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Recurrent American Cutaneous Leishmaniasis

To the Editor: Leishmaniasis recidivans is an unusual clinical Old World disease primarily associated with *Leishmania tropica* (*1*). Recurrence of previously cured cutaneous leishmaniasis (CL) lesions is found in American CL, for which a specific nosologic form known of disease known as leishmaniasis recidiva cutis (LRC) has been identified. Although <30 cases of LRC have been reported from Brazil, Colombia, Peru and Ecuador; these cases were caused mainly by *L. braziliensis*, *L. amazonensis*, and *L. panamensis* (*2*). We report 7 cases of recurrent American CL caused by *L. guyanensis* in French Guiana.

Forty-eight military personnel who lived in France spent 3 months in French Guiana in 2004 and took part in a military training program in the rainforest for 15 days. Despite similar exposure conditions, American CL, confirmed by positive direct examination of Giemsa-stained tissue smears, developed in 21 persons. These patients were treated with 1 or 2 courses of either 3 intravenous or 2 intramuscular injections of pentamidine isethionate (4 mg/kg on alternate days). All lesions were cured 1–3 months after treatment had ended. Recurrence of the CL lesion was observed in 7 patients after a disease-free interval of 3–6 months (Table).

New lesions appeared on the edge of a healed scar for each patient, regardless of the location of the primary lesion (Table), and were diagnosed at Rennes University Hospital (positive direct examination or culture) in 2005. For positive cultures, *L. guyanensis* was identified by genomic and isoenzymatic characterization at the Centre National de Référence des *Leishmania*, Université de Montpellier, Montpellier, France. Patients were treated with 4 intravenous injections of pentamidine isethionate (4 mg/kg every other day) and were cured without recurrence within 2 years. No differences in age or underlying diseases were noted in patients with recurrent CL.

L. (*Viannia*) *guyanensis* is highly prevalent in several leishmaniasis-endemic areas of Brazil, Colombia, French Guiana, Guyana, Surinam, Peru, and Ecuador. This organism accounts for >95% of the 5 *Leishmania* species found in French Guiana, commonly causes localized LCL, and occasionally causes disseminated CL and mucocutaneous leishmaniasis (*3*). Dedet et al. reported that 6.8% of patients with CL caused by *L. guyanensis* had a recurrent lesion at the site of a previously cured lesion, which occurred after a mean interval of 7.3 months (*4*). A total of 33% of our patients had a cured primary infection in <3 months but they had a recurrence after a disease-free interval 3–6 months after treatment.

Additional information on such a recurrent form of CL is needed. Clinical symptoms in our patients were suggestive of LRC as described by Berlin (*1*), i.e., a recurrence at the site of an original ulcer, generally within 2 years and often on the edge of a scar. LRC may not be uncommon in the New World but rather underreported (*2*). Few cases of LRC have been reported; these were caused by *L. braziliensis*, *L. amazonensis*, and *L. panamensis* (*2*,*5*,*6*). In CL caused by *L. guyanensis*, borderline clinical symptoms prevent clear distinction of the recurrent form of LRC from early treatment failures or reinfections. In our patients, the risk for reinfection was excluded because the military personnel lived in France and left French Guiana several months before the recurrence.

Although pentavalent antimony is the recommended treatment for American CL, pentamidine isethionate is widely used in French Guiana. Retrospective analysis showed that 5%–25% of early treatment failures

occurred after 1 or 2 intramuscular injections of 4–7 mg/kg of pentamidine isethionate, depending on different risk factors (*7,8*). Our observational study was not designed to evaluate treatment efficiency; we observed 2 (9.5%) of 21 early relapses and 7 (33%) of 21 late-onset recurrences in this series. Although we lacked statistical power because of small numbers, a difference was observed in recurrence by treatment method in 7 (44%) of 16 with recurrent disease who received 3 intravenous pentamidine isethionate injections compared with 0 (0%) of 5 who received 2 intramuscular injections. Re-treatment with a regimen of 4 intravenous injections of pentamidine, under medical surveillance because of possible adverse effects, cured the disease. Physicians in countries in which *L. guyanensis* is endemic should be aware of these complicated forms of CL after treatment, forms that prompt long-term follow-up and evaluation of specific therapeutic protocols.

Finally, the mechanism of late-recurring leishmaniasis is poorly understood. Mendonça et al. suggested that clinical cure of American CL is rarely associated with sterile cure (i.e., elimination of the parasite) (*9*). Immunologic data based on skin hypersensitivity and histopathologic and immunohistochemical findings support the concept that LRC is a late-onset reactivation after persistence of living parasites around or in cured leishmaniasis by as-yet unknown stimuli such as local trauma (2 of our patients reported chronic lesions of the chin caused by a razor blade and 2 others had chronically scratched the scar lesion on their ears) or corticosteroid, and after an incomplete host immune response to an earlier episode (*2, 5,10*). Further immunologic studies of patients and identification of genetic characteristics of *L. guyanensis* are needed to address this question.

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Table. Epidemiologic characteristics, strain identification, and treatment of 21 cases of American cutaneous leishmaniasis, French Guiana, 2004–2005*

	Primary infection				Leishmaniasis recidiva cutis			
Case no.	Lesion(s), location (no.)	PI treatment†	Time to healed lesions, mo	Disease-free interval, mo	Direct examination	Strain identification	PI treatment	Outcome
1	Thorax (1)	IV, 4 mg/kg on alternate days × 3	1	4	+	*Leishmania guyanensis* MON-45	IV, 4 mg/kg on alternate days × 4	Cured
2	Right forearm (1)	IV, 4 mg/kg on alternate days × 3	3	6	+	*L. guyanensis* MON-45	IV, 4 mg/kg on alternate days × 4	Cured
3	Left leg (1) and chin (3)	IV, 4 mg/kg on alternate days × 3	1	4	+	Negative culture	IV, 4 mg/kg on alternate days × 4	Cured
4	Chin (3)	IV, 4 mg/kg on alternate days × 3	1	4	+	Negative culture	IV, 4 mg/kg on alternate days × 4	Cured
5	Behind left ear (1)	IV, 4 mg/kg on alternate days × 3	1	3	+	*L. guyanensis* MON-131	IV, 4 mg/kg on alternate days × 4	Cured
6	Left ear (1)	IV, 4 mg/kg on alternate days × 3	1	6	+	Negative culture	IV, 4 mg/kg on alternate days × 4	Cured
7	Right ankle (5)	IV, 4 mg/kg on alternate days × 3	2.5	4	+	Negative culture	IV, 4 mg/kg on alternate days × 4	Cured
8–21	Various	IV, 4 mg/kg on alternate days × 3 (for 9 patients) or IM, 4 mg/kg on alternate days × 2 (for 5 patients)†	1–3	–	–	–	–	–

*PI, pentamidine isethionate; IV, intravenous; IM, intramuscular.
†IV versus IM administration of pentamidine isethionate was not associated with recurrent forms.

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Leprosy as Immune Reconstitution Inflammatory Syndrome in HIV-positive Persons

To the Editor: More than 2 decades ago, when HIV was first detected, many investigators predicted the rise of leprosy secondary to opportunistic infection (*1*). Recently, the phenomenon of immune reconstitution inflammatory syndrome (IRIS), or leprosy reversal response, has received attention. IRIS often occurs secondary to initiating highly active antiretroviral therapy (HAART). The first indications of an interaction between HIV and *Mycobacterium leprae* occurred only recently, with the identification of IRIS after initiation of HAART in patients with HIV and previously undetected leprosy. A review by Pustianowski et al. discusses the paradox of HIV and leprosy with IRIS (*2*). In addition, Lawn et al. described the first case of IRIS after the onset of HAART in a patient who had tuberculoid leprosy that was never confirmed by molecular analysis (*3*).

Multiple reports (*4*–*7*) unmasked subclinical Hansen disease (*M. leprae* infection) occurring with HAART or spontaneously (*8*). In case reports by Lu et al. (*6*) and Sharma et al. (*7*), leprosy was associated with erythema nodosum leprosum. Pereira et al. discovered that patients known to have HIV and leprosy, when treated with HAART manifested a type 1 reversal reaction, acute leprosy inflammatory episode (*4*), or IRIS. We describe the first, to our knowledge, 2 cases in the United States of HIV and leprosy infections in which IRIS has occurred after HAART initiation and which has been confirmed by molecular analysis.

Three skin-biopsy samples, 2 from patient 1 and 1 from patient 2, were analyzed to confirm the presence of *M. leprae*. Patient 1 met the diagnostic criteria for leprosy according to biopsy result; patient 2's case was compatible with such criteria. Each patient was treated for leprosy, and each responded favorably. The purpose of our case study was to confirm *M. leprae* DNA in skin samples. The skin specimens were paraffin-embedded slides. DNA was extracted by standard molecular biologic methods that used xylene. PCR amplified the *M. leprae* heat shock protein 65 gene (*hsp65*). After amplification, restriction fragment-length polymorphism (RFLP)–polyacrylamide gel electrophoresis (PAGE) was performed with *Hae*III (*6*).

Patient 1 was a 60-year-old Hispanic man who was first evaluated in Los Angeles, California, with skin lesions covering >50% of his body. He reported having erythematous scaly plaques that had been waxing and waning for several months. Several skin biopsy samples were taken, and an HIV test was conducted; results showed that he had lepromatous leprosy and was HIV positive. Biopsy specimens were both Fite stain positive for numerous acid-fast bacilli. Three months after HAART was initiated, repeat skin biopsy samples were taken from nodules that had recently developed on his right arm and torso. Histologic assessment showed Fite stain–positive granulomatous dermatitis with many foamy cells. He was treated for leprosy and is continuing HAART.

Patient 2 was a 37-year-old West African black man from Burkina Faso who was evaluated in New York for gram-negative bacteremia. He was admitted and treated for disseminated salmonellosis and was found to be HIV positive. His T-lymphocyte count was 7/μL. He was promptly prescribed HAART and responded well to treatment: his T-cell count rose to 112/μL during 5 months and is currently >700/μL. Within 2 years of HAART initiation, multiple anesthetic, hypopigmented skin macules that failed to resolve over 6 months