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Case Report: Two Cases of Leprosy in Siblings Caused by *Mycobacterium lepromatosis* and Review of the Literature

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Abstract. We describe two leprosy cases in Mexican siblings caused by a new species *Mycobacterium lepromatosis*. This is likely the first report of family clustering of this infection. The patients showed severe prolonged leprosy reactions after antimicrobial treatment, raising a challenge for clinical management. The current status of *M. lepromatosis* infection is reviewed.

REPORT OF CASES

A 25-year-old male, living in Minneapolis but originally from Guerrero, Mexico, presented with a one-and-half year history of pruritus, swelling, and pain involving the distal extremities and the ears in January 2007. Physical examinations at the time and shortly after revealed madarosis (Figure 1), nonpitting edema of the ears, bilateral loss of eyelashes, and ill-defined, somewhat dusky, hyperpigmented patches scattered diffusely and symmetrically on his extremities with sparing of the trunk and neck. His hands and feet showed nonpitting edema and induration. No neurologic deficits were noted. Extensive laboratory workup revealed the following abnormal results: elevated erythrocyte sedimentation rate (ESR) of 54 mm/hour, reactive rapid plasma reagin, borderline fluorescent treponemal antibody absorption test, and an antinuclear antibody (ANA) titer of 1:320 with a speckled pattern. An anti-dsDNA antibody was negative. A skin biopsy from the left thigh was performed, and the patient was treated empirically with intramuscular benzathione penicillin in view of the borderline positive syphilis tests.

Histopathology of the skin biopsy demonstrated granulomatous infiltrates, with perineural and perivascular involvement, and a large number of acid-fast bacilli on Fite stain (Figure 2). These findings, together with clinical presentation and laboratory results, rendered the diagnosis of borderline lepromatous leprosy. The patient was treated with minocycline 100 mg daily, rifampin 600 mg monthly, and dapsone 50 mg daily.

Approximately 11 months into the multidrug therapy for leprosy, the patient developed signs and symptoms suggestive of both reversal reaction and erythema nodosum leprosum (ENL), including worsened skin lesions and swelling of hands and feet and new onset of fevers, recurrent crops of tender erythematous nodules on all extremities, and joint pains. He also reported a yellowish exudate from a preexisting lesion on the right leg. On examination, nonpitting edema and induration were noted on all distal extremities and a new dusky violaceous hue was observed on his hands and feet. The sore on his right leg appeared as a healing ulceration with an overlying hemorrhagic crust. Neurologic examination at this time revealed palpable and slightly tender ulnar nerves bilaterally and mild (scale 4 of 5) weakness of all distal extremities. Decreased sensation to pain and light touch was noted over most of his dorsal left hand and the lower legs, from the mid-calves to dorsal feet. Reflexes were symmetric and intact. A bluish discoloration on his nose and ears was also observed, which was thought to be the effect of minocycline, leading to discontinuation of the drug.

To treat the reactions, prednisone 40 mg daily and pentoxifylline 800 mg three times daily were used. Despite the treatment, the patient's reactions persisted, which led to an increase of prednisone to 100 mg daily and initiation of clofazamine 150 mg daily. Approximately 6 months later, the patient received thalidomide, and the drug dosage was escalated eventually to 400 mg daily over the ensuing months due to persistent fevers and ENL lesions. At his most recent follow-up, 7 years after initial presentation, the patient was still on treatment with thalidomide 50 mg daily and prednisone was increased from 2.5 to 5 mg daily due to mild flare of disease activity, as evidenced by sparse but new ENL lesions. His mild neurologic deficits had completely resolved. A skin biopsy also showed near complete resolution of inflammatory infiltrates along with rare degenerated acid-fast bacilli.

Approximately 5 years after the man's diagnosis, his elder sister, originally from Mexico and also living in Minnesota, presented with skin lesions at the age of 41. The lesions were violaceous patches on her bilateral malar cheeks as well as multiple hypoesthetic erythematous to hyperpigmented violaceous plaques on her upper back, both arms, left upper thigh, and distal legs (Figure 3). No neurologic deficits were noted at that time. Biopsies from her left thigh and right lower leg showed granulomatous inflammation and acid-fast bacilli to suggest borderline lepromatous leprosy. She was treated promptly with rifampin 600 mg monthly, clarithromycin 500 mg daily, and clofazamine 200 mg daily.

Since acid-fast bacilli could not be demonstrated within cutaneous nerves, and therefore the identity of the organisms could not be established histologically, one of the biopsies was analyzed for the etiologic agent by a polymerase chain reaction (PCR) test to differentiate the well-known *Mycobacterium leprae* and new agent *Mycobacterium lepromatosis*. The PCR results were negative for *M. leprae*, but sequencing of a portion of the 16S ribosomal RNA (rRNA) gene revealed a match for *M. lepromatosis*. A follow-up deeper skin biopsy was performed later, which confirmed the presence of acid-fast bacilli inside cutaneous nerves.

The sister's clinical course was also complicated. Three months after the initiation of multidrug therapy, she developed fever, tender erythematous nodules on her extremities, joint pain, and swelling of the hands and feet (Figure 4) as

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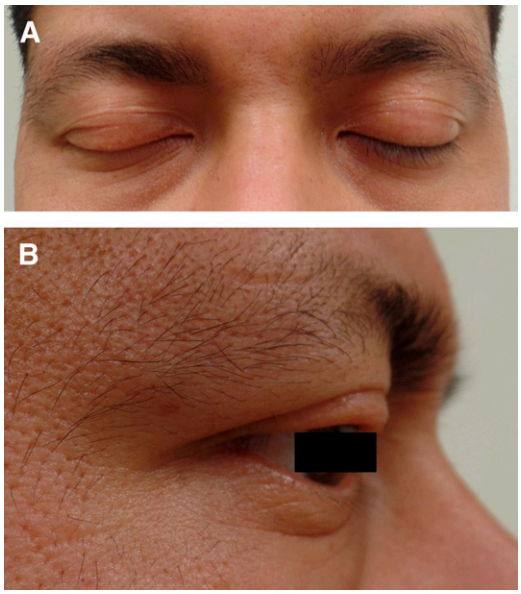

FIGURE 1. Clinical image: recent clinical photographs demonstrating madarosis affecting the bilateral lateral eyebrows and right eyelashes.

well as preexisting skin lesions. These signs and symptoms as well as subjective complaints of shortness of breath led to hospitalization, during which sleep apnea and obesity were found to be the cause of dyspnea. Laboratory workup revealed abnormal ESR of 77 mm/hour and C-reactive protein of 62 mg/dL and a low vitamin D level (30 ng/mL). Complete blood cells and metabolic profiles were unremarkable except for an elevated glucose (149 mg/dL), which led to an HbA1c test, diagnosis of diabetes, and initiation of metformin treatment. During this 24-hour hospitalization in Minnesota, the patient was given intravenous methylprednisolone and discharged on prednisone 40 mg daily for transfer to the National Hansen's Disease Programs (NHDP) in Baton Rouge, Louisiana, for further management.

At the NHDP, slit skin smears demonstrated the following bacteriologic results: 4+ (right ear), 1+ (left elbow), 2+ (bilateral knees), and no bacilli from the left ear and right elbow smears. The bacteriologic index was calculated to be 1.7. Thalidomide 300 mg daily and high dose vitamin D supplementation of 50,000 units weekly were started at this time. The patient remained hospitalized for 23 days due to severe neuritis, which, at one point, made her unable to walk. Prednisone was increased up to 80 mg. Aspirin 81 mg daily and

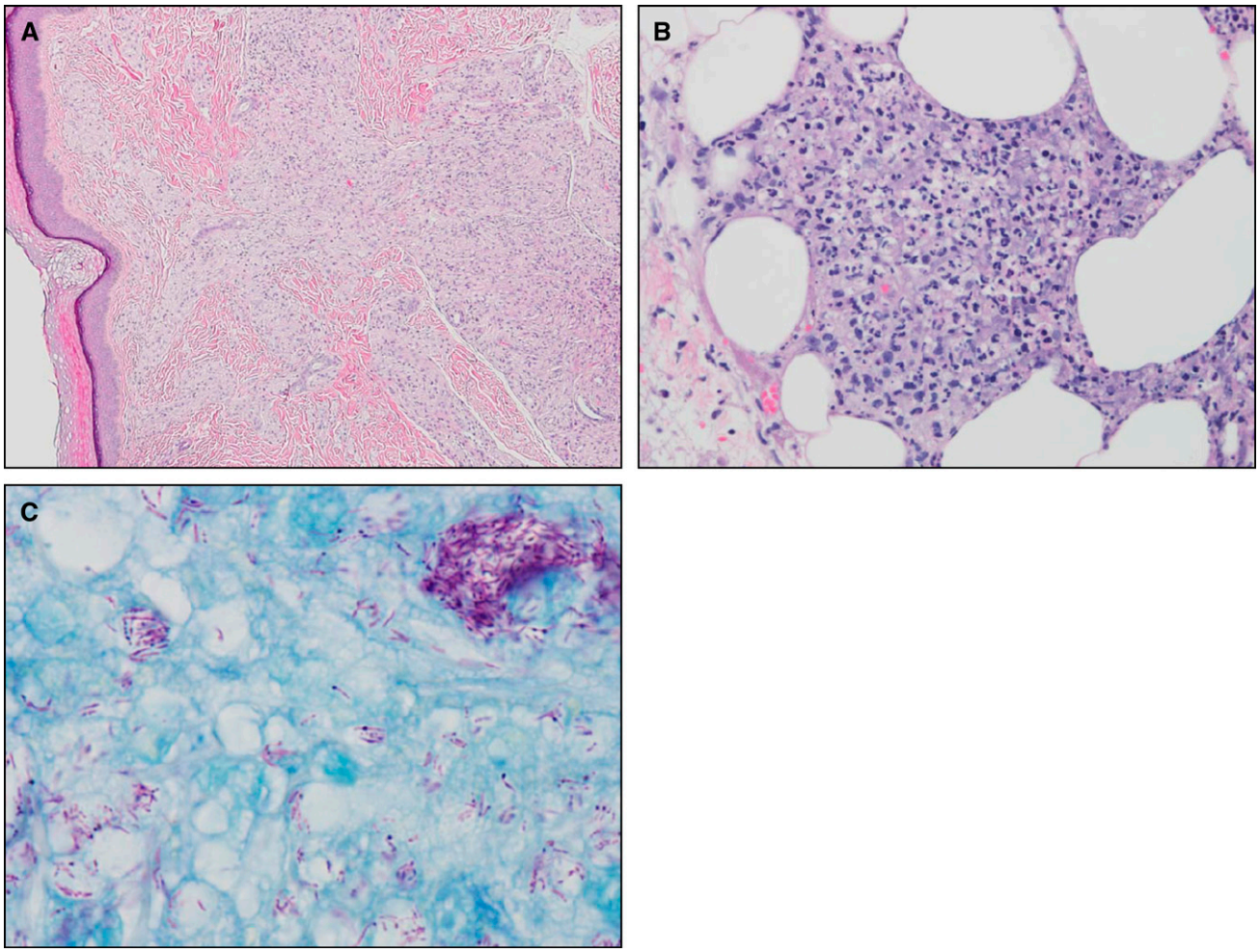

FIGURE 2. Histopathology of the skin biopsy of a 25-year-old man with *Mycobacterium lepromatosis* infection. (**A**) Low power view of dense histiocytic infiltration (hematoxylin and eosin [H and E], 100×). (**B**) Panniculitis due to deeper infiltration (H and E, 400×). (**C**) Heavy burden of acid-fast bacilli (Fite, 1000×).

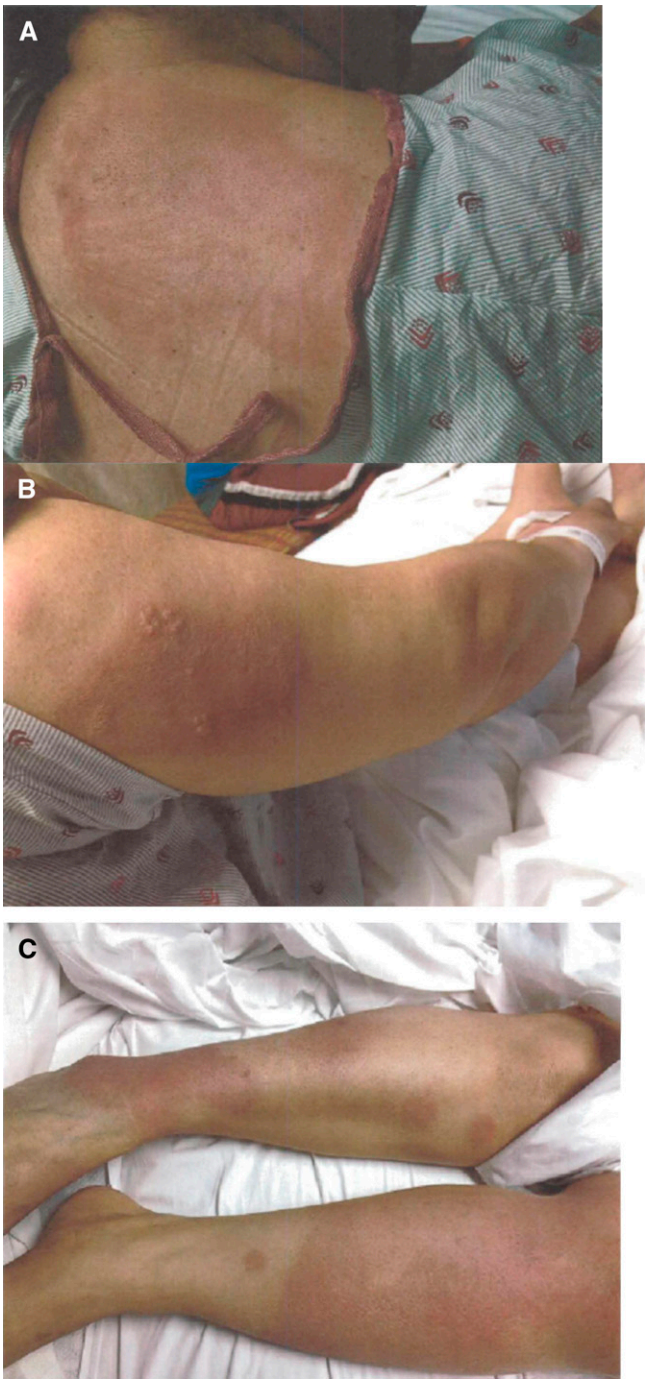

FIGURE 3. Clinical image: presenting skin lesions of a 41-year-old woman (sibling) with *Mycobacterium lepromatosis* infection. Hypoesthetic erythematous to violaceous plaques scatter on the (**A**) upper back, (**B**) right arm, and (**C**) legs.

clopidogrel 75 mg thrice weekly were also started to prevent deep venous thrombosis in view of the concomitant use of thalidomide and prednisone, obesity, and immobility. After discharge, she was continued on thalidomide at 200 mg daily and prednisone 60 mg daily that resulted in improvement of her joint pain and swelling.

Approximately 14 months after her initial diagnosis, the patient presented with a mild relapse of her symptoms,

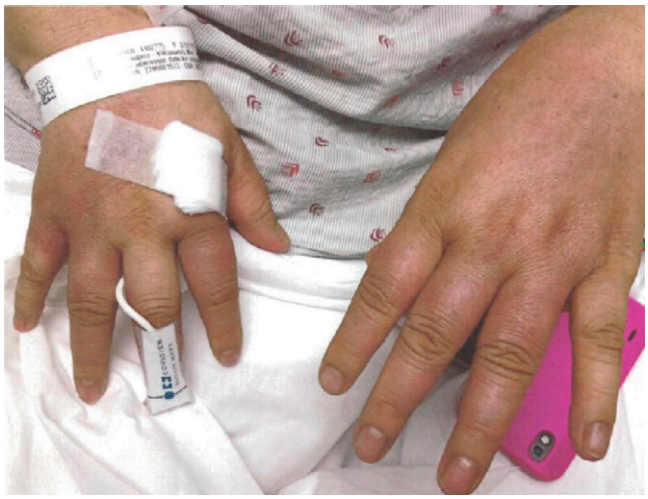

FIGURE 4. Severe hand edema of the woman after the initiation of multidrug therapy.

which was found to be due to a lapse of the prednisone dosage due to her illiteracy in English. She experienced fevers and joint pain at that time and was again hospitalized at the NHDP for 1 week. Physical examination revealed tender ulnar nerves along with decreased dermal sensation in the nerves' distribution, which were not noted on initial examination. However, the sensation of distal lower extremities was improved. Therefore, at discharge, she was continued on daily doses of prednisone 35 mg (with taper by 5 mg every month), thalidomide 100 mg, rifampin 600 mg, clarithromycin 500 mg daily, and clofazamine 100 mg.

After the sister's diagnosis of *M. lepromatosis*, a retrospective PCR analysis of the brother's original biopsy was performed; it confirmed the presence of *M. lepromatosis*, not *M. leprae*. Thus, family clustering of the cases was likely. Further family history was then elicited.

Although living in Mexico, the siblings never shared the same household. The brother lived with his mother and five other siblings (none affected to date) in the state of Guerrero, ~60 miles from the sister, who shared a house with her husband and children. The sister was the first family member to immigrate to the United States, approximately 10 years before her diagnosis of Hansen's disease, and eventually settling in St. Paul, Minnesota. The brother moved to Minnesota approximately 2 years later or 4 years before his leprosy diagnosis. He lived with his sister for the first year, which was the only time the sibling pair ever lived together. After immigration, the siblings remained within the United States without return visits. The brother mentioned a history of frequent handling and consumption of armadillos while living in Mexico.

DISCUSSION AND LITERATURE REVIEW

This report describes a pair of siblings who both contracted leprosy caused by *M. lepromatosis*. They showed similar clinical manifestations and protracted reactions on antileprosy treatment. The cases suggest likely family clustering of the infection as is well documented in leprosy.

Mycobacterium lepromatosis was recognized as a new *Mycobacterium* species and a cause of leprosy from two

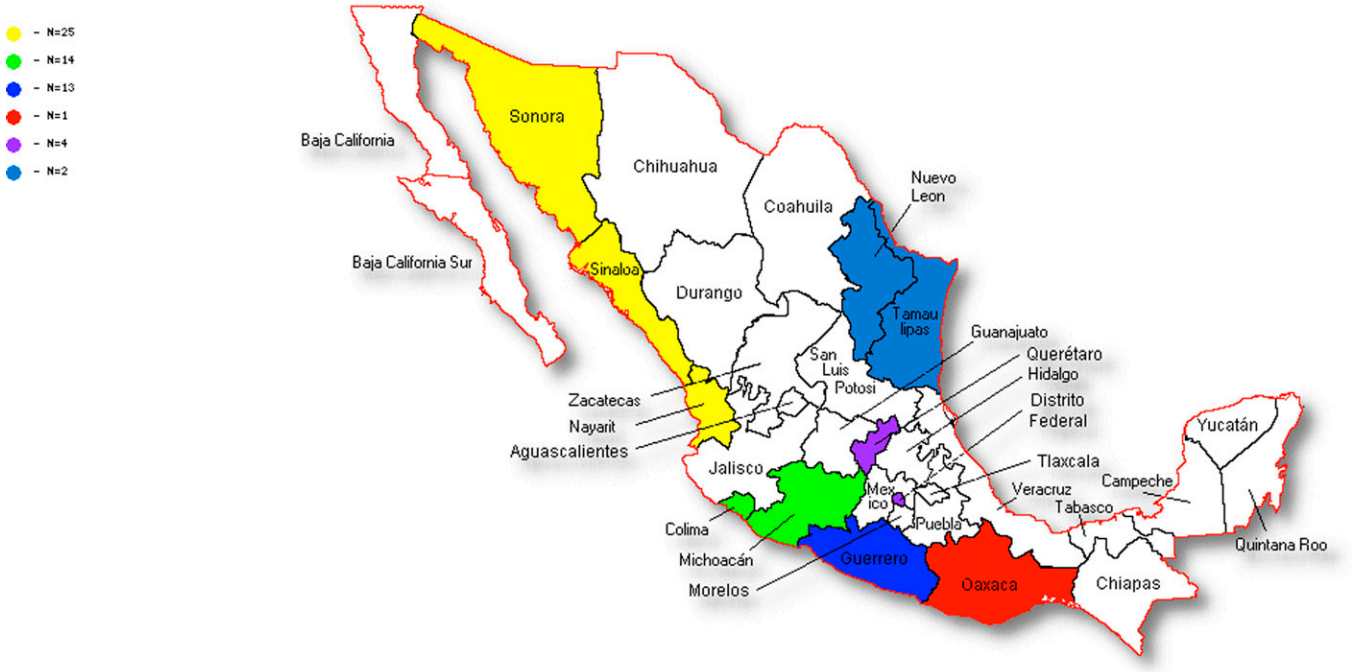

FIGURE 5. Cases of *Mycobacterium lepromatosis* infection reported to date in Mexico by States (59 cases total, including the present cases). Guerrero (13), Nuevo Leon (1),Tamaulipas (1), Sonora (7), Sinaloa (7), Nayarit (11), Colima (1), Michoacán (13),Oaxaca (1), Queretaro (3), and Distrito Federal (1).

patients of Mexico origin who died of diffuse lepromatous leprosy (DLL). Initial DNA sequencing analysis of a few genes suggested a 7.4% difference with *M. leprae*.[1] Further analysis of 20 genes and pseudogenes from *M. lepromatosis* showed a 9.1% genetic difference with *M. leprae* substantiating the species-level difference and further comparisons suggested a divergence time of the two species of approximately 10 million years ago from the last common ancestor.[2] Most recently, genomes of two *M. lepromatosis* strains were sequenced, revealing an ~13% genome-wide difference.[3,4] Analysis of one of the draft genomes refined the divergence time to 13.9 million years and showed similar genomic organization of the two bacilli.[3] Thus, *M. lepromatosis* and *M. leprae* are closely related species distinguishable at the genomic level that cause similar clinical manifestations on infection of humans.

On the basis of the *M. lepromatosis* gene sequences, PCR tests were developed in different laboratories to differentiate *M. leprae* and *M. lepromatosis*.[5–7] The 16S rRNA gene of each of the bacilli contained signatory sequences to allow species distinction.[1,5,8] PCR amplification of smaller targets (from 135 base pairs [bp] to 450 bp) were also used for work on formalin-fixed paraffin-embedded biopsy tissue.[1,5,8,9] Although agarose gel electrophoresis of amplified DNA fragments has been used to identify *M. lepromatosis* in some biopsy specimens, more definitive tests based on DNA sequencing should become the standard mode of testing to avoid false positives that can occur with DNA fragment analysis on gels.

To date, a total of 64 cases of leprosy caused singly by *M. lepromatosis* have been reported in Mexico or patients of Mexican origin, including the present cases.[1,5–9] *Mycobacterium lepromatosis* infection showed endemic regions in western and central Mexico along the Pacific coast (Figure 5).[8] These areas coincided with the historical distribution of DLL in Mexico.[10,11] Less frequent or rare *M. lepromatosis* cases have been described in the northeastern and northern Mexico States, such as Nuevo Leon,[6,12] Tamaulipas,[9] and Coahuila,[9] and the southeastern tip of the country.[13]

Elsewhere in the world, reports have shown five cases caused or contributed by *M. lepromatosis*, including two cases of Singaporean Chinese,[5] one case of a native Canadian,[7] and two cases in native Costa Ricans who now live in the United States (B. M. Stryjewska, unpublished data). To date, there have been eight cases in the United States, the above mentioned two Costa Ricans, as well as six patients of Mexican origin. Thus, based on evidence available to date, *M. lepromatosis* appears to be localized primarily to North and Central America.

Because of the long incubation and insidious onset of leprosy, the transmission of leprosy agent(s) has been difficult to pinpoint, but it is generally accepted that the average incubation period is around 7 years.[14] Among the reported *M. lepromatosis* cases mentioned above, excluding the present siblings, how the patients acquired the infection was either difficult to assess or entirely unknown.

The likely family clustering of the present cases led us to sketch a scenario of transmission based on history obtained from the siblings and onset of their respective illnesses. The brother contracted the infection in Guerrero, an endemic area; he immigrated to the United States in 2003 with subclinical disease and lived with his sister for 1 year (2003–2004), during which time, he was infectious and passed the bacillus to his sister; and he sought care in early 2007, followed by the sister in 2012. The fact that the brother presented with one-and-half year history of illness, madarosis,

hair loss, heavy bacilli in tissue, and a high ANA titer (nonspecific) suggested considerable duration of infection. He could have been infectious in 2004 or 1 year before the onset of his illness in mid-2005. In support of this, previous authors[9] have shown that, in a well-documented case of *M. lepromatosis* infection, the patient exhibited heavy bacillary burden in the lymphatics 6 months before overt leprosy manifestation. Nasal mucosal presence of acid-fast bacilli, the purported route of leprosy transmission, has also been described in three reports of *M. lepromatosis* infection.[7,9,13] The likely incubation span for the sister's disease was about 8 years (2004–2012), well within the average prodromal period known for leprosy.[14]

By contrast, the role of the siblings' exposure to armadillos was uncertain in view that there have been no surveys on armadillos in Mexico to show their carriage of leprosy bacilli. Thus far, no armadillo infections with *M. lepromatosis* have been reported, although this deserves greater study. In the southern United States, a significant percentage of human cases of *M. leprae* infection share the same genotypes found in infected armadillos in the region.[15]

DLL is a diffuse non-nodular form of leprosy that is endemic in Mexico but rare elsewhere.[10,14,16,17] If untreated, such as during the preantibiotic era or due to misdiagnosis, DLL may progress to late-stage skin necrosis, ulceration, dermal vascular occlusion, and systemic bacillary burden. This is known as Lucio's phenomenon.[16,18] Previous studies involving Mexican leprosy patients[8] have associated *M. lepromatosis* with DLL. DLL represents a clinicopathologic diagnosis; thus, in view of the lack of skin nodules, the present sibling cases also have this feature. However, there was no evidence for Lucio's phenomenon in the present cases.

Reversal reaction and ENL are common leprosy complications that often present as severe inflammatory syndromes and are associated with exacerbation of nerve injury and functional impairment. These reactions may occur before, during, or after completion of antimycobacterial treatment.[19] The present cases showed severe and prolonged reactions, which presented as a challenge to clinical management. In this instance of family clustering, it is important to note that genetic factors are of great importance in host responsiveness to *M. leprae*, and presumably also to *M. lepromatosis*.[20] Substantial evidence also suggests that human genetic determinants are major risk factors for leprosy reactions.[21] Two cases of *M. lepromatosis* infection with severe ENL and Lucio's reaction as presenting signs have also been described.[9] With so few cases reported thus far, it remains to be seen whether severity of reactions is associated with *M. lepromatosis* infections. Also of note, the brother's positive syphilis tests and high ANA titer can be attributed to cross-reactive antibodies in lepromatous leprosy.[2,3,9]

Therefore, based on the above literature review and discussion, we summarize *M. lepromatosis* leprosy as the following: 1) *M. lepromatosis* causes a range of clinical manifestations comparable to typical *M. leprae* infection in patients in Mexico and elsewhere; 2) the clinical manifestations of patients vary remarkably as seen with *M. leprae* infections, and it remains to be determined whether differences between infections with *M. leprae* and *M. lepromatosis* can be recognized clinically; 3) the pathologic diagnosis is identical for both *Mycobacterium* species (species distinction requires DNA analysis); 4) the treatment with a multidrug regimen should be effective although more experience is needed. At this time, the identification of *M. lepromatosis* is primarily of epidemiologic value.

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