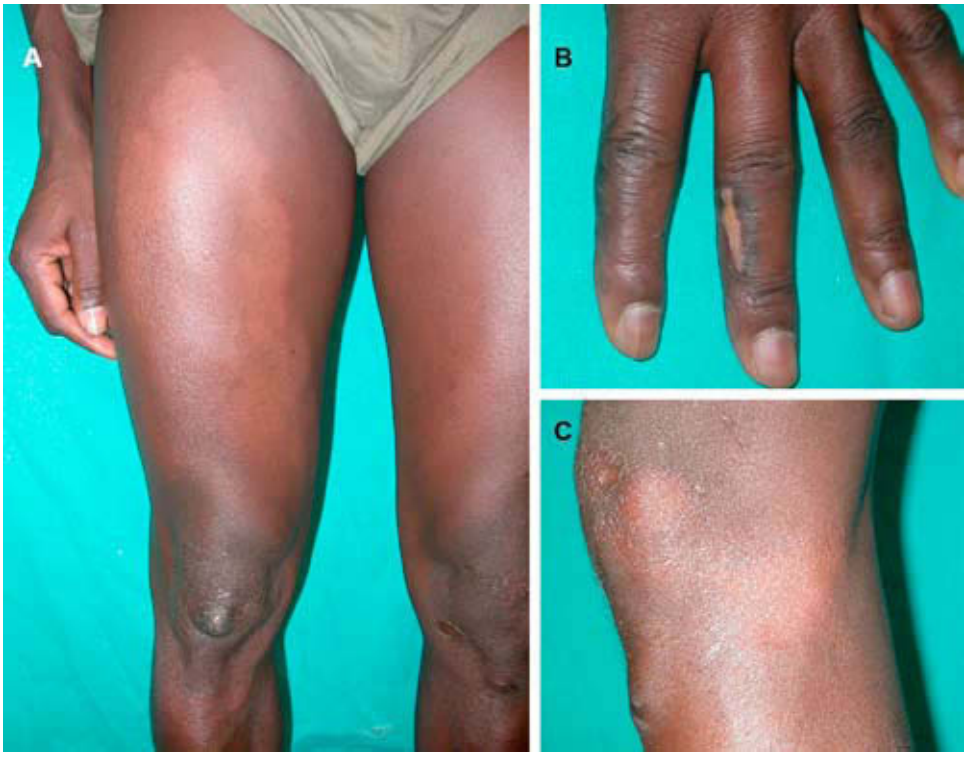

Figure 1 Case 2, Patient diagnosed with indeterminate leprosy. Note the large long and hypochromic macules (up to 20 cm) that occupy a large proportion of the lower extremities (A and C) and the presence of traumatic ulcers on the fingers that scarred spontaneously (B).

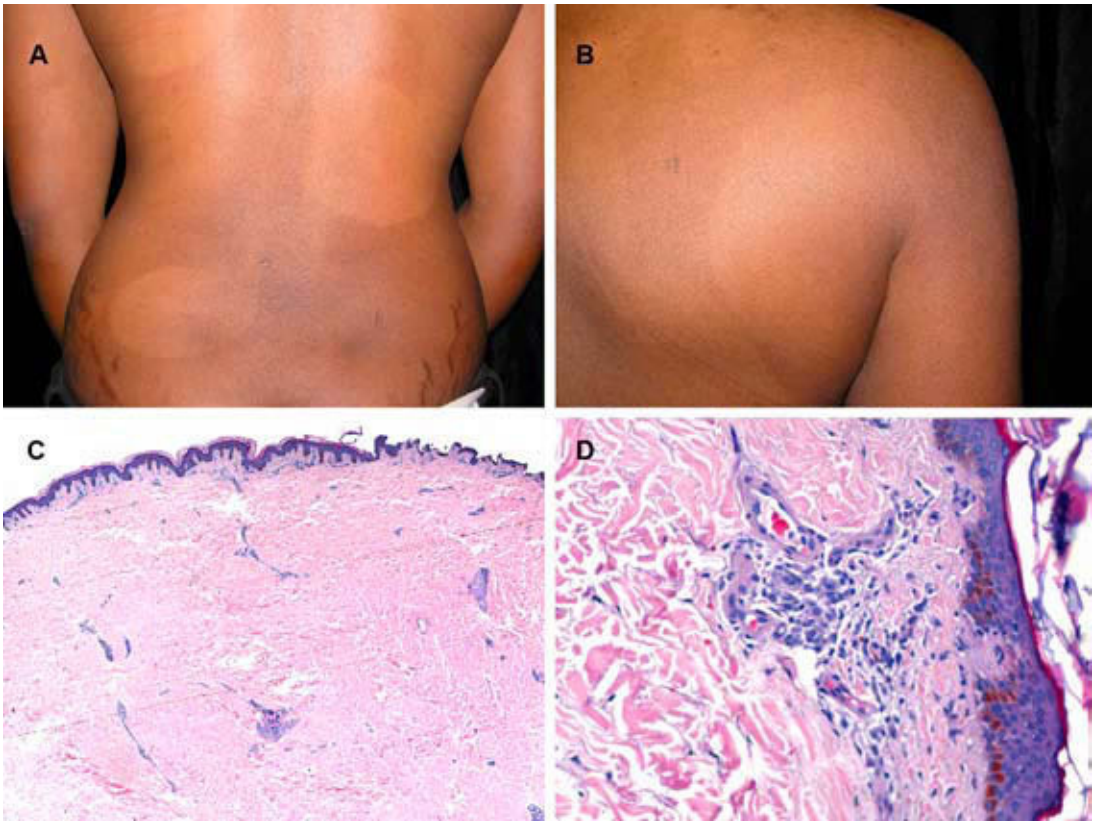

Figure 2 Case 3, Patient diagnosed with indeterminate leprosy. Serpiginous hypopigmented annular plaques with precise borders and of varying size are observed. Some of these are confluent and distributed on the back and abdomen (A and B). Skin biopsy revealed a mild lymphohistiocytic infiltrate in the superficial and profound dermis (hematoxylin-eosin: C, ×100; D, ×300). Ziehl-Neelsen staining was negative.

were found both on the trunk and on the extremities (Figure 4).

None of the patients presented nerve thickening, although they all had altered thermal sensitivity.

All the patients were classed as having paucibacillary leprosy (tuberculoid, borderline tuberculoid, and indeterminate), unlike the classic and Spanish-born cases, which were generally multibacillary (lepromatous pole). The mucus and lymph smears were repeatedly negative and Ziehl-Neelsen staining revealed no bacilli inside the histocytes.

Except for 1 patient who was diagnosed at another hospital (Case 2), most had been wrongly diagnosed in primary care and had even been prescribed oral and topical corticosteroids and antifungals.

In all cases, the epidemiological pattern facilitated diagnosis, which was based on cutaneous symptoms, neurological examination, laboratory results, and histopathology results.

As all the patients presented paucibacillary forms, they received sulfone at 100 mg/d and rifampicin at 600 mg/mo, according to the treatment schedule of the World Health Organization (WHO). Response and tolerance were good. Patient 1 presented severe hemolytic anemia after taking sulfone, due to a glucose-6-phosphate dehydrogenase deficiency.

All the patients were followed at 3, 6, 12, 18, and 24 months of treatment. The skin lesions gradually disappeared in 5 patients (Cases 1, 2, 3, 4, and 5), whereas in the other 2 patients discreet residual hyperpigmentation remained. Patients are monitored yearly and none show signs of activity or sequelae.

Discussion

The present series reveals a modification in the clinical and epidemiological profile of leprosy in Spain, with imported leprosy being the most common form today.

Although the prevalence of leprosy has fallen considerably during the last few decades in developed and developing countries (largely due to improved social and hygiene measures, correct diagnosis, and effective treatment), around 700 000 new cases are diagnosed every year. According to the WHO, leprosy affects 2 000 000 people worldwide.[7,8] Extensive use of treatment based on polychemotherapy regimens has reduced morbidity considerably. However, despite such important achievements, the disease has not been eradicated.[9]

In Spain, leprosy continues to be a public health problem, mainly as a result of the increase in the number of imported cases. In the last 10 years, we have witnessed a change in the clinical and epidemiological characteristics of patients with leprosy in our setting, and we believe that these should be brought to the

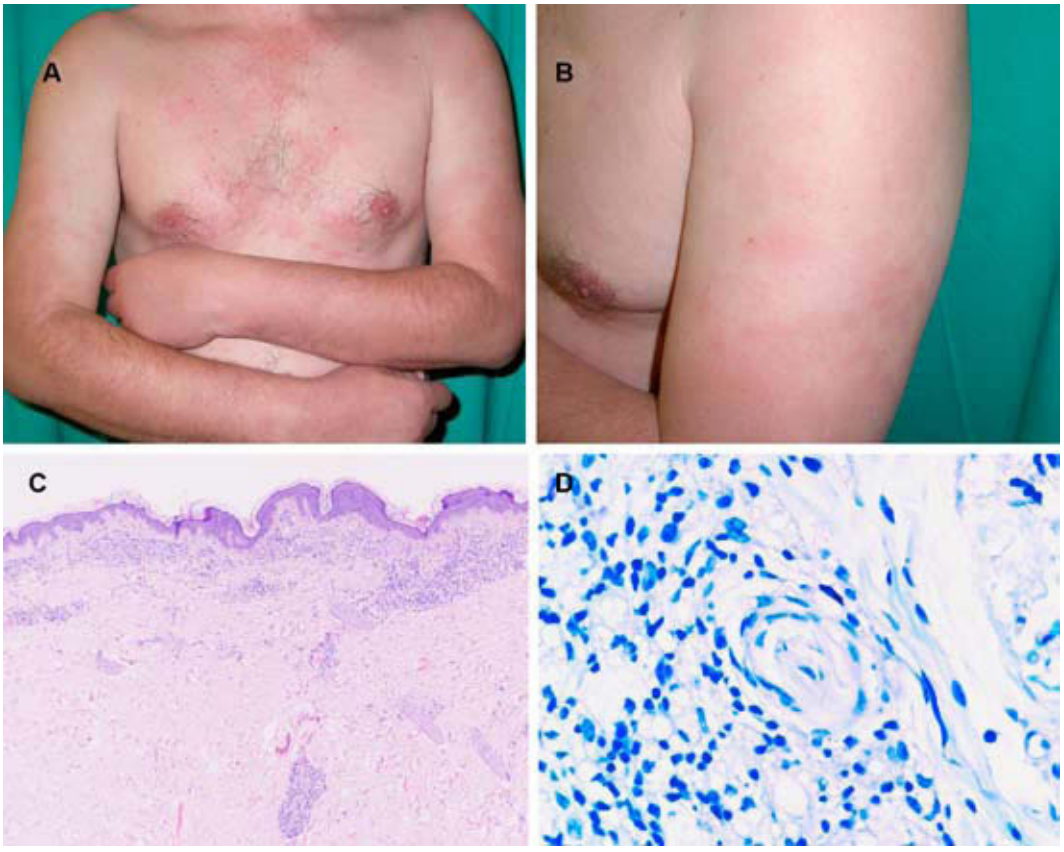

Figure 3 Case 6, Patient diagnosed with borderline tuberculoid leprosy. Note the erythematous macules distributed symmetrically on the trunk (A) and extremities (B). Histopathology (hematoxylin-eosin: C, ×100; D, ×300) revealed a diffuse infiltrate in the papillary lesion that extended to the reticular dermis and was arranged in a perivascular, periadnexal, and perineural distribution. Note that a band in the superficial dermis was respected (Grenz zone). Ziehl-Neelsen staining was negative.

attention of the dermatologist.[10] Patients with leprosy were traditionally male, had a low sociocultural level, and lived in the countryside. By contrast, new cases of leprosy involve immigrants from underdeveloped countries in endemic areas of Latin America and Sub-Saharan Africa.[11] The disease affects both sexes equally. Patients are generally young adults who were infected during the first years of life in their countries of origin and were later diagnosed in Spain.[12] It is noteworthy that most of the cases of imported leprosy that we diagnosed were paucibacillary (indeterminate, tuberculoid, and borderline tuberculoid), unlike the classic Spanish-born cases, which were predominantly multibacillary (borderline-borderline, lepromatous, and borderline lepromatous),[13] probably because mean time to consultation for patients with tuberculoid leprosy is around 3 years, whereas that of patients with lepromatous leprosy is 8 years. One possible explanation would be that neurological involvement occurs later in lepromatous leprosy and, therefore, patients do not seek medical attention early, because they think that their symptoms correspond to a trivial disease.[14] Patients with lepromatous leprosy are the most contagious, as the number of bacilli in their secretions is high; therefore, a timely diagnosis is essential in order to prevent the disease from spreading to the healthy population.[15]

From a medical viewpoint, this disease presents a diagnostic challenge due to the difficulty in obtaining an early diagnosis and correct classification, especially in a low-prevalence area.[16] As leprosy closely mimics other skin diseases, it can go undetected.[17,18] Of note, 3 of our patients were initially diagnosed incorrectly (Case 3, pityriasis versicolor and vitiligo; Case 4, cutaneous mycosis; and Case 7, erythema annulare centrifugum) and, consequently, were treated with oral and topical medication (corticosteroids, antifungals). While these agents did not improve symptoms, they did modify the initial lesions, to the extent that establishing a final diagnosis was even more difficult. In fact, Case 7 initially presented with tuberculoid leprosy, confirmed by frank granuloma formation in the biopsy specimen taken from the lesion on his arm. However, the biopsy specimen taken from the lesion on his leg only revealed a diffuse perineural, periadnexal, and perivascular infiltrate with no distinct formation of granulomas, leading us to make a final diagnosis of borderline tuberculous leprosy. The absence of granulomas could be explained by the immunosuppression resulting from the oral corticosteroids that the patient received for almost 1 year, which prevented their formation in new lesions.

The difficulty in making a diagnosis of leprosy based on symptoms is compounded by the difficulty in demonstrating

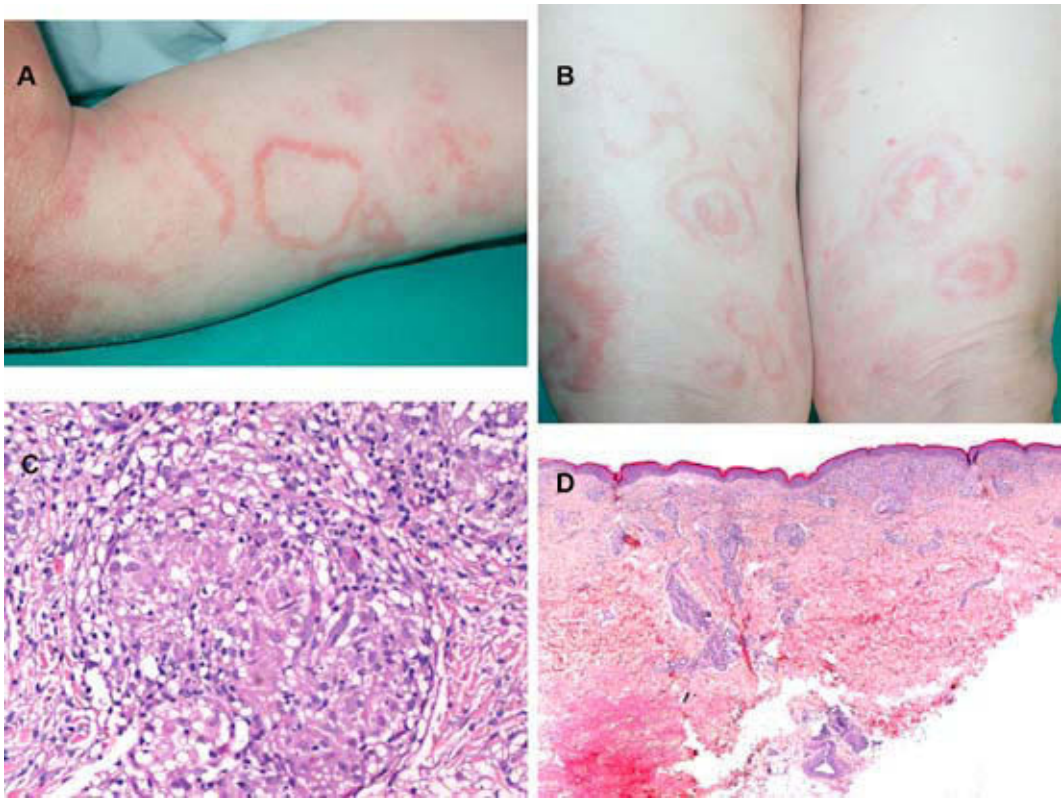

Figure 4 Case 7, Patient diagnosed with borderline tuberculoid leprosy. Note the annular plaques on the upper (A) and lower (B) extremities. The plaques have an erythematous border and palpable infiltrate with a clearer center. Histopathology of the lesion on the arm revealed a granulomatous inflammation with formation of granuloma (hematoxylin-eosin; C, ×300). Biopsy of the thigh revealed an intense diffuse inflammatory infiltrate with perivascular, periadnexal, and perineural involvement (hematoxylin-eosin: D, ×100).

the presence of the bacillus, a key factor in any infectious disease, which depends not only on the patient's immune status, but also on the availability of inexpensive, specific, and sensitive tests in the relevant department.[19]

Smear tests require trained staff who know how to take samples correctly and can spend sufficient time studying them before finally classifying them as negative. Depending on the type of leprosy and the disease stage, the sample can be repeatedly negative, as was the case in all of our patients.

The Mitsuda test is applied to evaluate the immune response against the bacillus, making it very useful for classifying leprosy, but not for diagnosing it (Table 2). However, this test is increasingly difficult to apply, due to the lack of availability of the reagent. New techniques can determine the serological changes associated with infection, although they are not universally available. They could prove useful in cases of incipient or subclinical leprosy, even though their sensitivity and specificity are very variable.[20,21]

Histopathology is essential in the study of leprosy, although it is difficult to detect bacilli inside histiocytes; consequently, in many cases we have to accept a compatible diagnosis.[22]

As *M leprae* cannot be cultured in vitro, molecular tests have recently been developed for the diagnosis and prognosis of leprosy. Of particular interest are polymerase chain reaction (PCR) and serology tests such as enzyme-linked immunosorbent assay and its variants, as well as the lateral flow test (ML-Flow).[23]

The serology tests used to detect a humoral response are often affected by cross-reactions with other mycobacteria, although the development of specific antigens enabling species-specific responses may have resolved this problem. Several antigens have been used in serology testing, the most specific being phenolic glycolipid-1 (GLP-1), which is present in infected tissue.[24] As GLP-1 is not the most

Table 2 Ridley-Jopling and World Health Organization Classifications

Ridley-Jopling	World Health Organization
Indeterminate	Paucibacillary
Tuberculoid	1 to 5 cutaneous lesions
Borderline tuberculoid	
Borderline borderline	Multibacillary
Borderline lepromatous	More than 5 cutaneous lesions
Lepromatous	

Table 3 World Health Organization Treatment Schedule

Leprosy	Dapsone	Rifampicin	Clofazimine	Duration
Paucibacillary	100 mg/d	600 mg/mo		6 mo
Multibacillary	100 mg/d	600 mg/mo	50 mg/d + 300 mg/mo	12 mo

suitable antigen for routine tasks, glycoconjugates such as disaccharide bovine serum albumin have been synthesized and show excellent replicability. The newly developed ML Flow test is an immunochromatographic assay in which a single drop of whole blood or serum is added to a microtiter plate.[25]

Given the difficulty in identifying acid-fast bacteria using traditional histopathologic methods during early stages of the disease, PCR has proved satisfactory for detecting small quantities of bacilli in different tissues, both from patients and from their healthy contacts. The main advantages of PCR over other diagnostic approaches are its speed, specificity, and sensitivity for identification of organisms by analysis of fresh samples that do not require prior culture.[26] Of all the amplification techniques available for detection of leprosy, real-time PCR is the most sensitive. In addition, as it becomes more widespread, devices and reagents will become cheaper, thus enabling any reference laboratory to use it.[27]

Leprosy is treated with standard WHO regimens comprising 3 drugs for the multibacillary forms (dapsone, rifampicin, clofazimine) and 2 for the paucibacillary forms (dapsone and rifampicin)[28] (Table 3). Given the lack of supply, obtaining dapsone to treat leprosy is increasingly difficult in Spain. In fact, since May 2009, it can only be prescribed as a foreign medication. Before initiating treatment with dapsone, it is important to determine levels of glucose-6-phosphate dehydrogenase, since patients deficient in this enzyme could suffer from severe hemolytic anemia, which may even require admission to hospital, as with our Case 1. In 1997, the WHO proposed an alternative regimen for the treatment of solitary cutaneous lesions in patients with paucibacillary leprosy and no nervous system involvement. This regimen was based on a clinical trial carried out in India involving a single dose of ROM (rifampicin at 600 mg, ofloxacin at 400 mg, and minocycline at 100 mg).[29] However, more studies demonstrating its long-term efficacy are necessary; therefore, it cannot currently be considered a first-line strategy.

To conclude, we wish to highlight the epidemiological changes we observed in cases of leprosy diagnosed in our department during the last 5 years, namely, that imported cases account for 77.8% of the total. We believe that it is particularly important to consider leprosy in patients with granulomatous dermatitis from endemic countries, even when we cannot detect bacteria using specific techniques. Therefore, the commitment of the health authorities is essential if we are to develop sensitive and specific diagnostic techniques and maintain the different forms of treatment. Only in this way can we prevent leprosy from becoming another emerging disease.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Lain-Entralgo P, Montiel L, Picazo JJ. Las enfermedades infecciosas y la historia. In: Garcia Rodriguez JA, Picazo JJ, editors. Microbiología médica. 2. Madrid: Mosby; 1996. p. 1-10.
2. Walker SL, Lockwood DNJ. Leprosy. Clin Dermatol. 2007;25:165-72.
3. Carrada-Bravo T. Lepra: visión nueva de una enfermedad milenaria. Piel. 2004;19:67-73.
4. Garcia Perez A. Clínica y clasificación de la lepra. Actas Dermosifiliogr. 1983;74:339-40.
5. Terencio de las Aguas J. Historia de la lepra en España. Piel. 2005;20:485-97.
6. Boletin epidemiologico del Ministerio de Sanidad y Consumo. Instituto de Salud Carlos III. Archivo de enfermedades de declaración obligatoria. 2002;10:277-84.
7. Organización Mundial de la Salud. Comité de expertos de la OMS en lepra. Informe 847: Quimioterapia de la lepra. Ginebra: OMS; 1994. p. 1-22.
8. Organización Mundial de la Salud. Comité de expertos de la OMS en lepra. Informe 874: Séptimo informe. Ginebra: OMS; 1998. p. 1-47.
9. Britton WJ, Lockwood DNJ. Leprosy. Lancet. 2004;363:1209-19.
10. Urbija JR, Garcia MP, Leton MM, Ruiz R. Epidemiologia de la lepra a través del estudio de la frecuenciación en el Hospital especializado de Trillo durante el periodo de 1943-1995. Rev Esp Salud Publica. 1997;71:463-77.
11. Goulart IM, Goulart LR. Leprosy: diagnostic and control challenges for a worldwise disease. Arch Dermatol Res. 2008;300:269-90.
12. Organizacion Mundial de la Salud. Informe 716: Epidemiologia de la lepra en relación con la lucha antileprosa. Ginebra: OMS; 1985. p. 17-29.
13. Lopez N, Bosch RJ, Ruiz del Portal G, Castillo R, Tejera A, Herrera E. Lepra en el tercer milenio. A propósito de cuatro casos en Málaga, dos autóctonos y dos importados. Med Cutan Iber Lat Am. 2007;35:219-24.
14. Freedman VH, Weinstein DE, Kaplan G. How Mycobacterium leprae infects peripheral nerves. Lepr Rev. 1999;70:136-9.
15. Parkash O. Classification of leprosy into multibacillary and paucibacillary groups: an analysis. FEMS Immunol Med Microbiol. 2009;55:1-5.
16. Gonzalez CE, Abreu A. Vigilancia de la lepra en situaciones de baja prevalencia. Rev Panam Salud Publica. 2001;9:94-101.
17. Boggild AK, Correia JD, Keystone JS, Kain KC. Leprosy in Toronto: an analysis of 184 imported cases. Can Med Assoc J. 2004;170:55-9.

18. Nery JA, Schreuder PA, De Mattos PC, De Mendonça a LV, Tardi RT, De Mello S, et al. Hansen's disease in a general hospital: uncommon presentations and delay in diagnosis. J Eur Acad Dermatol Venereol. 2009;23:150-6.
19. Terencio de las Aguas J. Lepra: aproximacion epidemiologica, clinica y terapeutica. Jano. 1997;1231:1613-21.
20. Lopez Anturiano FJ. Diagnostico y tratamiento de la lepra. Salud Publica Mex. 1998;40:1-10.
21. Dirmeros Kustner E, Pascual Cruz M, Piñol Dansis, Viñals Iglesia H, Rodriguez de Rivera Campillo ME, Lopez Lopez J. Lepromatous leprosy: A review and case report. Med Oral Patol Cir Bucal. 2006;11:474-9.
22. Terencio de las Aguas J. Estudio actual de la investigación en lepra. Leprologia. 2000;3:417-8.
23. Oskam L, Slim E, Buhrer-Sekule S. Serology: recent developments, strengths, limitations and prospects: a state of the art overview. Lepr Rev. 2004;75:192-3.
24. Hatta M, Makino M, Yadi RM, Sabir M, Tandirogang N, Rusyati LMM, et al. Detection of serum antibodies to *M. leprae* major membrane protein-II in leprosy patients from Indonesia. Lepr Rev. 2009;80:402-9.
25. Lyon S, Lyon AC, Da Silva RC, De Faria Grossi MA, Lyon SH, Buhrer-Sekula S, et al. A comparison of ML Flow serology and slit skin smears to assess the bacterial load in newly diagnosed leprosy patients in Brazil. Lepr Rev. 2008;79: 162-70.
26. Martinez AN, Lahiri R, Pittman TL, Scollard D, Truman R, Moraes MO, et al. Molecular determination of *Mycobacterium lepra* viability by use of real-time PCR. J Clin Microbiol. 2009;47:2124-30.
27. Kramme S, Bretzel G, Panning M, Kawuma J, Drosten C. Detection and quantification of *Mycobacterium leprae* in tissue samples by real-time PCR. Med Microbiol Immunol. 2004;193:189-93.
28. Terencio de las Aguas J. Historia de la terapéutica de la lepra. Leprologia. 2001;4:117-24.
29. Sousa AL, Stefani M, Pereira G, Costa MB, Rebello P, Gomes MK, et al. *Mycobacterium leprae* DNA associated with type I reactions in single lesion paucibacillary leprosy treated with single dose rifampin, ofloxacin and minocycline. Am J Trop Med Hyg. 2007;77:829-33.