Case Report from the New York-New Jersey Intercity Infectious Disease Rounds
Edited by Donald B. Louria, MD

Hansen's Disease in a Native-Born, United States Resident, after a Brief Stay in an Endemic Area Abroad

Purnendu Sen, MD;* Rajiv Ranjan, MD;* and John R. Middleton, MD*

A 70-year-old female was seen in the office for evaluation of non-healing skin lesions. She had a history of insulin-dependent diabetes mellitus for 13 years and was well until 6 months previous to presentation, when she developed raised erythematous lesions initially on her left arm and subsequently involving both upper extremities and the posterior thoracic wall.

She was seen by several physicians and was treated with antifungal and steroid-containing creams without any improvement. She had no fever, sore throat, or acute joint pain. She had history of long-standing osteoarthritis.

She had been born and raised in central New Jersey. She travelled to China about 12 years prior to this incident, where she stayed for 2 weeks in both rural and urban areas. Three years before presentation she had travelled to Hawaii for vacation and stayed in major city hotels.

Pertinent physical examination revealed body temperature, 36°C; pulse, 80 beats per minute; respiratory rate, 16 per minute; blood pressure, 190/80 mm Hg. There were indurated erythematous lesions on both upper extremities and the posterior thoracic wall (Figure 1). There were no oral lesions, no adenopathy, and no abnormalities of peripheral nerves. The rest of physical examination was unremarkable.

Significant laboratory findings showed hemoglobin of 14.5 g/dL and white blood cell count of 9200/ mm^3 with normal differential count. Blood chemistry values were normal except for a slightly high serum glucose level of 151 mg/dL (normal range [N] = 70-150 mg/dL) and a cholesterol level of 231 mg/dL (N = 142-200 mg/dL).

The initial differential diagnosis included sarcoidosis, lymphoma, and vasculitis. However, hypoesthesia over the skin lesions was noted, and a diagnosis of leprosy was entertained by the infectious disease physician despite the absence of a clear exposure history. A full-thickness biopsy of skin was performed and demonstrated granulomatous dermatitis and an overwhelming number of acid-fast organisms by both Ziehl-Neelsen and Fite stains consistent with the diagnosis of lepromatous leprosy (Figure 2). The patient was treated with dapsone and rifampin. Ten months later, her skin lesions worsened. This was considered to be secondary to a hypersensitivity phenomenon with reversal reaction. A repeat skin biopsy was performed and showed a chronic inflammatory infiltrate with foamy macrophages. Fite stains again revealed numerous small acid-fast bacilli with no apparent microorganism decrease within cutaneous nerves compared to the initial biopsy. This was consistent with a reversal reaction or failure of therapy. Additional treatment with clofazamine and minocycline was started. The patient also was treated with oral prednisone, 60 mg daily initially, with subsequent tapering doses for a possible reversal reaction related to her therapy. Follow-up showed no new skin lesions and satisfactory regression of existing lesions.

Eighteen months later, the patient developed cough and fever. Chest radiograph revealed an infiltrate, and she was treated for pneumonia with apparent improvement. Six months later, she sustained fracture of the pelvis from

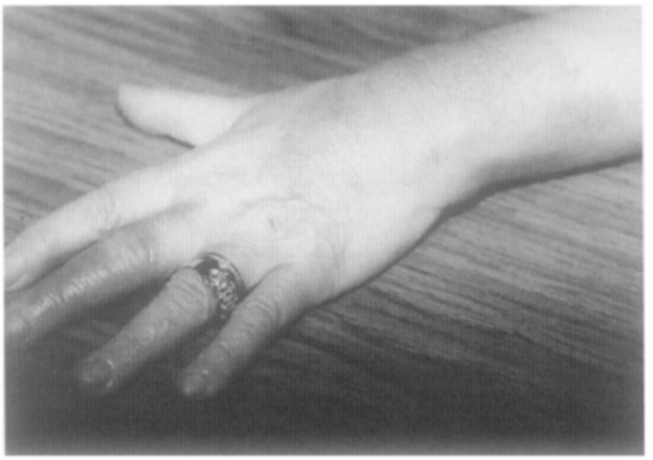

Figure 1. Hypoesthetic raised erythematous lesions on the dorsum of the hand.

*Infectious Diseases Division, Raritan Bay Medical Center, Perth Amboy, New Jersey.

Address correspondence to Dr. Purnendu Sen, Raritan Bay Medical Center, Perth Amboy Division, 530 New Brunswick Avenue, Perth Amboy, NJ 08861. E-mail: Ovargas@rbmc.org.

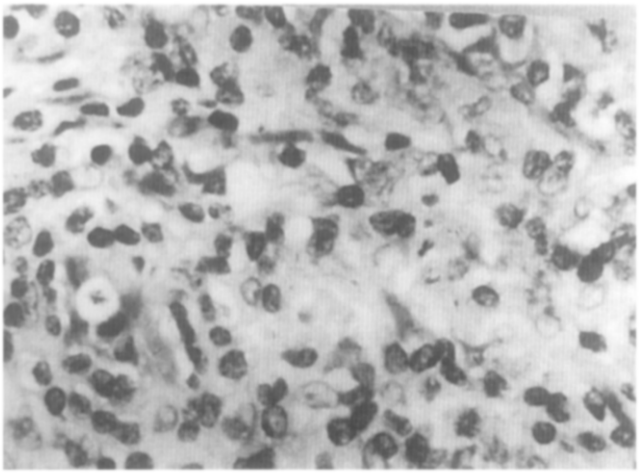

Figure 2. Skin biopsy showing numerous leprosy bacilli. (Fite stain, original magnification ×400).

a fall. She had persistent mild cough. Chest radiograph showed increased markings in the left mid and lower lung fields. Bronchoscopic biopsy showed organisms in the lung parenchyma consistent with *Cryptococcus neoformans*. Serum cryptococcal antigen was positive at a dilution of 1:512. The patient was treated with intravenous amphotericin followed by oral fluconazole with satisfactory improvement in the respiratory symptoms. Follow-up chest radiograph showed significant improvement, and serum cryptococcal antigen declined. Antileprosy medications were discontinued after total treatment of 2.5 years.

The patient's human immunodeficiency virus (HIV) serology was negative. Interestingly, her T-cell subset studies were completely normal when leprosy was diagnosed, but did deteriorate during steroid therapy (Table 1), with a dramatic decline in both CD4 and CD8 cells. However, after pulmonary cryptococcal infection was diagnosed, during treatment with amphotericin and small tapering doses of prednisone, her T-cell subset studies had reverted to normal.

DISCUSSION

Leprosy or Hansen's disease (HD) presents a major public health problem, particularly in the Third World countries. In 1991, 5.5 million active cases were reported throughout the world.[1]

Table 1. Profile of T Lymphocytes in Patient Diagnosed with Leprosy

Date	*CD3* *(N = 1654 ± 449)*	*CD3 + CD4* *(N = 1080 ± 310)*	*CD3/CD8* *(N = 507 ± 185)*
February 1995	1619 (74.9%)	945 (43.7%)	603 (27.9%)
January 1996	362 (69.9%)	192 (36.9%)	148 (28.5%)
January 1998	1290 (76.0%)	810 (63.0%)	447 (35.0%)

N = normal range.

In the United States there have been approximately 6000 known cases.[2] The incidence increased in the 1980s compared to 1950s,[3,4] and in 1996, 112 newly diagnosed cases were reported to the Centers for Disease Control and Prevention (CDC).[5] The majority of these patients were foreign-born,[2] but 31 cases per year of HD among native-born persons were reported between 1970 and 1981. Most of these individuals were born in three states: Texas (56%), Louisiana (14%), and California (4%). In Hawaii, 255 cases of HD were reported during the years 1951 to 1981.[6] Indigenous cases of HD still are being reported from Louisiana, California, Hawaii, and New York City.[7]

The case reported here raises some interesting epidemiologic questions. The patient was born and lived in central New Jersey and travelled to Hawaii and China for brief periods, but she had no contact with persons known to have HD. New Jersey is not known to have any endemic leprosy focus. In the past 10 years, 17 cases of HD have been reported to the New Jersey Department of Health and Senior Services (State Department of Health. Personal communication). To the authors' knowledge, all these individuals, except for the patient reported here, were immigrants.

In a report of 100 cases of HD in New York City, 99% were foreign-born and presumably acquired infection while abroad.[8] Interestingly, in one report, 70% of native-born citizens of the United States with HD had no history of leprosy contacts.[6] The mechanisms of transmission of *Mycobacterium leprae*, the causative agent of HD, still are unclear. It is believed that human-to-human transmission probably occurs through the respiratory route by airborne droplets from the nasal mucosa.[9,10] Skin contact no longer is considered to be important for transmission, although trauma to the skin might provide a route for direct transmission. Although not proven, observations from Louisiana, Texas, and Mexico suggest that HD may be acquired from contact with armadillos.[11] Since armadillos are not present in New Jersey, this is an unlikely source of *M. leprae* in the reported case. Repeated exposure to patients with active leprosy has been considered necessary for human-to-human transmission, but this theory may not be altogether true. Even brief exposure might be sufficient to contract the infection if large numbers of viable *M. leprae* are shed by the patient.[12]

The patient reported here could have been exposed to patients with active leprosy while in China, Hawaii, or even in New Jersey without her knowledge and then years later developed the disease when her specific immunity to *M. leprae* declined. However, casual contact resulting in transmission of the disease is not important from a public health point of view since there has been

no documented secondary transmission from imported cases within the continental United States.[12]

This patient was 70 years of age at the time of diagnosis. The existence of subclinical or asymptomatic leprosy has been postulated, suggesting that late reactivation of the disease may occur because of declining immune function in older individuals.[13] Among indigenous cases of leprosy reported from Louisiana, three patients had some type of potentially immunosuppressive illness, including Hodgkin disease, cervical carcinoma, and diabetes mellitus, but there were no specific data on their immunologic status.[11] There are no large studies to indicate that HD is more common or worse in compromised hosts, including those with HIV.[11] Studies during World War II suggested worsening of leprosy in malnourished individuals,[14,15] but convincing data are lacking.

Patients with HD often are not anergic and respond normally to intradermal skin tests.[16] However, there is evidence of specific anergy to *M. leprae* in patients with lepromatous leprosy, perhaps as a result of the illness rather than as a causative factor.[17,18] This patient had normal T-cell studies at the time of diagnosis, although specific studies to determine anergy to *M. leprae* were not done. In active skin lesions, T-lymphocyte subsets appear to vary depending on the type of leprosy. Helper cells predominate in tuberculoid skin lesions, whereas in the lepromatous type, the majority are suppressor cells. In this patient, specific studies to determine the T-lymphocyte subtype predominance were not done. There was another interesting feature in this case. After HD-related skin lesions healed, the patient developed pulmonary cryptococcosis. Patients with cell-mediated immune dysfunction are at increased risk for cryptococcosis. This patient's susceptibility to cryptococcal infection may have resulted from the steroid therapy that was accompanied by reduction in circulating T cells. Subsequently, during treatment for cryptococcal disease, her peripheral lymphocyte studies were within the normal range, but intradermal reaction to delayed-type antigens, such as purified protein derivative (PPD), was not performed.

Genetic factors have been mentioned as influencing susceptibility to leprosy.[19] A study done among the Karimui people of New Guinea demonstrated that the risk for contracting leprosy in the offspring of parents with leprosy was not influenced by the severity or infectivity of the disease but was higher where there was a family history of leprosy. Specific human leukocyte antigen haplotypes may determine the clinical forms of leprosy, influencing the helper T-lymphocyte, and thereby, the specific immune response.[20,21]

Most cases in native-born patients in the United States are the multibacillary form of the disease,[6] in which a significant number of acid-fast bacilli are present in skin biopsies, as was evident in the case presented here. This may represent a poor cellular response to *M. leprae*.

The clinical features of various forms of HD, including lepromatous, tuberculoid, and borderline cases have been well described.[9,22] Misdiagnosis is common, even in patients from endemic areas, particularly if those with lepromatous type leprosy present with only chronic nonhealing skin lesions without typical leonine facies, deformities of extremities, or nerve abnormalities. Diagnosis is even more difficult in indigenous cases without any history of contact with patients known to have leprosy. The diagnosis of HD should be considered in any person presenting with unexplained skin lesions, and a careful assessment should be made for sensory loss in the lesions; however, in patients with lepromatous leprosy, sensory loss may not be present until later stages of the disease. Consequently a careful search should be made, looking for nodules in the ears, nose, and eyebrows and for subtle eye changes. Eye changes in lepromatous leprosy may include partial or complete loss of eyebrows (madarosis), persistent red eye or incomplete closure of eyelids due to seventh nerve palsy (lagophthalmosis).[9,23]

Skin lesions often worsen after chemotherapy, owing to reversal or erythema nodosum leprosum (ENL) reaction. Reversal reactions represent changes in the cell-mediated immunity in the skin lesions, with proliferation of T lymphocytes and worsening of inflammatory response, and may worsen the clinical picture of borderline leprosy. There may even be increased bacterial proliferation locally in the skin lesions.[9] Erythema nodosum leprosom reaction often follows chemotherapy in all forms of leprosy and not only may complicate the skin lesions with tender nodules or extensive ulceration but also may be associated with development of systemic reactions including fever, lymphadenopathy, neuritis, glomerulonephritis, and secondary amyloidosis.[24] The mechanism of ENL reaction involves immune complex formation in skin lesions that enhance helper T cells.[25]

The differential diagnosis of skin lesions in a patient with HD includes superficial fungus infection, Kaposi's sarcoma, sarcoidosis, lymphoma, lupus vulgaris, syphilis, and granuloma annulare. A skin biopsy from the edge of the lesion or nasal smears for acid-fast bacilli are the only methods for establishing the diagnosis.

Table 2 enumerates the various drugs currently available in the United States for treatment of HD.[26,27] It is preferable that physicians with experience with the disease should evaluate the patient at least initially and then periodically if there are adverse drug reactions or failure of therapy owing to drug resistance. In general, multiple drugs, including dapsone, rifampin with or without clofazimine, are necessary to prevent drug resistance and should be continued for at least 24 months. The clinical presentations of drug reactions often are complex and require prompt and careful evaluation. Since adverse reactions to treatment in patients with lepromatous leprosy include type-I reversal reaction and ENL, repeat skin biopsy may be necessary to determine the type of reaction.

Table 2. Drugs for Treatment of Leprosy

Usual Regimen	*Other Useful Drugs*
Dapsone	Minocycline
Rifampin	Ofloxacin
Clofazimine	Pefloxacin
	Clarithromycin

Adjunct therapy with corticosteroids may be necessary and thalidomide has been advocated for men with ENL.[28]

SUMMARY

Despite the overall decline in number of leprosy cases in the United States, small numbers of patients with the disease continue to be reported, predominantly among immigrant populations. Occasional cases occur among native-born American residents, predominantly from the southern United States. The source of the reservoir and transmission among indigenous HD cases remains unexplained, although armadillos in the state of Texas and Louisiana have been implicated. Since most patients among the indigenous cases occur in older age groups, the possibility of reactivation of the disease through immunosenescence has been raised. In most patients, unfamiliarity with the clinical picture of HD among physicians in the United States accounts for delayed or incorrect diagnosis. High index of suspicion in a patient with unusual skin lesions, particularly with sensory loss, should be followed by a biopsy looking for the characteristic histologic changes found in various forms of leprosy. Reversal reactions and erythema nodosum leprosum are relatively frequent complications of treatment. Treatment and periodic follow-up of these patients should be done, preferably by physicians with experience with the disease entity.

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