

Histoplasmosis-associated immune reconstitution inflammatory syndrome*

Síndrome de restauração imune associada à histoplasmose

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Abstract: A 27-year-old HIV-positive male patient with disseminated cutaneous histoplasmosis was treated with both HAART and amphotericin B (total accumulated dose of 0.5g). Amphotericin B was later replaced with itraconazole (200mg/day). Two months after therapy had been started and the cutaneous lesions had healed, the patient interrupted both treatments voluntarily and his health deteriorated. HAART was then re-introduced and CD4+ cell count increased sharply at the same time as lymph node histoplasmosis was diagnosed. This paradoxical response ? the relapse of histoplasmosis and concomitant increase in CD4+ cell count and undetectable viral load after resumption of HAART ? suggests that this was a case of immune reconstitution inflammatory syndrome (IRIS).

Keywords: *Histoplasma*; Histoplasmosis; Polymerase chain reaction

Resumo: Paciente masculino, 27 anos, portador de HIV, com quadro de histoplasmose cutânea disseminada. Terapia antirretroviral oral e anfotericina B por via EV (dose total acumulada 0,5g) foram introduzidas, verificando-se rápida cicatrização das lesões após duas semanas. A anfotericina B foi substituída por itraconazol (200mg/dia). O paciente interrompeu voluntariamente os tratamentos. A terapia antirretroviral foi reintroduzida, havendo aumento da contagem de células T CD4-positivas (No restante do texto, a autora usa o símbolo “+” (T CD4+) ao invés da palavra “positiva”. O que fazer neste caso? Seguimos o padrão do restante do texto ou acatamos essa opção da autora no resumo?!). Neste momento, diagnosticou-se histoplasmose ganglionar. O aumento da contagem de células T CD4-positivas (de novo aqui), associado à redução da carga viral a níveis inferiores ao limite de detecção após a reintrodução da terapia antirretroviral, sugere que essa piora clínica paradoxal seja uma síndrome de restauração imune.

Palavras-chave: Histoplasma; Histoplasmose; Reação em cadeia da polimerase

INTRODUCTION

Diseases associated with immune reconstitution (DAIR), which are also known as immune reconstitution inflammatory syndrome (IRIS), immune reconstitution disease (IRD) or immune recovery syndromes (IRS), are important conditions, particularly in AIDS patients during the first months of antiretroviral treatment (ART). Before the first reports of IRIS in AIDS patients, there had already been descriptions of

tuberculosis (TB) cases whose clinical condition had worsened paradoxically after the introduction of specific treatment. Deitel, assessing 23 patients with enlarged cervical lymph nodes associated with tuberculosis in 1984, found inexplicable enlargement of the lymph nodes during the first five months of chemotherapy in three cases.¹ Rao observed an unusual phenomenon in 1995, which was also paradoxical,

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in four patients being treated for tuberculous meningitis who developed new, progressive lesions, particularly in the form of cerebral tuberculomas, that regressed when corticosteroids were administered along with the specific treatment.² In the literature, these episodes of worsening of the clinical symptoms of tuberculosis during treatment are referred to as a paradoxical response.²⁻⁴

According to French et al (1992), since zidovudine (AZT) was first used to treat AIDS in the 90s, there have been reports of paradoxical reactions, with worsening of the clinical symptoms of opportunistic infections and severe inflammatory reactions in some patients.⁵ These reactions were associated with partial recovery of the immune system and the presence of pre-existing infectious processes; the manifestations varied according to the pathogen, were self-limiting or disseminated and could lead to sequelae or death. The same group subsequently reported that there had been a significant worldwide increase in cases of these paradoxical responses since the introduction of potent antiretroviral combinations (HAART).⁶

The introduction of HAART in 1996 led to a significant drop in AIDS-related mortality.⁷ In Europe the number of deaths over a two-year period fell by 50% compared with the previous period. A reduction in viral replication and an increase in the number of CD4+ T cells is observed in patients on HAART.⁸

However, in a significant number of patients, immune recovery can induce IRIS.^{8,9} The condition is reported in 15-25% of patients on HAART and probably has a greater prevalence (30-45%) in those with a pre-existing opportunistic infection.^{10,11} According to Lehloeny & Meintjes (2006), 52% to 78% of patients with IRIS can have dermatological manifestations.¹⁰

In addition to tuberculosis, other infectious diseases with different etiologies have been described in association with immune recovery. According to Myes et al. (2010), the main diseases associated with immune recovery are mycobacterioses, mycoses, viral infections, parasite infections, autoimmune diseases and hematologic cancers. Recently, the first case of IRIS associated with *Leishmania guyanensis* was described.¹²

We report the case of a patient with AIDS and disseminated cutaneous histoplasmosis who developed a clinical picture suggestive of IRIS while taking HAART irregularly.

CASE REPORT

A 27-year-old male patient born, and still living, in Parintins, AM, seen at the dermatology service in September 2007, presented with a clinical picture of disseminated cutaneous histoplasmosis, which was confirmed by histopathological examination and cul-

ture (Figures 1A and 1B). The patient had been diagnosed as HIV seropositive six months previously and was not on HAART. He complained of weight loss and general malaise, and enlarged axillary and inguinal lymph nodes were observed on examination. CD4⁺ T-cell count was 42 cells/mm³, and the viral load was 153,024 RNA copies/mL (5.2 log₁₀ copies of RNA/mL), confirming the diagnosis of AIDS (Figure 1A, Table 1). Because of the clear clinical picture at the time, the case was published.¹³

The patient was treated with amphotericin B (cumulative dose of 0.5g) and HAART (zidovudine - 600mg/day; lamivudine - 300mg/day; and efavirenz - 600mg/day) and responded well to the therapy. After the patient was discharged and the cutaneous manifestations had regressed, amphotericin B was replaced with itraconazole (200mg/day p.o.) for 30 days; the dose was then reduced to 100mg/day. The cutaneous manifestations regressed, and several months later the patient voluntarily decided to discontinue the antifungal treatment (Figure 1C). CD4⁺ T-cell count at that time was 434 cells/mm³, and HIV-1 viral load was undetectable. In August 2008 the patient voluntarily decided to stop HAART (when he had a CD4⁺ T-cell count of 394/mm³ and undetectable viral load). Five months after the treatment had been interrupted, his

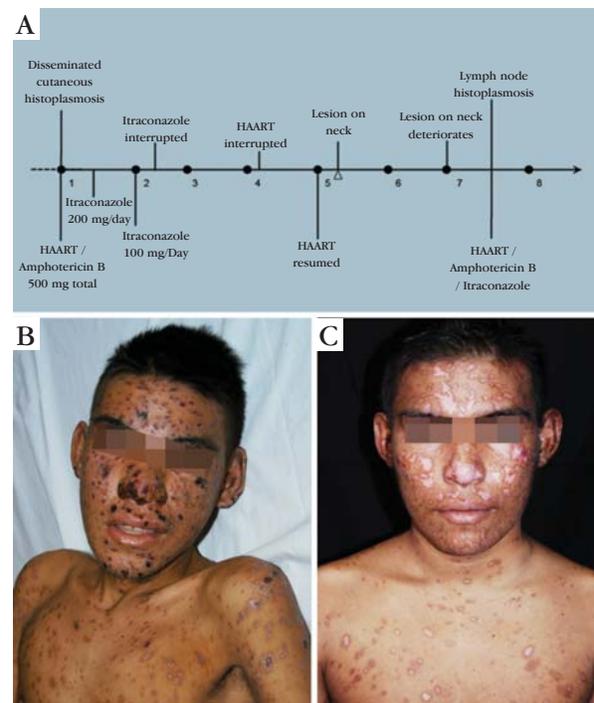


FIGURE 1: A. Timeline showing the clinical and therapeutic events and laboratory results; B. Patient before start of treatment; C. Patient after treatment with amphotericin B/itraconazole

general condition worsened (58 CD4⁺ T cells/mm³ and a viral load of 68,821 RNA copies/mL, 4.8 log₁₀ RNA copies/mL) and HAART was then resumed. The patient was re-examined in January 2010 and found to have symmetrical, fistulous lesions of the cervical lymph nodes suggestive of scrofuloderma (Figures 2A and 2B). Tuberculin skin test was negative and both the sputum PCR and sputum smear to detect acid-alcohol fast bacilli (AAFB) failed to identify *Mycobacterium tuberculosis*; a hypothesis of scrofuloderma was therefore eliminated. Histopathological examination of the lymph node biopsy revealed granulomatous dermatitis with numerous basophilic, rounded structures compatible with a diagnosis of histoplasmosis (Figures 3A and 3B). The diagnosis of *Histoplasma capsulatum* infection was confirmed by PCR (Figure 3C). At that time the patient's CD4⁺ T-cell count was 303 cells/mm³ and the viral load was undetectable (Table 1). Treatment with amphotericin B was started (cumulative dose of 0.5g iv), and the lesions healed quickly after two weeks. Amphotericin B was then replaced with itraconazole (200mg/day) (Figures 1A and 4). Six months after the patient had been discharged there was no dermatologic evidence of disease reactivation; CD4⁺ cell count was 360 cells/mm³ and viral load was undetectable.

Analysis of the evolution of the CD4⁺ cell count and CD4/CD8 ratio revealed a significant increase in CD4⁺ T cells: from 58 cells/mm³ in January 2009 to 221 cells/mm³ in August 2009 (381%), and 303 cells/mm³ in January 2010 (522%) (Graphs 1A and 1B). When the CD4/CD8 ratio was analyzed, a similar profile was found. With the excep-



FIGURE 2: Lymph node histoplasmosis after resumption of HAART. Symmetrical cervical lymph node lesions. A. Gumma-like lesions and ulcerations on the right side of the neck and B. on the left side

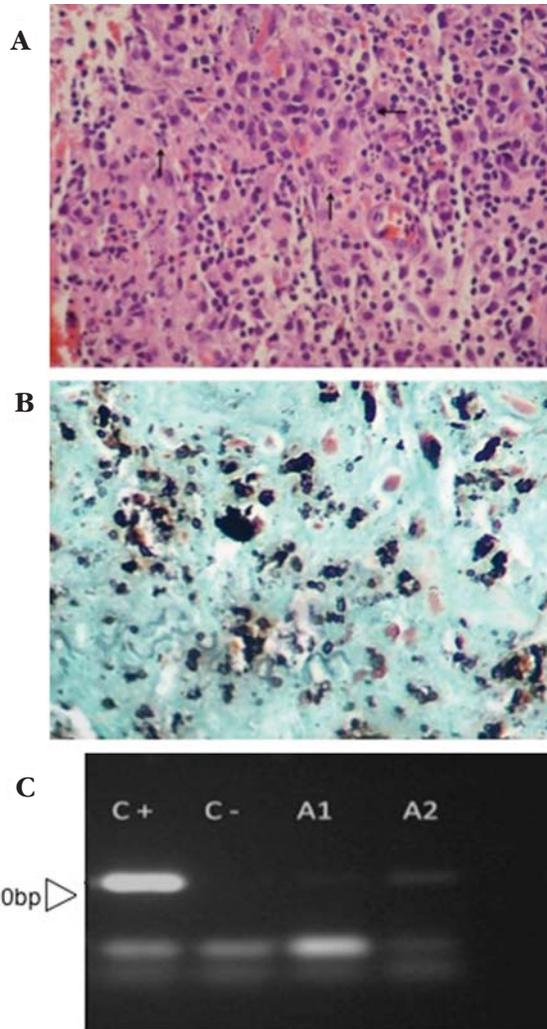


FIGURE 3: Histopathological and molecular diagnosis of *Histoplasma capsulatum* infection. A. Hematoxylin-eosin-stained slide (400x magnification, pathogen is shown with arrows); B. Histopathological slide stained with Grocott stain (400x magnification); and C. Agarose gel showing the specific amplicon for *Histoplasma capsulatum* (200bp, sample C+ = positive control, C- = negative control, A1 and A2 = patient samples)

tion of those at the time when the first diagnosis of AIDS was made (September 2007) and when HAART was restarted (January 2009), HIV-1 viral load remained below the detection threshold (Table 1). The paradoxical response observed in this patient, i.e., the onset of lymph node histoplasmosis concomitantly with increased CD4⁺ T-cell count and a reduction in viral load below the detection threshold after HAART was restarted, was interpreted as IRIS.



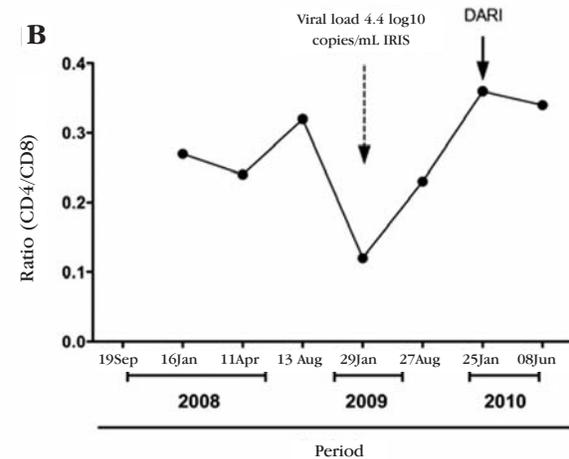
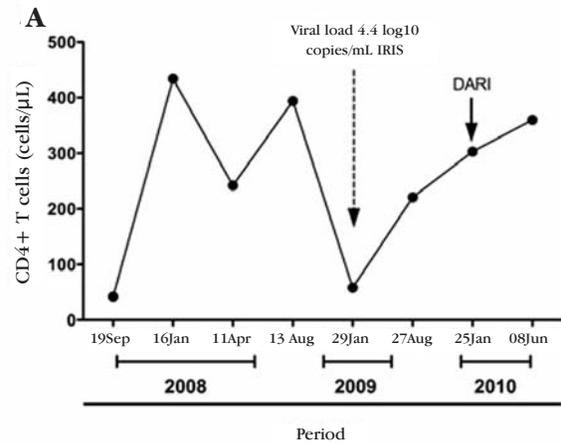
FIGURE 4: Cicatrization of cervical lesions due to lymph node histoplasmosis after treatment with amphotericin B for two weeks

DISCUSSION

In patients with IRIS, memory T cells (CD45RO+) are redistributed from lymphoid tissue to organs, and the number of CD4+ and CD8+ T cells increases faster than that of regulatory T cells, a phenomenon that leads to an imbalance in the immune system.¹⁴ This imbalance is reflected in a significant increase in the inflammatory tissue response to antigens or various infectious agents after exacerbated production of proinflammatory chemokines and cytokines.¹⁴

Muller et al (2010) carried out a meta-analysis of 54 studies of IRIS covering more than 13,000 patients in 22 countries.¹⁵ They found that the condition is more common in patients who start HAART with a CD4+ T-cell count ≤ 50 cells/mm³. Analysis of CD4+ T-cell counts over time for the case described here showed that in September 2007 (the start of HAART) the patient had 42 CD4+ T cells/mm³, while in January 2008 this had increased 10.3 fold (434 CD4+ T cells/mm³). This significant increase in CD4+ T-cell count was associated with a significant reduction in viral load to 5.2 log₁₀ RNA copies/mL, below the detection threshold.

IRIS cases can be divided into two groups: the first, characterized by a paradoxical worsening of the pre-existing opportunistic disease during the course of antiretroviral treatment, and the second, characterized by the onset of IRIS during HAART for the first time, a clinical picture referred to as the "unmasking type" of IRIS.¹⁰ According to Meys et al.,⁹ diseases associated with immune reconstitution cover four subgroups: 1) immune reconstitution inflammatory syndrome, related to mycobacterioses and other infectious diseases; 2) diseases that occur during immune



GRAPH 1: Patient's immunologic status. A. CD4+ T-cell count and B. CD4/C8 ratio. Arrows indicate the deterioration in the patient's immunologic status after he voluntarily stopped HAART, the onset of IRIS after resumption of HAART and the sudden increase in CD4+ T-cell count

reconstitution, with a pathogenesis that is not associated with inflammation (e.g., Kaposi's sarcoma); 3) autoimmune diseases - Graves' disease and diseases of unknown etiology, such as sarcoidosis, are examples of this subgroup; and 4) diseases frequently seen in patients on HAART, including herpes simplex, herpes zoster, molluscum contagiosum and human papillomavirus infection.

The case described here falls in the first subgroup, i.e., immune reconstitution inflammatory syndrome. It has specific characteristics, particularly in relation to differential diagnosis between a relapse of histoplasmosis secondary to failure of retroviral therapy or interruption of antimycotic prophylaxis and

TABLE 1: Patient immunologic and virologic status

Date	2007		2008			2009		2010	
	19/Sep		16/Jan	11/Apr	13/Aug	29/Jan	27/Aug	23/Jan	08/Jun
Outpatient/Hospitalized	1		2	3	4	5	6	7	8
Viral Load*	5.2		BDT***	BDT	BDT	4.8	BDT	BDT	BDT
CD4**	42		434	242	394	58	221	303	360
CD8**	--		1617	1020	1238	475	971	849	1051
CD4/CD8	--		0.27	0.24	0.32	0.12	0.23	0.36	0.34

* - HIV viral load expressed in log10 number of RNA copies/mL

** - CD4+ and CD8+ T-cell count expressed in number of cells/ μ L

*** - BDT = Below detection threshold

immune reconstitution syndrome. The absence of active lesions on scars and the appearance of very fistulous lymph node lesions in the cervical region are similar to what is observed in tuberculosis and histoplasmosis patients undergoing antiretroviral treatment.¹ The reduction in viral load, increase in CD4+ T-cell count since the diagnosis of AIDS and quick response to the specific treatment allow a differential

diagnosis to be made between a relapse secondary to a reduction in immunity and IRIS. A knowledge of the clinical pictures associated with this paradoxical deterioration is of great importance both for the patient and the physician treating him, as it allows unnecessary tests or changes in antifungal treatment or antiretroviral agents to be avoided. □

REFERENCES

- Deitel M, Saldanha CF, Borowy ZJ, Ronald AC, Krajden S. Treatment of tuberculous masses in the neck. *Can J Surg*. 1984;27:90-3.
- Rao GP, Nadh BR, Hemaratnan A, Srinivas TV, Reedy PK. Paradoxical progression of tuberculous lesion during chemotherapy of central nervous system tuberculosis. *J Neurosurgery*. 1995;83:359-62.
- Race EM, Adelson-Mitty J, Kriegel GR, Barlam TF, Reimann KA, Letvin NL, Japour AJ. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet*. 1998;351:252-5.
- Park JA, Park SS, Park SE. A paradoxical reaction during an antituberculosis therapy for congenital tuberculosis. *Int J Infect Dis*. 2009;13:e279-81.
- French MA, Mallal SA, Dawkins RL. Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. *AIDS*. 1992;6:1293-7.
- French MA. HIV/AIDS immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis*. 2009;48:101-7.
- Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22-9.
- Elston JW, Thaker H. Immune reconstitution inflammatory syndrome. *Int J STD AIDS*. 2009;20:221-4.
- Meys R, Gotch FM, Bunker CB. Human papillomavirus in the era of highly active antiretroviral therapy for human immunodeficiency virus: an immune reconstitution-associated disease. *Br J Dermatol*. 2010;162:6-11.
- Lehoenya R, Meintjes G. Dermatologic manifestations of the immune inflammatory syndrome. *Dermatol Clin*. 2006;24:549-70.
- Colebunders R, John L, Huyst V, Kambugu A, Scano F, Lynen L. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int J Tuberc Lung Dis*. 2006;10:946-53.
- Chrusciak-Talhari A, Ribeiro-Rodrigues R, Talhari C, Silva RM Jr, Ferreira LC, Botileiro SF, et al. Case Report: Tegumentary Leishmaniasis as the Cause of Immune Reconstitution Inflammatory Syndrome in a Patient Co-infected with Human Immunodeficiency Virus and Leishmania guyanensis. *Am J Trop Med Hyg*. 2009;81:559-64.
- Talhari C, Talhari S, Massone C. Widespread crusted lesions in a patient with HIV-quiz case. *Arch Dermatol*. 2009;145:1447-52.
- Lederman MM. Immune restoration and CD4+ T-cell function with antiretroviral therapies. *AIDS*. 2001;15(Suppl 2):S11-5.
- Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10:251-61.

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