Two Patients Coinfected with *Mycobacterium leprae* and Human Immunodeficiency Virus Type 1 and Naïve for Antiretroviral Therapy Who Exhibited Type 1 Leprosy Reactions Mimicking the Immune Reconstitution Inflammatory Syndrome[▽]

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Two case reports of patients with human immunodeficiency virus type 1 (HIV-1) infection who developed leprosy are presented. Both developed type 1 leprosy reactions in the absence of antiretroviral therapy. Reactions have been described for a number of HIV-1- and *Mycobacterium leprae*-coinfected patients and have been considered to be part of an immune reconstitution inflammatory syndrome (IRIS) since the reactions were usually linked to the administration of highly active antiretroviral therapy. The reports of our two patients suggest that the type 1 reactions in patients with leprosy and HIV may not always be an IRIS manifestation but may be akin to the classical reactional state described for the natural course of leprosy infection, which occurs in leprosy patients due to the fluctuations of the antimycobacterial immune response, whether they are coinfecting with HIV or not.

CASE REPORT

Case 1. The first patient, a 36-year-old woman, had a 2-year history of erythema, edema, and paresthesia on the right cheek. On examination, an infiltrated, erythematous plaque on the right malar region with altered thermal sensitivity was seen (Fig. 1A). Leprosy and lupus erythematosus were considered in the differential diagnosis. The laboratory investigation for the latter was negative, but Mitsuda's reaction was positive, and the lesion's histopathology showed a chronic granulomatous nodular dermatitis with edema permeating the inflammatory infiltrate (Fig. 2A). Staining for alcohol-acid-fast bacilli (AAFB) (Fite-Faraco) and fungi (Grocott) was negative. The diagnosis of borderline tuberculoid leprosy with a type 1 leprosy reaction was made. Further tests showed that the patient was human immunodeficiency virus (HIV) positive and in the eighth week of pregnancy. The viral load was undetectable, and the CD4⁺ T-cell count was 120/mm³. Highly active antiretroviral therapy (HAART) was initiated (zidovudine, lamivudine, and nevirapine) during the fourth month of pregnancy and maintained until after delivery. At the same time, the patient was treated for paucibacillary leprosy for a period of 6 months, using the WHO guidelines for the therapy of this disease, after which the lesion had significantly improved. There were no detectable complications during the pregnancy. At postpartum, the plasma viral load was still undetectable,

and the CD4⁺ T-cell count was up to 301/mm³. Three months after delivery and 2 months after cessation of leprosy therapy, the lesion presented signs of activity again, and the patient was started on a 6-month treatment with prednisone, at 20 mg/day initially and then gradually reduced to 5 mg/day. The patient retained some paresthesia and mild erythema on the right cheek only; histopathology showed a chronic granulomatous infiltrate with neural "aggression," with negative staining for AAFB and fungi. The neonate was given zidovudine and did well, with an undetectable viral load and a normal CD4⁺ T-cell count. He remained free of any skin lesion for the first year of life.

Case 2. The second patient, a 33-year-old man, had a 2-year history of a hypopigmented lesion on the right forearm. Six months before admission, he developed five new, slightly tender erythematous lesions. The patient had known that he was infected with HIV for 8 years, but he had never sought any medical treatment either for HIV infection or for opportunistic infections. Physical examination showed six large hypopigmented, erythematous, and desquamating (scaling) plaques, with raised margins, on the forearm (Fig. 1B), and a painful and thickened left ulnar nerve. The histamine test performed on the lesions to detect damage to the cutaneous nerves was altered. Nails of the hands and feet showed signs of chronic onychomycosis. Mitsuda's reaction was positive (10 mm) after 48 h (Fernandez reaction) and after 28 days. Histopathology revealed a chronic granulomatous tuberculoid dermatitis (Fig. 2B), which was negative for AAFB by Fite-Faraco staining. A diagnosis of borderline tuberculoid leprosy with a type 1 leprosy reaction was made. The HIV type 1 (HIV-1) viral load was 85,400 copies/ml, and the CD4⁺ T-cell count was 353/mm³. According to the Brazilian guidelines, he was not yet eligible for antiretroviral treatment. The 6-month WHO-recommended treatment for paucibacillary leprosy was initiated,

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FIG. 1. (A) Erythematous and edematous plaque on the right cheek of patient 1. (B) Erythematous, well-circumscribed plaque on the right forearm of patient 2.

with routine follow-up. This resulted in a marked improvement of the lesions. After that, the patient progressively developed a persistent cough, weight loss, and worsening of his general condition. The plasma viral load increased to 1,200,000 copies/ml, and the CD4⁺ T-cell count decreased to 251/mm³. HAART was initiated with good compliance. The leprosy lesions continued to improve, and after 1 year, the patient had only one slightly erythematous and hypopigmented lesion, which on histopathology showed a regressive chronic granulomatous nodular infiltrate.

Discussion. Leprosy is a chronic infection caused by *Mycobacterium leprae* leading to a spectrum of clinical manifestations, which are determined, at least in part, by the host's cell-mediated immune response to the mycobacterium. It is therefore expected that the extent and quality of the cellular immune status of the patient should strongly influence the course of the disease. This view is supported by the observation that pregnancy is associated with relapses of leprosy in previously treated and presumably cured women (5, 11). However, the association of leprosy with other immunosuppressed con-

ditions is not so evident. There are only scanty reports of leprosy in renal transplant recipients, despite the increasing number of transplants performed in areas where leprosy is highly endemic (16). There have been a number of publications on leprosy and HIV coinfection. The level of HIV-associated immunosuppression in these patients seemed neither to significantly modify the natural course of leprosy nor to predispose patients to clinical leprosy (12, 13). Anti-*M. leprae* immunity and granuloma formation could be detected even when CD4⁺ T-cell counts were low (15). However, with the advent of HAART, a new syndrome called immune reconstitution inflammatory syndrome (IRIS) has been diagnosed in previously immunosuppressed patients in association with subclinical or clinical opportunistic infections. It is characterized by the appearance or worsening of inflammatory responses related to these organisms in patients presenting with some degree of immunological recovery (6). Reactional states have been described recently for a small number of *M. leprae*- and HIV-coinfected patients and linked to the introduction of HAART (4, 7, 10, 13, 14, 17, 19), and as such, they were diagnosed as IRIS. However, in the two *M. leprae*- and HIV-

FIG. 2. (A) Histopathology of a biopsy from the lesion of patient 1, showing a small tuberculoid granuloma in the dermis, dissociated by edema, next to a hair follicle. The arrows delimitate an area with a small collection of epithelioid histiocytes that are surrounded by a mantle of lymphocytes. The lesion was stained with hematoxylin-eosin stain. Original magnification, $\times 200$. (B) Histopathology of a biopsy from the lesion of patient 2, showing well-organized tuberculoid granulomas in the dermis. The arrows delimitate an area rich in epithelioid histiocytes, with numerous infiltrating lymphocytes at the periphery. The lesion was stained with hematoxylin-eosin stain. Original magnification, $\times 100$.

coinfected patients reported herein, type 1 leprosy reactions occurred in the absence of any antiretroviral therapy. Type 1 leprosy reactions are most commonly seen in borderline tuberculoid patients, as in the patients reported here, and are attributed to a "spontaneous" flare in the cellular immune reactivity against *M. leprae* antigenic determinants that switches on local Th1 immune responses (2). Thus, although anecdotal, these case reports show that IRIS due to HAART is not always the only cause of an increase in cell-mediated immune reactivity in *M. leprae*- and HIV-coinfected patients. The classical reactional state described for the natural course of leprosy infection may happen as well. Despite its rarity, this observation agrees not only with the remarkably low incidence of leprosy in HIV-infected or iatrogenically immunosuppressed patients but also with the observation that HIV does not seem to impair the local anti-*M. leprae* immune response (15). Even though the precise cellular immune mechanisms involved in the pathogenesis of type 1 leprosy reactions are still unclear, it is quite remarkable that these reactions, as well as a positive Mitsuda test, can occur in an HIV-1-infected patient with severely compromised cell-mediated immunity.

Among the possible mechanisms that have been suggested to underlie IRIS in HIV- and *M. leprae*-coinfected patients receiving HAART is the switch towards *M. leprae*-induced Th1 inflammation. However, in this setting, it would not be spontaneous but would be triggered by HAART (18). Alternatively, if one assumes that there is some degree of systemic anti-*M. leprae* immunosuppression in coinfecting patients (15), the underlying mechanism could then be the recovery of the anti-*M. leprae* immune response induced by HAART. Whatever the underlying mechanisms, both IRIS and classical type I leprosy reactions are characterized histologically by a dominant Th1 reactivity in the lesions (3, 9). These observations suggest that the host response to *M. leprae* is complex and may also rely on other mechanisms, e.g., innate immunity, and not solely on the acquired cell-mediated immune response. In this regard, the paradox of the apparently little impact of HIV on the natural history of leprosy in contrast with its profound effect on tuberculosis has been reviewed recently (18). Differences in the characteristics of the granulomatous response have been suggested as a possible explanation, as granulomas in leprosy are "less active" than those in tuberculosis, with a lower turnover rate of immune-activated cells, which provides for relatively lower levels of target cells for local HIV replication and spread (18).

Lastly, the case reported herein is, to the best of our knowledge, the first documentation of *M. leprae* and HIV coinfection in a pregnant woman. The woman was successfully treated with the WHO-recommended regimen for the therapy of paucibacillary leprosy, despite marked HIV-related ($120 \text{ CD4}^+ \text{ T cells/mm}^3$) and physiological, pregnancy-related immunosuppression. The increase in activity of the lesion after delivery was probably due to a physiological immune restoration after delivery and not the result of the 8-month HAART. She gave birth to a healthy child, who up to the last follow-up (1 year old) was free of HIV and leprosy. Both patients responded

adequately to the antimycobacterial therapy, reinforcing the impression that also in leprosy, as in other chronic granulomatous infectious diseases, such as tuberculosis and paracoccidioidomycosis, standard anti-infectious therapy regimens can be successfully used for most HIV-1-coinfected patients (1, 8).

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REFERENCES

- Benard, G., and A. J. S. Duarte. 2000. Paracoccidioidomycosis: a model for evaluation of the effects of human immunodeficiency virus infection on the natural history of endemic tropical diseases. *Clin. Infect. Dis.* **31**:1032–1039.
- Britton, W. J., and D. N. S. Lockwood. 2004. Leprosy. *Lancet* **363**:1209–1219.
- Cooper, C. L., C. Mueller, T. A. Sinchaisri, C. Primez, J. Chan, G. Kaplan, S. M. Young, I. L. Weisman, B. R. Bloom, T. H. Rea, et al. 1989. Analysis of naturally occurring delayed-type hypersensitivity reactions in leprosy by in situ hybridization. *J. Exp. Med.* **169**:1565–1581.
- Couppié, P., S. Abel, H. Voinchet, M. Roussel, R. Hélénon, M. Huerre, D. Sainte-Marie, and A. Cabié. 2004. Immune reconstitution inflammatory syndrome associated with HIV and leprosy. *Arch. Dermatol.* **140**:997–1000.
- Duncan, M. E., R. Melsom, J. M. Pearson, and D. S. Ridley. 1981. The association of pregnancy and leprosy. I. New cases, relapse of cured patients and deterioration in patients on treatment during pregnancy and lactation—results of a prospective study of 154 pregnancies in 147 Ethiopian women. *Lepr. Rev.* **52**:245–262.
- Goebel, F. D. 2005. What's new in HIV/AIDS? Immune reconstitution inflammatory syndrome (IRIS)—another new disease entity following treatment initiation of HIV infection. *Infection* **33**:43–45.
- Goodless, D. R., A. L. Vician, R. J. Pardo, and P. Ruiz. 1994. Borderline tuberculoid Hansen's diseases in AIDS. *J. Am. Acad. Dermatol.* **30**:866–869.
- Kassim, S., M. Sassan-Morokro, A. Ackah, L. Y. Abouya, H. Digbeu, G. Yesso, I. M. Coulibaly, D. Coulibaly, P. J. Whitaker, R. Doorly, et al. 1995. Two-year follow-up of persons with HIV-1- and HIV-2-associated pulmonary tuberculosis treated with short-course chemotherapy in West Africa. *AIDS* **10**:1185–1191.
- Lawn, S. D., L. G. Bekker, and R. F. Miller. 2005. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect. Dis.* **5**:361–373.
- Lawn, S. D., C. Wood, and D. N. Lockwood. 2003. Borderline tuberculoid leprosy: an immune reconstitution phenomenon in a human immunodeficiency virus infected person. *Clin. Infect. Dis.* **36**:e5–e6.
- Lyde, C. B. 1997. Pregnancy in patients with Hansen disease. *Arch. Dermatol.* **133**:623–627.
- Naafs, B. 2000. Leprosy and HIV: an analysis. *Hansen Int.* **25**:60–66.
- Pereira, G. A. S., M. A. M. Stefani, A. J. Araújo Filho, L. C. S. Souza, G. P. Stefani, and M. T. C. Martelli. 2004. Human immunodeficiency virus type 1 (HIV-1) and *Mycobacterium leprae* co-infection: HIV-1 subtypes and clinical, immunologic, and histopathologic profiles in a Brazilian cohort. *Am. J. Trop. Med. Hyg.* **71**:679–684.
- Pignataro, P., A. S. Rocha, J. A. C. Nery, M. A. Sales, A. M. H. Ferreira, V. Valentim, and P. N. Suffys. 2004. Leprosy and AIDS: two cases of increasing inflammatory reactions at the start of highly antiretroviral therapy. *Eur. J. Clin. Microbiol. Infect. Dis.* **23**:408–411.
- Sampaio, E., J. R. Caneshi, J. A. Nery, N. C. Duppre, G. M. Pereira, L. M. Vieira, A. L. Moreira, G. Kaplan, and E. N. Sarno. 1995. Cellular immune response to *Mycobacterium leprae* infection in human immunodeficiency virus-infected individuals. *Infect. Immun.* **63**:1848–1854.
- Shish, H.-C., T.-W. Hung, J.-D. Lian, S.-M. Tsao, N.-K. Hsieh, and J.-H. Yand. 2005. Leprosy in a renal transplant recipient: a case report and literature review. *J. Dermatol.* **32**:661–666.
- Trindade, M. A. B., M. I. P. Manini, J. H. Masetti, M. A. Leite, M. D. Takahashi, and B. Naafs. 2005. Leprosy and HIV co-infection in five patients. *Lepr. Rev.* **76**:162–166.
- Ustianowski, A. P., S. D. Lawn, and D. N. J. Lockwood. 2006. Interactions between HIV infection and leprosy: a paradox. *Lancet Infect. Dis.* **6**:350–360.
- Visco-Comandini, U., B. Longo, T. Cuzzi, M. G. Paglia, and G. Antonucci. 2004. Tuberculoid leprosy in a patient with AIDS: a manifestation of immune restoration syndrome. *Scand. J. Infect. Dis.* **36**:881–883.