Leprosy Reversal Reaction as Immune Reconstitution Inflammatory Syndrome in Patients with AIDS

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We report 2 instances in which reactional borderline leprosy manifested itself as an immune reconstitution phenomenon in patients with acquired immunodeficiency syndrome. We discuss the clinical, laboratory-based, histopathologic, and immunohistochemical characteristics of both patients. Furthermore, we review similar reports from the literature.

Ten percent to 25% of patients who commence HAART experience immune reconstitution inflammatory syndrome (IRIS), which is characterized by the presence of clinical manifestations of previously latent infection after improvement of the immune system resulting from antiretroviral therapy [1, 2]. There have been reports of tuberculosis [3, 4], herpes zoster [5], cytomegalovirus infection [6], Mycobacterium avium complex infection [7], hepatitis B [8] and C [9], and other infections described as immune reconstitution processes. Leprosy has been described as a manifestation of IRIS in few instances [10–18]. We describe 2 patients with AIDS who developed reactional borderline leprosy as a manifestation of IRIS after they started receiving antiretroviral treatment, and we review reports regarding similar patients from the literature.

Reports. Patient 1 was a 32-year-old black Brazilian man who received a diagnosis of pulmonary mycobacteriosis after he presented with weight loss, dyspnea, and fever. A sputum sample was obtained for culture, from which Mycobacterium kansasii (a Mycobacterium species other than Mycobacterium tuberculosis) was isolated. His HIV-1 serologic test result was positive, with blood CD4+ lymphocyte count of 14 cells/mm³ and an HIV load of 213,000 copies/mm³. Treatment with rifampin, isoniazid, and pyrazinamide plus azithromycin was started and resulted in resolution of pulmonary symptoms. Antiretroviral treatment, with zidovudine, lamivudine, and nelfinavir, was introduced at the same time.

Approximately 2 months later, the patient presented with disseminated, raised, warm, infiltrated, and hyperesthetic skin lesions. The centers of some lesions were apparently normal skin, which is consistent with typical cases of borderline leprosy. Cutaneous lesions were hyperesthetic, and the ulnar and lateral popliteal nerves were thickened. He also developed lateral popliteal neuritis that resulted in a left foot drop. Skin biopsy revealed diffuse granulomatous inflammation associated with vacuolated histiocytes, epithelioid cells, and occasional nodular epithelioid granuloma, with rare acid-fast bacilli—findings consistent with borderline tuberculoid leprosy. Immunohistochemical study revealed a marked predominance of CD4+ lymphocytes over CD8+ lymphocytes. The lepromin test and slit-skin smear results were negative. Diagnosis of borderline tuberculoid leprosy with reversal reaction was established.

At this time, the patient’s CD4+ lymphocyte count had increased to 172 cells/mm³, and his HIV load had decreased to 69,000 copies/mm³. He was initially treated with nonsteroidal anti-inflammatory drugs, as recommended by his general physician. Dapsone and clofazimine were added to his previous treatment regimen. Two months later, with an improvement of his clinical features, prednisone (0.5 mg/kg per day) was introduced into the patient’s treatment regimen. The patient did not present with any complications other than mycobacterial coinfection. Approximately 3 months after the commencement of therapy, the patient’s condition improved, with a marked reduction of skin infiltration and edema and slow recovery of strength in the left foot.

Patient 2 was a 53-year-old white Brazilian man who had been HIV positive for 10 years and who had a 2.5-year history of a nonpainful plaque on the right lumbar region (figure 1A). He underwent dermatological examination and skin biopsy. At this time, his CD4+ lymphocyte count was 104 cells/mm³, and antiretroviral treatment with zidovudine, lamivudine, and efavirenz was started. Two months later, the lumbar lesion became erythematous and edematous (figure 1B), and the patient developed a new hyperesthetic lesion on his right leg that was associated with paresthesia of the right leg and foot. He also developed a loss of strength in the right foot. His ulnar and lateral popliteal nerves were thickened. His CD4+ lymphocyte count had increased to 235 cells/mm³, and the HIV load was...
undetectable. The first skin biopsy of the lumbar lesion was performed before the commencement of antiretroviral treatment, revealing a granulomatous reaction comprising lymphocytes and epithelioid cells—a typical tuberculoid granuloma (figure 2A). Immunohistochemical study revealed few CD4+ lymphocytes in the inflammatory infiltrate (data not shown).

After the commencement of antiretroviral treatment, a second biopsy was performed at the same site; there was an increase in the tuberculoid granulomatous infiltrate, which comprised lymphocytes, epithelioid cells, and Langhans giant cells, with intercellular edema (figure 2B). There was also a higher expression of CD4+ lymphocytes in the immunohistochemical study, compared with a previous biopsy specimen. The lepromin test result was positive (induration diameter, 7 mm). Histologic analysis of the site of the lepromin test revealed a tuberculoid granulomatous reaction on the dermis. The patient received a diagnosis of reactional tuberculoid leprosy, and treatment with dapsone, clofazimine, and rifampin was started. He was also treated with prednisone (initially at 0.5 mg/kg per day, with slow tapering of the dosage during a 9-month period). The lesions and symptoms of neuritis improved.

**Discussion.** No increase in the prevalence of multibacillary forms of leprosy among HIV-infected patients has been reported [19]. Although a shift in the spectrum of leprosy from the tuberculoid to the lepromatous form might be expected, studies have shown that HIV-1 coinfection does not alter either the clinical or the histological spectrum of leprosy [19].

The diagnosis of IRIS depends on the existence of immunopathological damage associated with the reversal of immunosuppressive processes [1]. In HIV-infected patients, as the immune function is restored by antiretroviral treatment, there is an increase in inflammatory response, leading to clinical manifestations of previously latent infections [2]. IRIS has been described in HIV-infected patients who develop mycobacterial infections (e.g., tuberculosis [3, 4] and *M. avium* complex infection [7]) or other infections during or shortly after commencement of antiretroviral therapy.

In both patients described here, the reconstitution of immune functions after the initiation of antiretroviral treatment brought an intense inflammatory response against *Mycobacterium leprae*, which was previously not apparent, possibly because of the patients’ profound immunosuppression. The increased response against *M. leprae* could be due to the increase in memory CD4+ lymphocytes that had specific T cell receptors to mycobacterial antigens, as suggested in previous reports regarding infection with *M. avium* complex [7]. Interestingly, patient 1 presented with clinical manifestations of *M. kansasi* infection when his serum CD4+ cell counts were still low, and after the introduction of antiretroviral therapy and the increase in his CD4+ cell count, he developed active leprosy with reversal reaction. Cellular immune response, however, was not totally reconstituted, because the lepromin reaction was negative. An explanation for this finding could be that the response at lesion sites was more intense or precocious in relation to the lepromin injection site. CD4+ and CD8+ cells sensitized to *M. leprae* could be sequestered in skin lesions, thus not increasing significantly at the lepromin injection site.

In patient 2, reconstitution of the immune system was demonstrated histologically by the presence of a more intense granulomatous reaction, with an increase in the CD4+ cell infiltrate. Pre- and post-HAART histopathologic analyses confirmed the importance of CD4+ cells in the immune response to leprosy. The increase in the number of circulating CD4+ cells after the introduction of HAART in this patient caused a significant CD4+ lymphocyte tissue infiltrate, which was associated with signs of reactional leprosy. In this patient, the positive lepromin test result and histologic analysis of the injection site revealed a granulomatous reaction.

In spite of blood CD4+ lymphocyte depletion in HIV-infected patients, there has been a previous report of skin biopsy of a
leprosy lesion in HIV-infected patient in which half of the lesional cells were CD4+ [20]. Another study analyzed the histologic features of 12 HIV–M. leprae–coinfected patients and found a predominance of CD4+ lymphocytes, with few CD8+ lymphocytes in the infiltrate [21]; this is consistent with the immunohistochemical findings for the patients we describe. The increase in cell-mediated immunity was histologically evident on the basis of a granulomatous response with a predominance of CD4+ cells.

Concurrent leprosy and HIV infection has been reported previously. In one report, 4 of 5 patients with concurrent disease developed type 1 reactions; in 1 case, this happened 6 months after the end of leprosy treatment. Two other patients developed type 1 reaction while receiving leprosy treatment after 10 and 14 months after the introduction of HAART. The final patient developed the reaction 2 months after the commencement of HAART and at the time of diagnosis of leprosy. Serial serum CD4+ cell counts were not available, but the authors highlighted that clinical manifestations may have been caused by immunological changes associated with HIV infection and HAART [22].

In addition to the 2 cases described here, there have been 14 other reports of leprosy as a manifestation of IRIS [10–18]. The reports are listed in table 1. In all reports, patients were originally from areas of endemicity (Uganda, French Guiana, Brazil, and India).

In one report, 6 patients with concurrent HIV infection and leprosy were observed. After the introduction of HAART, 2 of these patients (patients 8 and 9) developed leprosy type 1 reaction as a manifestation of IRIS (table 1). The 2 patients who developed IRIS had a larger increase in their CD4+ cell counts after HAART (3.6- and 2.8-fold increases for patients 8 and 9, respectively) than did the 4 patients who did not develop leprosy type 1 reaction (1.2–1.8-fold increase; data not shown) [14]. In all other reported cases of leprosy as a manifestation of IRIS, there was a significant change in the CD4+ cell count after the commencement of HAART (range, 1.6–12.8-fold increase). This could suggest a higher risk of developing IRIS in HIV–M. leprae–coinfected patients with rapid increases in the CD4+ cell count. However, for other coinfections, the size of the increase in the CD4+ cell count has been considered a contradictory risk factor for the development of IRIS [23–25].

Another risk factor for the development of IRIS is the commencement of HAART in patients with advanced immunodeficiency [26]. This aspect was observed in all reported cases of IRIS associated with leprosy. Type 1 reactions were triggered within 6 months after the introduction of HAART and the increase of CD4+ cell counts. Thus, follow-up for these HAART recipients is very important to avoid the occurrence of disabilities.

It is interesting to notice that, in the majority of cases reported (15 of 16, including the 2 patients we describe), the clinical manifestation of inflammatory syndrome after the start of HAART was leprosy type 1 reaction. Type 1 reactions occur during the course of leprosy if there is an increase in cellular immune response. Type 2 reactions are mediated by immunocomplexes with high TNF-α levels and happen in patients with multibacillary disease. IRIS has not been described in patients with multibacillary diseases (borderline lepromatous and lepromatous forms); this is probably because the patients are anergic against these mycobacteria. Thus, as HAART increases...

Figure 2. A, Skin biopsy of the lumbar lesion with typical tuberculobous granuloma in patient 2, before commencement of HAART (hematoxilin-eosin stain; original magnification, ×40). B, Intense tuberculobous infiltrate, comprising lymphocytes, epithelioid cells, and Langhans giant cells, in patient 2 two months later, after the commencement of HAART (hematoxilin-eosin stain; original magnification, ×100).
cellular immune response, it is more likely to trigger type 1 reactions.

Patients with HAART-associated type 1 reactions can present with uncommon clinical features, such as ulceration of lesions [27]. Type 1 reactions also rarely occur in patients with concurrent HIV infection and leprosy who are not receiving HAART. In these patients, type 1 reactions may be due to the spontaneous increase in cell-mediated immunity that occurs during the natural course of leprosy [28]. The management of classic type 1 reactions and IRIS are similar, but IRIS could be considered a useful marker of improvement of cellular immunity in patients with AIDS.

Although the incidences of tuberculosis and of infection with Mycobacterium species other than M. tuberculosis have increased during the AIDS epidemic, a high rate of concurrent leprosy in these individuals has not been observed. The introduction of HAART changed the natural history of leprosy in HIV-infected patients. Reactional leprosy type 1 can be considered a marker of IRIS in HIV-infected patients who are receiving HAART.

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References


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