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Leprosy Initially Misdiagnosed as Sarcoidosis, Adult-Onset Still Disease, or Autoinflammatory Disease

Sara Simeoni, MD, Antonio Puccetti, MD,† Elisa Tinazzi, MD,* Orazio Michele Codella, MD,* Michele Sorleto, MD,* Giuseppe Patuzzo, MD,* Chiara Colato, MD,‡ Gianpaolo Tessari, MD,§ and Claudio Lunardi, MD**

Abstract: Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*. We describe the case of a 20-year-old man from India living in Italy since 2003, who presented with erythematous papules and nodules distributed on his arms, legs, and face in 2006. He also had episodes of high fever, polyarthritis, and episcleritis. Sarcoidosis was suspected on the basis of elevated angiotensin-converting enzyme and bronchoalveolar lavage fluid, and the patient was treated with corticosteroids for about a year. A flare of the disease occurred each time corticosteroid was tapered or suspended. An autoinflammatory disease was then suspected and treated with immunosuppressant. Only the third deep skin biopsy revealed the presence of *M. leprae*. The lack of clinical suspicion and the unfamiliarity with the histology of leprosy delayed diagnosis and treatment. Leprosy should be considered in the differential diagnoses of patients presenting with rheumatic and cutaneous manifestations especially when they come from countries where the disease is endemic.

Key Words: leprosy, sarcoidosis, Still disease

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Hansen disease (HD), known as leprosy, is a chronic granulomatous disease affecting the skin and nerves caused by *Mycobacterium leprae*, an obligate intracellular infectious agent.[1,2] Leprosy continues to be a challenge to health worldwide, with about 250,000 new cases being detected every year, and it is the leading infectious cause of disability.[3] *Mycobacterium leprae* is spread principally by aerosolized droplets from nasal secretions and may rarely enter through broken skin. Human beings are the principal reservoir of infection, except in the Americas, where armadillos also provide a reservoir.[3] Most people are not susceptible to leprosy and after exposure to the bacterium do not develop the disease. Those who do, after an incubation period of several years (2–12 years), may have only a single lesion that spontaneously heals in 75% of cases.[1,3]

Polymorphisms of the tumor necrosis factor α, interleukin 10, or interferon γ promoter region have been shown to be associated with increased susceptibility or with resistance to leprosy.[2,4] A genome-wide association study of leprosy patients and healthy controls identified new associations between variants of the NOD2-mediated signaling pathway, which regulates the innate immune response and the risk and form of the disease.[3] Moreover, innate immune response, in particular the role of pattern recognition receptors in recognizing pathogen-associated molecular patterns of *M. leprae*, has been recently studied and has provided insight into immunoregulation in human infectious disease.[5,6] The type of immune response to the infection, that is, a prevalent cell-mediated or humoral response, determines the type of the disease: tuberculoid HD is the result of a cell-mediated response, whereas lepromatous HD is of a humoral response.[7] Between these 2 types of disease, there are the borderline leprosy types, in which patients have some cell-mediated immune response, multiple lesions, and unstable immunity.[3]

Although HD may have classic features such as erythematous or hypopigmented plaques and alopecia, HD is like a chameleon. Clinically, it can resemble many entities, such as systemic lupus erythematosus,[8] sarcoidosis, cutaneous leishmaniasis, tertiary syphilis, lymphomas, systemic mycosis, traumatic lesions and malignant neoplasms, tinea, contact dermatitis, vitiligo, pityriasis alba, or myxedema.[2,7] Histologically, HD ranges from paucibacillary forms, in which there are essentially no bacilli, to multibacillary forms with countless bacilli.[7] Tests for HD include serologic assays, slit-skin smears, biopsies, probes, polymerase chain reaction, and the lepromin test.[1,7] Conclusive diagnosis can be made on finding Kinyoun-negative acid-fast bacilli in an appropriate histologic background such as in nerves or in foamy histiocytes (lepra cells). The diagnosis is less clear in paucibacillary lesions and/or treated cases. Treatment is difficult, and it must be continued for long periods and may be complicated by severe adverse reactions. The most commonly used drugs are dapsone, rifampicin, and clofaz mine.[1,2] Quinolones, such as ofloxacin and pefloxacin, as well as some macrolides, such as clarithromycin and minocycline, are also effective.[9]

CASE REPORT

We present a 20-year-old man who moved to Italy from India in 2003; in September 2006, he was admitted to a hospital in northern Italy for the presence of high continuous fever; erythematous papules, macules, and nodules on his arms, legs, and face, with no hypopigmentation or anesthesia; arthritis of the wrists and ankles; and episcleritis in both eyes (Figs. 1A–C). His family history was noncontributory (at first he denied any familiar disease), and his medical history was otherwise unremarkable. F1

Laboratory investigations showed neutrophilic leukocytosis (white blood cells, 21,400/μL; neutrophils, 87%), very high erythrocyte sedimentation rate (65 mm in the first hour; normal value, <22 mm/hr) and C-reactive protein (300 mg/L; normal value, <5 mg/L), and increased serum angiotensin-converting

From the *Internal Medicine B, Unit of Autoimmune Diseases, Department of Medicine, University of Verona, Verona; †Institute G. Gaslini and Department of Experimental Medicine, University of Genova, Genova; Departments of ‡Pathology, and §Medicine, Section of Dermatology, University of Verona, Verona, Italy.

The authors declare no conflict of interest.

Correspondence: Claudio Lunardi, MD, Section of Internal Medicine, Department of Clinical and Experimental Medicine, University of Verona, Policlinico GB Rossi, Piazzale LA Scuro, 37134 Verona, Italy. E-mail: claudio.lunardi@univr.it.

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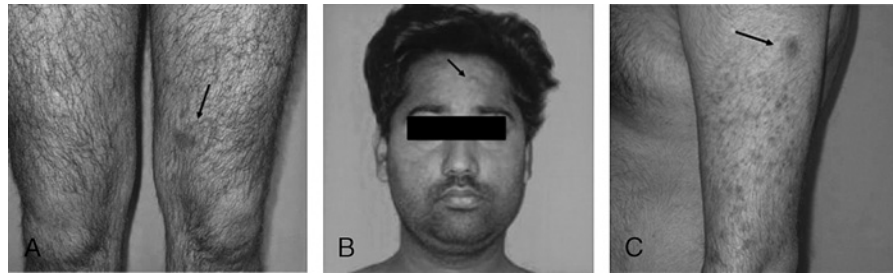

AQ1 **FIGURE 1.** Pomphoid erythematous lesions on the leg (A), face (B), and arm (C). Color online figure is available at http://www.jclinrheum.com.

enzyme (ACE) (101.0 IU/L; normal value, 8–54 IU/L). Liver and kidney function tests, thyroid hormones, protein electrophoresis, and serum levels of IgM, IgG, and IgA were normal. Serum antinuclear antibodies, rheumatoid factor, anticitrulline antibodies, anticardiolipin antibodies, and antineutrophil cytoplasmic antibodies were negative. Complement fractions 3 and 4 were normal. Lactate dehydrogenase, creatine phosphokinase, and aldolase were normal. Blood cultures and antibodies against bacteria and viruses were negative.

Chest x-ray, abdomen ultrasonography, transthoracic echocardiogram, and x-ray of the hands, wrists, and ankles did not show abnormalities. Chest computed tomography showed a nonspecific, diffuse interstitial lung disease. Analysis of bronchoalveolar lavage fluid showed an increase in lymphocytes (30%) and macrophages (70%) and an increased ratio of CD4 to CD8 T lymphocytes (5.1; normal value, <3).

Although no skin or transbronchial biopsy was performed on that occasion, "possible sarcoidosis with prevalent extrapulmonary involvement" was diagnosed, and the patient was administered high-dose corticosteroid therapy (1 mg/kg per day) with sudden clinical improvement. After 6 months when the tapering of prednisolone reached 12.5 mg/d, a severe flare of the disease occurred with the same symptoms present at the beginning of the disease. On that occasion, a gallium (Ga) 67 scintigraphy revealed accumulation of Ga at the orbits, wrists, and skin lesions. No evidence of pulmonary accumulation of

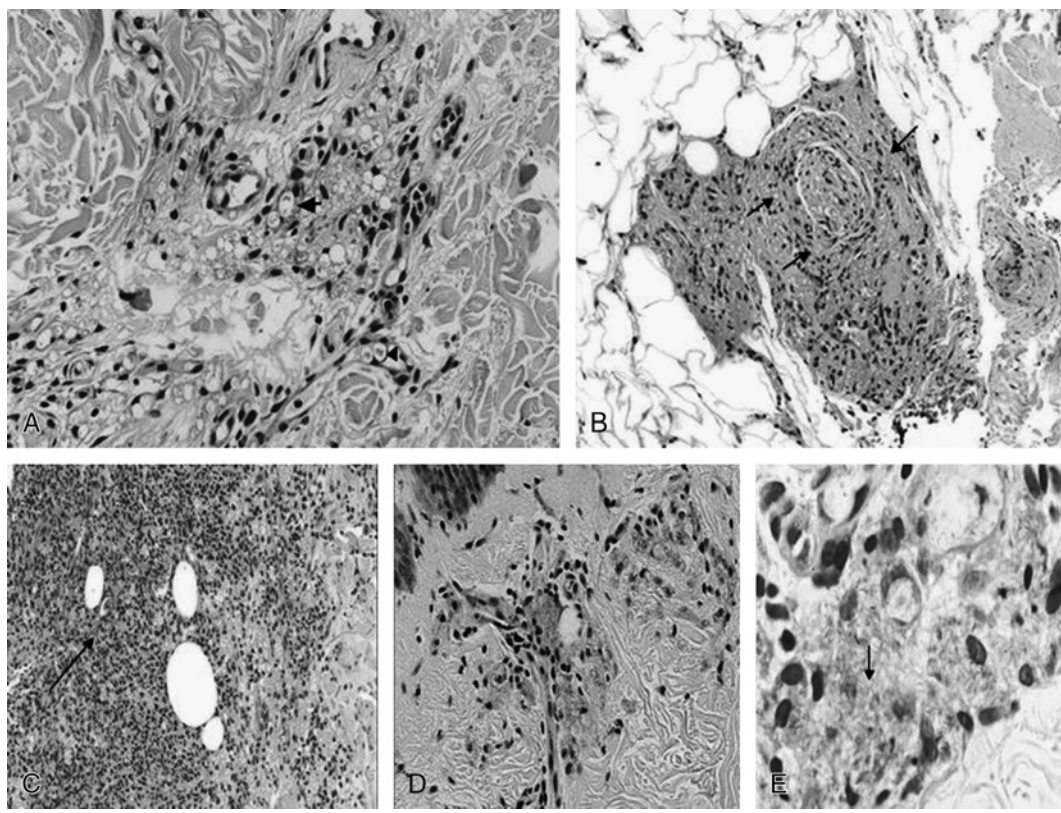

FIGURE 2. Features of leprosy in the skin biopsy. A, Collection of macrophages with bubbly and grayish cytoplasm in the dermis. The leprosy bacilli may be arranged in large groups or globi in histiocytes (arrow) or vascular endothelium (head arrow) (hematoxylin-eosin stain, magnification: × 40). B, Small nerve infiltrated by lepra cells into the subcutaneous fat (hematoxylin-eosin, magnification: × 20). C, Erythema nodosum leprosum features: numerous neutrophils are intermingling with the lepra cells (hematoxylin-eosin, magnification: × 26). D, Ziehl-Neelsen stain reveals acid-fast bacilli (magnification: × 40). E, Numerous acid-fast bacilli (oil immersion). Color online figure is available at http://www.jclinrheum.com.

Ga was present. On the basis of the clinical history, the diagnosis of sarcoidosis was considered unlikely, and a possible adult-onset Still disease was taken into account, although the ferritin level was not very high: 817 μg/L (normal value, 30–250 μg/L). The dosage of prednisolone was increased to 50 mg/d with immediate beneficial effects, and methotrexate 10 mg/wk plus hydroxychloroquine 200 mg/d were added as corticosteroid-sparing agents. In November 2007, the patient was admitted to the casualty area because of an acute perforated appendicitis treated with open appendicectomy. Corticosteroid and immunosuppressive therapy was stopped for a week, but in a few days, there was a severe relapse of dermal lesions with high temperature and all the clinical symptoms previously described. The patient was readmitted to the same hospital in December 2007, and a biopsy of a dermal lesion of the arm was performed: no evidence of epithelioid granuloma was found, and a severe dermal reaction to hydroxychloroquine was suggested because of the presence of superficial and deep perivascular dermatitis characterized by a mixed infiltration of lymphocytes, histiocytes, and neutrophils and presence of dermal edema and subepidermal vesicles with necrosis of the epidermis.

The patient restarted prednisolone therapy at 50 mg/d and methotrexate 10 mg/wk. In February 2008, a second skin biopsy was performed, and the features were again nonspecific, suggesting either a possible poststeroid panniculitis or a Sweet syndrome with hypodermal involvement or an erythema nodosum with dermal involvement.

In June 2008, when prednisolone was tapered to 20 mg/d, the patient had another flare of the disease and was admitted to our Unit of Autoimmune Diseases. We decided to stop corticosteroids and to start treatment with ibuprofen, suspecting an autoinflammatory disease such as periodic fever or Schnitzler syndrome. In that occasion, laboratory tests confirmed high levels of erythrocyte sedimentation rate (97 mm in the first hour; normal value, <14 mm/hr), C-reactive protein (173 mg/L; normal value, <5 mg/L), and fibrinogen: 787 mg/dL (normal value, 150–400 mg/dL). Full blood count showed the presence of leukocytosis (16,120/μL with 87% of neutrophils), mild hypochromic-microcytic anemia (hemoglobin, 11 g/dL; normal value, 13–17 g/dL), and thrombocytosis (441,000/μL; normal value, 150–400/μL), interpreted as related to chronic inflammation. Autoantibodies were again negative, and serum ferritin was 417 μg/L (normal value, 30–250 μg/L). Because the diagnosis was still undefined, and a good response was present only to high dose of corticosteroids and because the blood tests were suggestive of an important inflammatory state, we decided to perform a third deep (dermal-hypodermal) skin biopsy.

Leprosy was diagnosed by finding acid-fast bacilli, indicative of *M. leprae*, within macrophages (Figs. 2A–E). A history of exposure (as a child when in India, he had been living for a long time with an uncle affected by leprosy) was at that moment reported by the patient and his parents. The patient was then referred to the Italian National Centre for Leprosy at San Martino Hospital in Genova and started multidrug therapy/World Health organization. He was therefore administered rifampicin, clofazimine, and dapsone plus prednisolone 25 mg/d with a good response to the treatment. He is still followed up at the National Centre for Leprosy in Genova, and at the moment, he is taking rifampicin, minocycline, and prednisolone.

DISCUSSION

We describe here the case of a patient with lepromatous leprosy, acquired within a contagious family setting during childhood and adolescence, diagnosed as a possible sarcoidosis first and then as an autoimmune/autoinflammatory disorder. The results of bronchoalveolar lavage and the high levels of serum ACE probably induced the physicians to consider an acute-onset sarcoidosis as the first possible diagnosis, although no biopsy was performed at that time. As already reported, sarcoidosis can mimic lepromatous leprosy.[10] Indeed, high levels of ACE are present also in leprosy,[8,11] in particular in patients with Lucio phenomenon,[12–14] a leprosy reaction characterized by skin ulcerations and by systemic manifestations that occurs after 1 to 3 years from the first manifestations of the disease. It seems to be due to a severe immune response deficiency with free replication of *M. leprae* in endothelial cells followed by vasculitis, thrombosis, and necrosis.[13] Lucio phenomenon typically affects patients from Central and South America.

Leprosy reactions are characterized by the appearance of symptoms and signs of acute inflammation in the lesions and are due to acute hypersensitivity to antigens of *M. leprae*.[13] Type I reactions, associated with cell-mediated hypersensitivity, are also called reversal reaction, occur primarily in borderline leprosy, and are characterized by skin changes and neuritis. Type II reactions are associated with immune complex deposition, occur in patients with multibacillary disease, and cause acute inflammation in any organ or tissue where the mycobacterium is found. It is clinically expressed as erythema nodosum, neuritis, bone pain and arthralgias, fever, malaise, iritis, orchitis, and so on.[13] Three different clinical variants of type II leprosy reactions are described: (1) erythema nodosum leprosum (ENL), (2) erythema polymorphous-like reaction, and (3) Lucio phenomenon. However Lucio phenomenon is sometimes designated as type III reaction.[15]

Erythema nodosum leprosum is the most common form of type II leprosy reaction and affects patients with the lepromatous spectrum of the disease like the patient we have described here. Indeed, ENL is characterized by erythematous or deep purple nodules, variably distributed on the body, mostly occurring on the legs, arms, and face. On the contrary, idiopathic erythema nodosum is confined to the anterior portion of the lower legs. It is therefore possible that our patient showed an ENL, although this is usually a complication of the treatment. Prednisolone and methotrexate have been proposed as a possible therapy in resistant ENL.[16] In the patient we describe here, corticosteroid and immunosuppressive therapy obtained an apparent response for their effect on the immune response that is responsible for the majorities of the leprosy reactions.

Hansen disease is unfamiliar to European clinicians and pathologists, and lack of clinical suspicion and unfamiliarity with the histology of indeterminate leprosy delayed diagnosis and treatment in the patient we describe here.

Typical cutaneous and neurologic manifestations of leprosy are more easily diagnosed. Indeed, it is important to recognize the infection as early as possible so that early nerve damage can be identified and treated rapidly.

However, leprosy can mimic several rheumatologic disorders, and physicians sometimes ignore that leprosy may present with rheumatic symptoms. A plethora of rheumatic manifestations is associated with leprosy, particularly with lepra reactions.[17] Paira and Roverano[18] investigated the rheumatic and laboratory features in 25 patients with HD and found that 16 (64%) developed a broad range of rheumatic manifestations, the most common being a distinctive syndrome of swollen hands observed in 10 patients (66.5%). These manifestations were more frequent in patients with lepromatous leprosy.

In a similar work, Vengadakrishnan et al.[19] studied 70 cases of leprosy and found that arthritis may be the first symptom of leprosy and that rheumatic manifestations are present in

61.42% of cases. In particular, arthritis was seen in 54.28% and presented as symmetric peripheral polyarthritis most commonly involving the knee, elbow, and the metacarpophalangeal and interphalangeal joints of the hands, clinically similar to rheumatoid arthritis. Musculoskeletal manifestations can occur at any time during the infection. All patients with arthritis were subjected to x-ray of the affected joints, and nonspecific changes were commonly found. Also sacroiliitis (based on the presence of sclerosis, erosions, and narrowing of the cartilage space in the sacroiliac joints with or without low back pain) is often present in patients with leprosy.[20]

Laboratory abnormalities in leprosy include an elevated sedimentation rate in 100% of the patients, the presence of autoantibodies such as rheumatoid factor in 18.7%, and presence of antinuclear antibodies in 3.1%.[21] In a more recent study, however, both rheumatoid factor and anti–cyclic citrullinated peptide antibodies were present in a similar percentage in lepromatous patients and in normal subjects.[22]

Interestingly, 42% of multibacillary and 17% of paucibacillary leprosy patients have been found positive for anti–β2 glycoprotein I IgM,[23] suggesting the presence of an autoimmune response induced by *M. leprae* chronic infection.

Bacterial infections such as tuberculosis and leprosy; viral arthropathies such as O'nyong-nyong, chikungunya, and dengue; and parasitic infections such as filariasis, schistosomiasis, and amebiasis may present with rheumatic manifestations.[24] With the increasing world traveling and migration, internal medicine, rheumatology, and clinical immunology specialists must be aware of these aspects in clinical practice.

REFERENCES

1. Jacobson RR, Krahenbuhi JL. Leprosy. *Lancet*. 1999;353:660.
2. Walker SL, Lockwood DNJ. The clinical and immunological features of leprosy. *Br Med Bull*. 2006;77–78:103–121.
3. Rodrigues LC, Lockwood NJ. Leprosy now: epidemiology, progress, challenger, and research gaps. *Lancet Infect Dis*. 2011;11:464–470.
4. Cardoso CC, Pereira AC, Brito-de-Souza VN, et al. IFNG +874 T> A single nucleotide polymorphism is associated with leprosy among Brazilians. *Hum Genet*. 2010;128:481–490.
5. Modlin RL. The innate immune response in leprosy. *Curr Opin Immunol*. 2010;22:48–54.
6. Montoya D, Modlin RL. Learning from leprosy: insight into the human innate immune response. *Adv Immunol*. 2010;105:1–24.
7. Anderson H, Stryjewska B, Bobby L, et al. Hansen disease in the United States in the 21st century: a review of the literature. *Arch Pathol Lab Med*. 2007;131:982–986.
8. Flower C, Gaskin D, Marquez S. A case of recurrent rash and leg numbness mimicking systemic rheumatic disease. *J Clin Rheumatol*. 2007;13:143–145.
9. Chimenos KE, Pascual CM, Pinol DC, et al. Lepromatous leprosy: a review and case report. *Med Oral Patol Oral Cir Bucal*. 2006;1:E474–E479.
10. Thaipisuttikul Y, Katteruttanakul P. Sarcoidosis mimics lepromatous leprosy: a case report. *J Med Assoc Thai*. 2007;90:171–174.
11. Lieberman J, Rea TH. Serum angiotensin-converting enzyme in leprosy and coccidioiomycosis. *Ann Intern Med*. 1977;87:422–425.
12. Roverano S, Paira S, Somma F. Lucio's phenomenon: report of two cases and review of the literature. *J Clin Rheumatol*. 2000;6:210–213.
13. Carvalho Costa IM, Barbosa Kawano L, Pereira CP, et al. Lucio's phenomenon: a case report and review of the literature. *Intern J Dermatol*. 2005;44:566–571.
14. Guedes-Barbosa LS, Batista EV, Martins DC, et al. Necrotizing cutaneous vasculitis in multibacillary leprosy disease (Lucio's phenomenon). *J Clin Rheumatol*. 2008;14:57–58.
15. Cuevas J, Rodrìguez-Peralto JL, Carrillo R, et al. Erythema nodosum leprosum: reactional leprosy. *Semin Cutan Med Surg*. 2007;26:126–130.
16. Kar BR, Babu R. Methotrexate in resistant ENL. *Int J Lepr Other Mycobact Dis*. 2004;72:480–482.
17. Samant R, Nadkar MY, Vaidya SS, et al. Leprosy: a close mimic in a rheumatology clinic. *J Assoc Physicians India*. 1999;47:576–579.
18. Paira SO, Roverano S. The rheumatic manifestations of leprosy. *Clin Rheumatol*. 1991;10:274–276.
19. Vengadakrishnan K, Saraswat PK, Mathur PC. A study of rheumatological manifestations of leprosy. *Indian J Dermatol Venereol Leprol*. 2004;70:76–78.
20. Cossermelli-Messina W, Festa Neto C, Cossermelli WJ. Articular inflammatory manifestations in patients with different forms of leprosy. *J Rheumatol*. 1998;25:111–119.
21. Chavez-Legaspi M, Gomez-Vazquez A, García-De La Torre I. Study of rheumatic manifestations and serologic abnormalities in patients with lepromatous leprosy. *J Rheumatol*. 1985;12:738–741.
22. Ribeiro SL, Pereira HL, Silva NP. Anti-cyclic citrullinated peptide antibodies and rheumatoid factor in leprosy patients with articular involvement. *Braz J Med Biol Res*. 2008;41:1005–1010.
23. Brochado MJ, Figueiredo JF, Mendes-Junior CT. Correlation between beta-2-glycoprotein I gene polymorphism and anti–beta-2 glycoprotein I antibodies in patients with multibacillary leprosy. *Arch Dermatol Res*. 2010;302:583–591.
24. Adebajo AO. Rheumatic manifestations of tropical diseases. *Curr Opin Rheumatol*. 1996;8:85–89.

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