Immune Reconstitution Inflammatory Syndrome Associated With HIV and Leprosy

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Background: Immune reconstitution inflammatory syndrome (IRIS) is an unusual inflammatory reaction to an opportunistic infection that occurs in human immunodeficiency virus (HIV)–positive patients with profound immunosuppression during the reconstitution of the immune system in the initial months of highly active antiretroviral treatment.

Observations: We describe 3 cases of leprosy occurring in patients treated with a combination of 3 antiretroviral drugs who fulfilled the criteria for IRIS. A reactional state occurred in all 3 cases. Two of the 3 patients presented an unusual ulcersous progression of the lesions not generally observed in cases of leprosy. The outcome was favorable in all 3 cases. The frequency of IRIS associated with leprosy in French Guiana and Martinique is estimated at 3 cases per 1000 HIV-positive patients receiving highly active antiretroviral treatment.

Conclusion: Leprosy should be recognized as an IRIS-associated infection with possibility of atypical presentation.

Arch Dermatol. 2004;140:997-1000

The introduction of highly active antiretroviral treatment (HAART) has led to the emergence of a new clinical syndrome, immune reconstitution inflammatory syndrome (IRIS). This syndrome affects human immunodeficiency virus (HIV)–positive patients at an advanced stage of the disease (CD4 lymphocyte counts <200/µL). In these patients, clinical signs of inflammation appear mostly in association with opportunistic infection, when HAART triggers a generalized immune activation during the transition phase of viral load suppression and CD4 lymphocyte counts increase. The infectious agent may have been treated previously or may have been present in a latent state, but is always present in the patient’s body before the introduction of antiretroviral treatment. In the first situation, the opportunistic infection, which is initially improved by specific treatment, then leads to generalized or localized inflammation. In the second situation, the opportunistic infection is first detected when the CD4 lymphocyte count increases.

In the first reported cases of IRIS, in 1998, the infectious agents were mycobacteria (Mycobacterium avium complex and Mycobacterium tuberculosis). The syndrome has since been described in association with more than a dozen different infectious conditions, with herpes zoster (41 cases), M tuberculosis (37 cases), M avium complex (32 cases), and cytomegalovirus (22 cases) in 73% of the first 182 published cases. In some cases, IRIS appears in the absence of opportunistic pathogens and manifests itself as an autoimmune or granulomatous disease, of which sarcoidosis is the most frequent (10 cases).

The first case of leprosy diagnosed after HAART initiation was reported in 2003. We present the cases of 3 patients from a cohort followed up for HIV infection in French Guiana and Martinique. HAART led to the diagnosis of reactional leprosy, complicated by an unusual ulcerous progression in 2 of the 3 cases.

Report of Cases

Case 1

The patient was a 54-year-old Haitian man admitted to the Centre Hospitalier de Cayenne in May 2002 for bacterial pneumonia.
On admission, HIV infection was diagnosed by enzyme-linked immunosorbent assay testing and Western blotting. Clinical examination revealed prurigo of the limbs and oral candidiasis, with no other dermatologic lesions. The pneumonia resolved with antibiotic therapy. The patient’s CD4 cell count was 87/µL and his viral load was 19000 copies/mL.

Tritherapy with zidovudine, lamivudine, and abacavir was initiated in June 2002. Compliance was good despite poor digestive tolerance initially. On the 30th day of HAART, the viral load had decreased to 650 copies/mL.

On the 56th day of HAART, the patient consulted for cutaneous lesions that had appeared about 2 weeks previously. On clinical examination, the patient had no fever and was in good general condition. Dermatologic examination revealed a ring-shaped, papulous, edematous lesion of 5 cm in diameter on the left flank (Figure 1) and an 8-cm lesion along the major axis of the anterior aspect of the left thigh. The 2 lesions were hypoesthetic. There was also hypertrophy of the left cubital nerve. The clinical findings led to the diagnosis of tuberculoid leprosy associated with a type 1 reactional state. Histologic studies confirmed the diagnosis of leprosy, which the pathologist classified as borderline borderline, on the basis of the presence of an Unna band and the positive Ziehl-Neelsen staining of large numbers of Hansen bacilli grouped in globules with a bacillary index of 3. The CD4 lymphocyte count had increased to 257/µL.

Treatment was initiated with 600 mg of rifampicin once monthly, and 100 mg of dapsone plus 100 mg of clofazimine once daily. After 3 months of antileprosy treatment the progression of leprosy was unusual because the cutaneous lesions became completely ulcerous within a few days (Figure 2 and Figure 3). Additional biopsies were performed. Histologic examination provided evidence of progression of the lesions toward a tuberculoid mode, with the presence of numerous epithelioid and giant cells and mature granulomas and an absence of Ziehl-Neelsen staining. Necrotic lesions of classic leukocytic vasculitis were also observed.

The antiretroviral and antileprosy treatments were continued. The ulcerated lesions were covered with sterile dressings to prevent infection. The ulceration progressed favorably, with the development of a new epithelium on the lesions within 3 months.

CASE 2

The patient was a 40-year-old man of French Guianan origin, diagnosed as HIV-positive 7 years previously. He had a history of opportunistic infection (esophageal candidiasis). The patient had been lost to follow-up and had not received antiretroviral treatment. Regular follow-up for the HIV infection was initiated during a per-
period of incarceration. The patient had a CD4 cell count of 130/µL, and HAART consisting of zidovudine, lamivudine, and abacavir was initiated in September 2002. The viral load was 40,701 copies/mL.

By the 15th day of HAART, the viral load had fallen to 388 copies/mL and the CD4 cell count was 183/µL.

During the fourth month of HAART, the viral load was 68 copies/mL and the CD4 cell count was 278/µL. During the fifth month of HAART, the patient consulted a dermatologist for round skin lesions on the limbs and face, which had progressed over a 6-week period and had not improved with local antifungal treatment. Clinical examination revealed 4 round lesions that were well delimited, squamous, and moderately infiltrated. One of these lesions was on the face, between the eyes, and measured 1 cm in diameter. The other 3, which were on the internal aspect of the right forearm, on the internal aspect of the right ankle, and on the anterior aspect of the left leg, measured 3 to 5 cm in diameter. We observed a marked decrease in sensitivity to heat and pain in the vicinity of the skin lesions. This decrease in sensitivity was associated with a hypertrophy of the cubital and popliteal sciatic nerves, but there were no signs of deficiency along the distribution of either nerve. Pathological examination of 1 of the skin lesions provided evidence of a tuberculoid infiltration in contact with the epidermis, causing erosion of the epidermis. There were numerous giant cells and lymphocytes in the granuloma and signs of vasculitis. Ziehl-Neelsen staining provided no evidence of acid/alcohol-resistant bacilli.

The patient returned for a consultation 15 days later to start treatment for leprosy. He reported severe pain in the right elbow and left leg that had appeared 2 days previously, associated with a sensation of numbness. Clinical examination revealed a modification of the skin lesions, and the lesion on the left leg displayed ulceration (Figure 4). Palpitation of the hypertrophied nerves increased the pain. The patient presented a sensory deficit along the distribution of the right cubital and left external popliteal sciatic nerves. Based on the clinical and pathologic findings, a diagnosis of polar tuberculoid leprosy complicated by a type 1 reactional state was reached.

Antileprosy treatment consisting of 600 mg of rifampin once monthly, 100 mg of clofazimine once daily, and 100 mg of dapsone once daily was initiated, together with treatment with oral prednisone (1 mg/kg per day) for the nerve damage.

The pain and numbness rapidly decreased from the third day of corticosteroid treatment. The leprosy progressed favorably, with disappearance of the lesions during the sixth month of treatment.

CASE 3

The patient was a 39-year-old HIV-positive woman of Haitian origin who had been living in Martinique since 1990. Tritherapy with zidovudine, lamivudine, and nelfinavir was initiated in February 1999, when the patient had a CD4 cell count of only 31/µL. The viral load was 62,700 copies/mL. After 3 months of HAART the patient consulted for infiltrated cutaneous nodules and large, well-delimited plaques with hypopigmented centers localized on the left knee and the right leg. At this time, the CD4 cell count had increased to 171/µL and the viral load had decreased to 30 copies/mL. A biopsy of the lesions led to the diagnosis of typical tuberculoid leprosy. A few days later, after the initiation of antileprosy treatment, the patient was admitted to the hospital for neuritis of the right posterior tibial nerve. Corticosteroid treatment was initiated, together with an antileprosy treatment combining minocycline, oflaxacin, and clofazimine. The antiretroviral treatment was continued. The reactional state was rapidly followed by a favorable course, with no sequelae.

Immune reconstitution inflammatory syndrome most commonly occurs in patients who begin their first antiretroviral therapy regimen at a time when their CD4 lymphocyte count is very low, typically less than 100/µL. Inflammatory diseases tend to emerge 1 to 6 months after effective therapy is initiated, during a transitional period from unrestrained virus replication and immune suppression to suppressed viral load, increased CD4 lymphocyte count, and recovery of the inflammatory response. Anecdotal reports suggest that there may be some benefit from treatment with anti-inflammatory drugs if the inflammatory response compromises vital structures or has caused substantial systemic symptoms. It is appropriate to treat the opportunistic diseases as they appear, and not to wait for improved general immunity.

Skin manifestations associated with IRIS are relatively frequent but their presentation depends on the infectious agent or the antigenic stimulus involved. Herpes virus infections are the most frequently reported: herpes zoster (41 cases); genital or anal herpes simplex virus infection (4 cases with chronic erosive lesions), and cytomegalovirus infection (1 case causing cutaneous ulceration). Mycobacterial infectious diseases other than leprosy can also be associated with IRIS, although rarely with skin manifestations: Mycobacterium avium complex infection (2 cases with dermohypodermal nodules) and tuberculosis (1 case with dermohypodermal nodules, with necrotizing evolution) have been reported. Cryptococcosis (3 cases) causes subcutaneous indolent abscesses or...
umbilicated nodules. Kaposi sarcoma may appear with or be aggravated by IRIS (3 cases). Erythema nodosum associated with sarcoidosis has been described (3 cases).14-16

Our 3 cases of leprosy occurring in the clinical context of the introduction of antiretroviral therapy met the criteria for IRIS. The criteria were the following: (1) the patients had full-blown AIDS; (2) antiretroviral therapy was followed by a significant increase in CD4 lymphocyte counts; (3) this reconstitution of the immune system was accompanied by the detection of a latent infection—leprosy in all 3 cases; and (4) the symptoms were not consistent with the expected progression of a previously diagnosed opportunistic infection, the expression of a newly acquired infection, or the manifestation of undesirable effects of the therapy.

In our study, the cases of leprosy in patients with IRIS occurred during the first 6 months of HAART, with an estimated frequency of 3 per 1000 patients treated. This frequency is higher than the 6-month incidence of leprosy in HIV-positive patients in French Guiana (0.14/1000) and the 6-month incidence of leprosy in the general population (0.017/1000).

The case of leprosy in a patient with IRIS reported by Law et al in 2003 concerned a patient of African origin presenting a borderline tuberculoid form in a type 1 reactive state, which was difficult to control despite prolonged corticosteroid treatment.

Our 3 cases suggest that *Mycobacterium leprae* is a cause of mycobacterial IRIS, as well as *M. avium* complex and *M. tuberculosis*. Together with the first case described, they make it possible to characterize lepromatous IRIS, as signs appeared in the first 4 months of HAART in all 4 cases and leprosy was complicated in each case by a type 1 reactive state (infiltrated cutaneous lesions and/or signs of neuritis), requiring corticosteroid treatment in 3 of the 4 cases. This high frequency of type 1 reactive state is classically reported in cases of leprosy-HIV coinfection.

However, these 3 cases of leprosy in patients with IRIS display certain atypical features. The occurrence of a type 1 reactive state is surprising in cases 2 and 3 because tuberculoid forms of this type are usually stable. The ulcerous progression of all the lesions in case 1 and of 1 lesion in case 2 is also highly unusual. Uceration is rare in patients with leprosy, except for plantar ulcers and burns. Ulceration of particularly edematous cutaneous lesions may occur in patients in type 1 or type 2 reactive states. Furthermore, the epidemiological and clinical aspects of leprosy, unlike those of other mycobacterial diseases, have not yet been markedly modified by the HIV pandemic. Because access to HAART is increasing in countries where leprosy is endemic, the number of IRIS cases due to *M. leprae* will likely increase considerably in the near future. In our experience, these cases tend to have a tuberculoid clinical appearance from the outset. They are associated with type 1 reactive states, and vasculitis and ulcerous progression is possible. It should be noted that in 1 case of ulcerated leprosy with no serious damage to the nerves, the disease spontaneously resolved without the need for anti-inflammatory treatment, thus avoiding potential adverse effects of systemic steroids for the patient (e.g., immunosuppression or metabolic disorders). The prognosis therefore depends on the degree of associated neuritis, which determines whether corticosteroid treatment is required.

**Accepted for publication January 24, 2004.**

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