

CASE REPORT

Immune reconstitution inflammatory syndrome or upgrading Type 1 reaction? Report of two AIDS patients presenting a shifting from borderline lepromatous leprosy to borderline tuberculoid leprosy

CAROLINA TALHARI*,**, LUIZ CARLOS DE LIMA FERREIRA**,***, JOSÉ RIBAMAR ARAÚJO**,***, ANETTE CHRUSCIAK TALHARI*,** & SINÉSIO TALHARI*,**

**Department of Dermatology, Institute of Tropical Medicine of Amazonas, Manaus, Brazil*

***State University of Amazonas, Faculty of Medicine, Manaus, Brazil*

****Department of Pathology, Institute of Tropical Medicine of the Amazonas, Manaus, Brazil*

Accepted for publication 16 September 2008

Introduction

It would be expected that AIDS had a major impact on the incidence and clinical course of leprosy in countries where both diseases are public health problems. However, epidemiological changes such as those seen in tuberculosis have not been observed in leprosy and HIV coinfection.¹

Although a slight increase in HIV seroprevalence among leprosy patients has been observed in a few cohort and case control studies,^{2–5} there have been no changes in the leprosy incidence in the majority of leprosy endemic areas.^{6–9}

Currently, there are few reports of HIV-positive patients on HAART presenting with multibacillary leprosy. In a recent review there were only two cases (borderline-lepromatous and borderline-borderline leprosy).¹ The large majority were classified as borderline-tuberculoid leprosy.^{1,10–14}

It is well known that there is an important CD4 count increase during the first few months of HAART. During this phase, a subgroup of patients may present with clinical deterioration despite the CD4 count improvement. This immunopathological inflammatory response to a wide range of pre-existing infectious agents has been called immune reconstitution inflammatory syndrome

Correspondence to: Sinésio Talhari, Department of Dermatology, Institute of Tropical Medicine of Amazonas, Av. Pedro Teixeira, 25, Manaus, Amazonas, Brazil (e-mail: sinesiotalhari@terra.com.br)

(IRIS).¹⁰ Coinfection with *M. tuberculosis*, *Mycobacterium avium complex*, *Cryptococcus neoformans*, *Histoplasma capsulatum* and other infectious agents have been associated with this syndrome. IRIS has been also reported in association with leprosy.^{10–16}

We report two AIDS patients with multibacillary (MB) leprosy who presented with IRIS that during the follow-up converted to borderline tuberculoid (BT) leprosy. Both patients live in Manaus, the capital of the state of Amazonas in the Brazilian Amazon region, where leprosy and AIDS are endemic diseases.

Case 1. A 32 year-old man was diagnosed with HIV-1 infection (CD4 cell count of 71 cells per μL) and HAART was initiated in April 2001. In May 2001 he returned with disseminated cutaneous lesions. Dermatological examination revealed isolated and confluent erythematous plaques distributed over his trunk, upper and lower limbs (Figure 1A).

A skin biopsy showed dermal infiltrate composed of lymphocytes and numerous foamy macrophages. Wade staining showed multiple acid-fast bacilli (AFB). Based on clinical and histopathological findings a diagnosis of borderline lepromatous leprosy (BL) and Type 1 reaction was made. Multidrug therapy (MDT) for multibacillary leprosy was promptly started and HAART was continued.

In July 2001, he presented with swollen and ulcerated lesions (Figure 1B).

Nerve enlargement was not observed. A skin biopsy was taken and reactional borderline tuberculoid leprosy (BT) with scanty AFB was diagnosed. At that time, CD4 count was 257 cells per μL . The patient was given three pulses of methylprednisolone, 1 g every 15 days. Additionally, 20 mg oral prednisone was given daily between the pulses and for the following 5 months. Prednisone was then tapered and discontinued after 8 months. A staphylococcal sepsis occurred during the first pulse interval and was controlled with systemic antibiotic therapy.

MB-MDT was continued for 2 years and then stopped. The patient is currently under HAART. Although he still has atrophic scars, there is no evidence of active leprosy or neural disability after a 5-year follow-up.



Figure 1. Case 1 – patient with AIDS and borderline lepromatous leprosy. A) Isolated and confluent erythematous plaques on the trunk and upper limbs; B) Swollen and ulcerated lesions two months after initiating MDT.

Case 2. A 25 year-old man was diagnosed with AIDS in February 2005, while being treated for neurotoxoplasmosis. At that moment, CD4 count was six cells per μL and viral load 100,000 copies per mL. HAART was commenced 1 month after the diagnosis of AIDS was made. In August 2005 the CD4 count increased to 77 cells per μL and the viral load was undetectable.

In October 2005 the patient was examined by one of the authors (ST) with a 2-month history of cutaneous lesions on the lumbar region and lower limbs. Dermatological examination displayed erythematous nodules on the right knee, plaques on the lumbar region and hyperkeratotic lesions on the legs and feet (Figure 2). There was no nerve enlargement. CD4 count was 158 cells per μL at this time. A skin biopsy from the knee showed Virchow cells containing multiple AFB and areas with tuberculoid granulomas (Figures 3A and 3B). The diagnosis was BL leprosy. Immunohistochemical studies showed few CD4 cells and a high number of CD8 cells in the inflammatory infiltrate (Figure 4A). MB-MDT was associated to HAART. In December 2005 the patient developed a typical Type 1 reaction on the limbs (Figure 5).

Nerve enlargement was not observed. A skin biopsy from an infiltrated lesion on the lateral aspect of the right foot revealed tuberculoid granulomas consisting of lymphocytes and epithelioid cells (Figures 6A and 6B).

There were no Virchow cells. Scanty AFB were seen on Wade staining. CD4 count was 217 cells per μL . The histopathological diagnosis was BT leprosy and Type 1 reaction. Immunohistochemical studies revealed a high number of CD4 cells and a low number of CD8 cells (Figure 4B).

In order to prevent eventual ulceration of the lesions and neural disability, prednisone 60 mg daily was given and progressively tapered. Complete withdrawal of the prednisone was achieved after 5 months.

WHO-MDT was discontinued after 14 months. The cutaneous lesions disappeared slowly, leaving an intense hyperpigmentation at the site of the previous lesions. The patient is currently receiving HAART and has shown no disability and no more leprosy reaction after stopping cortisone and MDT after a 4-year follow-up.



Figure 2. Case 2 – patient with AIDS and borderline lepromatous leprosy. Hyperkeratotic lesion on the ankle.

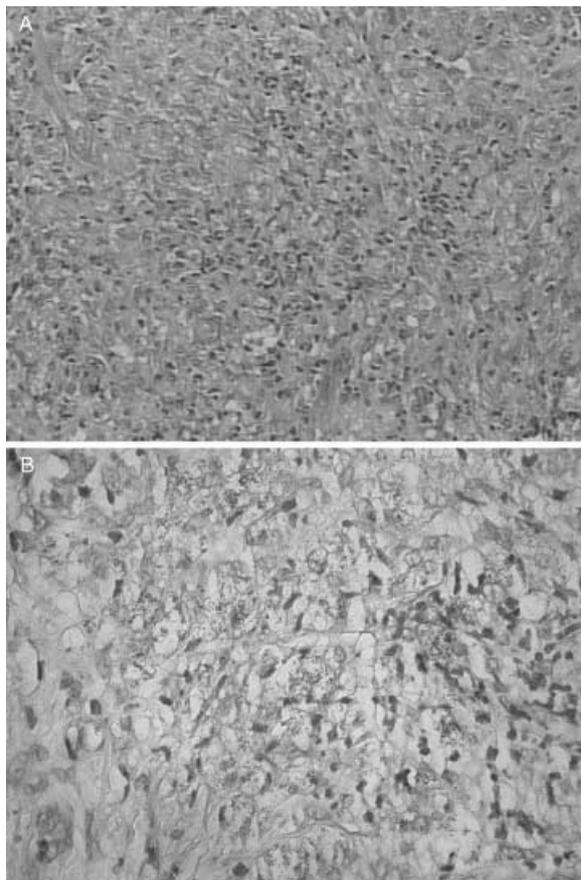


Figure 3. Case 2 – A) Inflammatory infiltrate consisting of Virchow cells (haematoxylin- eosin, original magnification, $\times 40$). B) Multiple acid-fast bacilli (Wade, original magnification, $\times 100$).

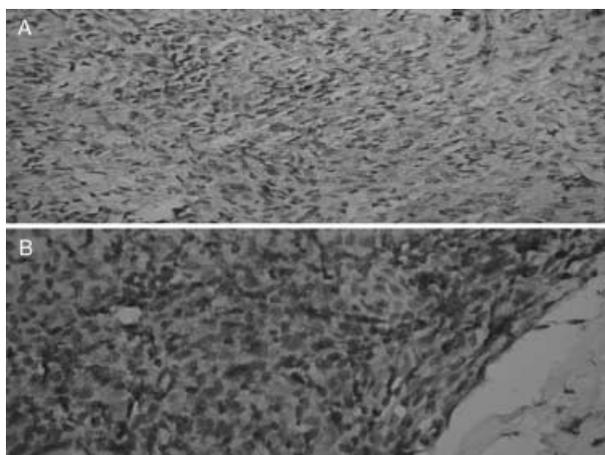


Figure 4. Case 2 – Immunohistochemical studies with CD4⁺ monoclonal antibodies in the inflammatory infiltrate. A) Few CD4 cells (original magnification, $\times 40$). B) High number of CD4 cells and a low number of CD8 cells (original magnification, $\times 100$).



Figure 5. Case 2 – Erythematous violaceous lesions 2 months after initiating MDT.

Discussion

Most of the reports of HIV and leprosy coinfection are associated with BT leprosy, usually presenting for the first time with Type 1 reaction. This fact poses a very important problem to the clinician: how does one manage a patient with AIDS, leprosy and Type 1 reaction? Is it safe to give HAART, MDT and corticosteroids to an immunosuppressed patient?

The two reported patients represent a sample from our 11-year experience with 20 cases of HIV and leprosy coinfection. Regarding the first case, it is interesting to point out that 3 months after initiating HAART and 2 months after MDT, there was a shift from reactional BL leprosy to severe ulcerated reactional BT leprosy. Although the patient presented with reactional leprosy, his low blood CD4 count (71 cells per μL) and our inexperience in managing such cases led to a delay in corticosteroid treatment. Only after the cutaneous lesions ulcerated and we were faced with the possibility of nerve damage did we decide to start methylprednisolone pulse therapy. Despite the staphylococcal sepsis which occurred

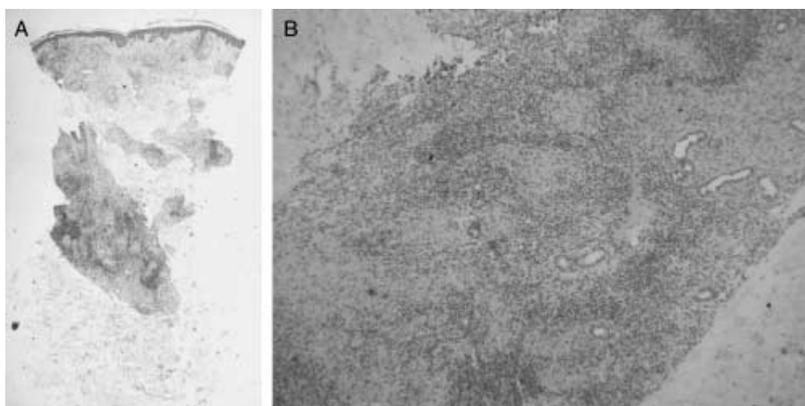


Figure 6. Case 2 – A) A skin biopsy revealed tuberculoid granulomas without Virchow cells (haematoxylin-eosin, original magnification, $\times 10$). B) Granuloma formation consisting of lymphocytes and epithelioid cells (haematoxylin-eosin, original magnification, $\times 40$).

after the first pulse, it was possible to control the reaction with a relatively low dose of corticosteroid. The atrophic scars that remained might have been prevented if prompt corticosteroid treatment had been initiated. Fortunately, the patient developed no disability secondary to nerve involvement.

A literature review of HIV and leprosy coinfection revealed no other reports like the two patients presented here, except a similar case reported by our group.¹⁷ Both patients initially presented with BL leprosy and after a few months under HAART and MB-MDT, developed an upgrading shift to BT leprosy. This clinical picture could be classified as either an upgrading Type 1 reaction or IRIS.

According to Ustianowski *et al.* 'It is not yet clear whether IRIS triggers the *normal* presentation of leprosy or whether the natural history of leprosy is actually accelerated by IRIS leading to the premature presentation of leprosy'.¹ In the two presented cases, leprosy might have appeared due to the increased CD4 count induced by HAART. It is possible that without HAART these patients would not develop clinically apparent leprosy. This is one theory that could explain the small number of patients with both leprosy and AIDS in regions where both diseases are endemic and HAART is not available.

Another interesting aspect in the evolution of our patients is the rapid change from BL to BT leprosy. If the leprosy diagnosis had been delayed for 3 or more months, the patients would have been classified as having BT leprosy and the recommended treatment, according to the histopathological examination, would have been paucibacillary MDT and not MB-MDT as we administered.

IRIS and reversal reaction may share considerable clinical overlap. Moreover, the presented cases demonstrate that corticosteroids should be promptly started in such patients with disseminated lesions. Excepting the sepsis in case 1, there were no clinical or laboratory abnormalities related to the treatment with corticosteroids.

Finally, we would like to comment on the tuberculoid granuloma 'paradox' related to HIV and leprosy coinfection. In the excellent review by Ustianowski *et al.* the following question was raised '... why does HIV have little discernable impact on leprosy granulomas but an extremely marked effect on tuberculous granulomas?'.¹ Most of the leprosy patients coinfecting with HIV reported until now were classified as BT leprosy. It is possible that if the diagnosis of these patients had occurred 3 or more months before, the histopathological findings would have been the same as those observed in our patients. In our patients, the viral load reduction and the CD4 count increase after initiating HAART were probably sufficient to mount an inflammatory response with T cell repopulation and to promote granuloma formation. In our view such interpretation presents no paradox. It would be interesting to see what would have happened to the granuloma formation if for any reason these patients had to stop HAART. Further studies in a larger group of patients are necessary for a better understanding of the HIV, leprosy and IRIS association.

Acknowledgements

To Michele Gonzalez and Bernardo Gontijo for their help in the preparation of this manuscript.

References

- ¹ Ustianowski AP, Lawn SD, Lockwood DN. Interactions between HIV infection and leprosy: a paradox. *Lancet Infect Dis*, 2006; **6**: 350–360.
- ² Meeran K. Prevalence of HIV infection among patients with leprosy and tuberculosis in rural Zambia. *BMJ*, 1989; **298**: 364–365.
- ³ Borgdorff MW, van den Broek J, Chum HJ *et al*. HIV-1 infection as a risk factor for leprosy; a case–control study in Tanzania. *Int J Lepr Other Mycobact Dis*, 1993; **61**: 556–562.
- ⁴ Broek J, Chum HJ, Swai R *et al*. Association between leprosy and HIV infection in Tanzania. *Int J Lepr Other Mycobact Dis*, 1997; **65**: 203–210.
- ⁵ Moses AE, Adelowo KA, Ajayi BB. Prevalence of HIV-1 infection among patients with leprosy and pulmonary tuberculosis in a semiarid region, Nigeria. *J R Soc Health*, 2003; **123**: 117–119.
- ⁶ Orege PA, Fine PE, Lucas SB *et al*. A case control study on human immunodeficiency virus-1 (HIV-1) infection as a risk factor for tuberculosis and leprosy in western Kenya. *Tub Lung Dis*, 1993; **74**: 377–381.
- ⁷ Frommel D, Teckle-Haimanot R, Verdier M *et al*. HIV infection and leprosy: a four-year survey in Ethiopia. *Lancet*, 1994; **344**: 165–166.
- ⁸ Munyao TM, Bwayo JJ, Owili DM *et al*. Human immunodeficiency virus-1 in leprosy patients attending Kenyatta National Hospital, Nairobi. *East Afr Med J*, 1994; **71**: 490–492.
- ⁹ Gebre S, Saunderson P, Messele T *et al*. The effect of HIV status on the clinical picture of leprosy: a prospective study in Ethiopia. *Lepr Rev*, 2000; **71**: 338–343.
- ¹⁰ Lawn SD, Wood C, Lockwood DN. Borderline tuberculoid leprosy: an immune reconstitution phenomenon in a human immunodeficiency virus-infected person. *Clin Inf Dis*, 2003; **36**: e5–e6.
- ¹¹ Pignataro P, Rocha AS, Nery JA *et al*. Leprosy and AIDS: two cases of increasing inflammatory reactions at the start of highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis*, 2004; **23**: 408–411.
- ¹² Couppie P, Abel S, Voinchet H *et al*. Immune reconstitution inflammatory syndrome associated with HIV and leprosy. *Arch Dermatol*, 2004; **140**: 997–1000.
- ¹³ Pereira GA, Stefani MM, Araujo Filho JA *et al*. Human immunodeficiency virus Type 1 (HIV-1) and *Mycobacterium leprae* coinfection: HIV-1 subtypes and clinical, immunologic, and histopathologic profiles in a Brazilian cohort. *Am J Trop Med Hyg*, 2004; **71**: 679–684.
- ¹⁴ Visco-Comandini U, Longo B, Cuzzi T *et al*. Tuberculoid leprosy in a patient with AIDS: a manifestation of immune restoration syndrome. *Scand J Infec Dis*, 2004; **36**: 881–883.
- ¹⁵ Sampaio EP, Caneshi JR, Nery JA *et al*. Cellular immune response to *Mycobacterium leprae* infection in human immunodeficiency virus-infected individuals. *Infect Immun*, 1995; **63**: 1848–1854.
- ¹⁶ Simone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1 infected persons after initiation of highly active antiretroviral therapy. *Ann Intern Med*, 2000; **133**: 447–454.
- ¹⁷ Talhari C, Machado PRL, Ferreira LC, Talhari S. Shifting of the clinical spectrum of leprosy in an HIV-positive patient: a manifestation of Immune Reconstitution Inflammatory Syndrome? *Lepr Rev*, 2007; **78**: 151–154.