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Journal of the International Association of Providers of AIDS Care (JIAPAC) published online 20 October 2014
DOI: 10.1177/2325957414555225

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Leishmaniasis as a Manifestation of Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV-Infected Patients: A Literature Review

Roberto Badaró, MD, PHD¹, Larissa O. Gonçalves¹,
Luana L. Gois, MSc^{2,3}, Zuinara Pereira Gusmão Maia, MSc¹,
Constance Benson, MD⁴,
and Maria Fernanda Rios Grassi, MD, PHD^{2,3}

Journal of the International
Association of Providers of AIDS Care
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DOI: 10.1177/2325957414555225
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Abstract

Introduction: After the onset of highly active antiretroviral therapy (HAART), some HIV-infected patients present a severe inflammation in response to a latent or a previously treated opportunistic pathogen termed immune reconstitution inflammatory syndrome (IRIS). Few reports of tegumentary and visceral leishmaniasis have been described in association with IRIS. **Methods:** A systematic literature review of IRIS in association with leishmaniasis identified 34 reported cases. **Results and Discussion:** The majority of these occurred in males 4 months following the onset of HAART. The mean CD4 count before HAART was 94 ± 77 cells/mm³, increasing to 5 times the initial value between the onset of HAART and IRIS presentation. Visceral leishmaniasis and post-kala-azar dermal leishmaniasis were the most commonly reported clinical manifestations, followed by tegumentary leishmaniasis and uveitis. **Conclusions:** Commonly found characteristics included cutaneous involvement, regardless of *Leishmania* species; appearance of lesions unrelated to time of probable *Leishmania* infection; rapid recovery of CD4 count following HAART; and rapid progression.

Keywords

HIV/AIDS, immune reconstitution inflammatory syndrome, IRIS, leishmaniasis, co-infection HIV/*Leishmania*

Introduction

Highly active antiretroviral therapy (HAART) has dramatically changed the natural course of HIV infection by decreasing the occurrence of opportunistic infections and, consequently, the mortality associated with AIDS. However, after the onset of HAART, some patients experience clinical deterioration following an increase in CD4 count and a decrease in HIV viral load. This worsening is usually due to the clinical manifestation of a latent or a previously treated opportunistic pathogen that paradoxically presents as a severe clinical manifestation. The immune response against these types of pathogens results in severe inflammation as a consequence of the restored immune response termed as immune reconstitution inflammatory syndrome (IRIS).^{1–3}

The majority of IRIS cases are associated with nonparasitic infections, including (a) bacteria (*Mycobacterium tuberculosis*, the *Mycobacterium avium* complex, and other nontuberculous mycobacteria); (b) viruses (cytomegalovirus, varicella zoster virus, herpes simplex virus, human herpes virus 8, JC virus, and hepatitis B and C); (c) fungi (*Pneumocystis jirovecii*, *Cryptococcus neoformans*, and *Histoplasma* spp).^{4,5} However, other

parasitic infections associated with IRIS, such as *Strongyloides stercoralis* and *Schistosoma mansoni*, have also been previously described.^{5,6} The risk of IRIS is mainly associated with severe immunosuppression at the start of HAART.⁵

To date, very few reports of tegumentary and visceral leishmaniasis (PL), as well as post-kala-azar dermal leishmaniasis (PKDL), have been described in association with IRIS in HIV-infected patients from several countries.^{7–17} Furthermore,

¹ Universidade Federal da Bahia, Complexo Hospitalar Prof Edgard Santos, Unidade docente de Infectologia, Salvador, BA, Brazil

² Fundação Oswaldo Cruz, Centro de Pesquisa Gonçalo Moniz, Laboratório Avançado de Saúde Pública, Salvador, BA, Brazil

³ Escola Bahiana de Medicina e Saúde Pública, Faculdade de Medicina, Salvador, BA, Brazil

⁴ University of California San Diego, Division of Infectious Diseases, La Jolla, CA, USA

Corresponding Author:

Roberto Badaró, Universidade Federal da Bahia, Complexo Hospitalar Prof. Edgard Santos, Unidade docente de Infectologia. Rua Augusto Viana, s/n - Canela 40110-060 Salvador, BA, Brazil.
Email: rbadaro884@gmail.com

Table 1. Reported Characteristics of HIV-Infected Patients with Leishmaniasis in Association with IRIS in the Literature.

Author, year	Country	N	Age/ Gender	Leishmaniasis IRIS	Primary Manifestation	<i>Leishmania</i> Species	Treatment
Ridolfo et al, 2000 ¹⁷	Italy	1	36/F	PKDL	VL	<i>L infantum</i>	LAmpHB
Gilad et al, 2001 ¹⁵	Ethiopia	1	32/M	PKDL	VL	<i>L sp</i>	SSG
Blanche et al, 2002 ¹⁸	Burkina Faso	1	34/M	Uveitis	DCL and ganglionic	<i>L major</i>	Corticosteroid, LAmpHB, INF- γ , Enucleation, Sbv
Bittencourt et al, 2003 ¹⁹	Brazil	1	28/M	PKDL	VL	NR	Sbv
Berry et al, 2004 ²⁰	France	2	45/F 36/M	LV	Asymptomatic Asymptomatic	<i>L infantum</i> , <i>L infantum</i>	AmphB AmphB
Meenken et al, 2004 ²¹	Netherlands	1	NR / M	Uveitis	VL	<i>L donovani</i>	Corticosteroid, SSG, Flu, Enucleation
Posada-Vergara et al, 2005 ¹⁴	Brazil	2	52/M 46/M	MCL MCL	Asymptomatic DCL	<i>L sp</i> , <i>L brasilienses</i>	AmphB, Sbv
Alsina-Gibert et al, 2006 ²²	Spain	1	48/M	PKDL	VL	<i>L sp</i>	LAmpHB, Sbv, allopurinol
Kerob et al, 2006 ¹¹	Senegal	1	55/M	CL	CL	<i>L major</i>	Flu
Rihl et al, 2006 ²⁶	Germany/ Spain	1	42/M	PKDL and VL	VL	<i>L sp</i>	SSG, miltefosine
Stark et al, 2006 ²⁴	Australia/ Greece	1	45/M	PKDL	VL	<i>L infantum</i>	LAmpHB
Antinori et al, 2007 ¹³	Italy	1	46/M	PKDL and uveitis	VL	<i>L infantum</i>	Pentamidine, miltefosine
Guffanti et al, 2008 ²⁵	Italy	1	40/F	PKDL	VL	<i>L sp</i>	Miltefosine
Sinha et al, 2008 ¹⁰	Nicaragua	1	39/M	DCL	Asymptomatic	<i>L chagasi</i>	LAmpHB
ter Horst et al, 2008 ⁸	Ethiopia	13	33 ^a /NR	VL	VL	<i>L sp</i>	NR
Chrusciak-Talhari et al, 2009 ¹⁶	Brazil	1	32/M	DCL	CL	<i>L guyanensis</i>	Sbv, prednisone
Patel et al, 2009 ¹²	India/Kuwait	1	35/M	VL	Asymptomatic	<i>L sp</i>	AmphB, antibiotic
Tadesse et al, 2009 ²³	Ethiopia	1	25/M	PKDL	VL	NR	SSG
Auyeung et al, 2010 ⁹	Australia/ Cyprus	1	60/M	VL	Asymptomatic	<i>L donovani</i>	Corticosteroid, LAmpHB
Gelane et al, 2010 ⁷	Ethiopia	1	38/M	PKDL and VL	Asymptomatic	<i>L donovani</i>	Sbv

Abbreviations: PKDL, post-kala-azar dermal leishmaniasis; VL, visceral leishmaniasis, MCL, mucocutaneous leishmaniasis, CL, cutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; INF- γ , interferon gamma; F, female; M, male; NR, not reported; Flu, fluconazole; SSG, sodium stibogluconate; Sbv, pentavalent antimonial; LAmpHB, liposomal amphotericin B; AmphB, amphotericin B; IRIS, immune reconstitution inflammatory syndrome.

^aMean age.

many cases may remain underreported due to the difficulty in diagnosing leishmaniasis in association with IRIS because of the absence of universal criteria. The present study conducts a review of the international literature pertaining to cases of leishmaniasis in association with IRIS.

Methods

The literature considering the cases of leishmaniasis as a manifestation of IRIS in HIV-infected individuals was analyzed. The search was performed in MEDLINE and BIREME, the Brazilian regional library of medicine, using the following key words: immune reconstitution inflammatory syndrome, cutaneous leishmaniasis, mucocutaneous leishmaniasis (MCL), PKDL, VL, and ocular leishmaniasis. No restrictions were placed with regard to the time of publication or language of publication. Articles were selected if all of the following criteria were met: the patient serology for HIV was positive, there was evidence of a decrease in viral load and an increase in the CD4 count following the onset of HAART, leishmaniasis presented with an inflammatory or atypical manifestation, and

Leishmania parasites were detected in lesions. All other literature reviews were excluded.

Literature Review

To date, 34 cases of leishmaniasis as a manifestation of IRIS have been described worldwide (Table 1). Males (77%) predominated among the cases described. The mean age of patients was 39 (ranging from 28 to 60 years). The most frequent clinical presentation was VL (19 cases),^{7-9,12,20,26} followed by PKDL (10 cases).^{7,13,15,17,19,22-26} In 2 cases, VL and PKDL were diagnosed simultaneously.^{7,26} Tegumentary leishmaniasis was reported in 5 cases^{10,11,14,16} and MCL was reported in 2 of the 5 cases,¹⁴ while diffuse cutaneous leishmaniasis (DCL) was reported in 2 others.^{10,16} Uveitis as a consequence of leishmaniasis was reported in 3 cases,^{13,18,21} wherein 1 was found to be associated with PKDL.¹³ The mean time between the onset of HAART and the occurrence of IRIS manifestations was 4 months (range: 6 days-111 months). Mean CD4 counts were 94 ± 77 cells/mm³, ranging from 4 to 256 cells/mm³ (Table 2). Sixteen patients had an increase in CD4 count following

Table 2. CD4 Counts and Viral Loads before and after HAART.

Author, year	CD4 Count prior to HAART	CD4 Count after HAART	% Increase in CD4 Count	Viral Load prior to HAART	Viral Load after HAART	Leishmaniasis IRIS	Time of HAART, Months
Ridolfo et al, 2000 ¹⁷	35	157	348	NR	<50	PKDL	8
Blanche et al, 2002 ¹⁸	4	91	2175	381 000	<50	Uveitis	4
Berry et al, 2004 ²⁰	186	226	21	1 700 000	NR	VL	10 days
Berry et al, 2004 ²⁰	15	66	340	354 000	NR	VL	6 days
Meenken et al, 2004 ²¹	60	740	1133	NR	NR	Uveitis	26
Posada-Vergara et al, 2005 ¹⁴	38	65	71	750 000	NR	MCL	1
Posada-Vergara et al, 2005 ¹⁴	24	283	1179	NR	400	MCL	1
Alsina-Gibert et al, 2006 ²²	69	158	128	578	<200	PKDL	11
Rihl et al, 2006 ²⁶	28	116	314	<50	NR	PKDL and VL	22
Stark et al, 2006 ²⁴	176	374	112	NR	NR	PKDL	84
Antinori et al, 2007 ¹³	71	321	352	73 000	<50	PKDL and uveitis	111
Guffanti et al, 2008 ²⁵	200	584	192	NR	<50	PKDL	2
Sinha et al, 2008 ¹⁰	115	200	74	700	<400	DCL	6
Chrusciak-Talhari et al, 2009 ¹⁶	16	184	1050	NR	NR	CL	10
Auyeung et al, 2010 ⁹	55	75	36	>100 000	562	VL	5

Abbreviations: HAART, highly active antiretroviral therapy; PKDL, post-kala-azar dermal leishmaniasis; VL, visceral leishmaniasis; MCL, mucocutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; NR, not related; IRIS, immune reconstitution inflammatory syndrome.

HAART, with an average gain of 235 ± 198 cells/mm³ (57-40 cells/mm³), corresponding to a 5-fold rise. The elapsed time between onset of HAART and manifestation of IRIS was not related to the degree of CD4 boost and viral load before therapy.

In the 2 cases reported by Berry et al,²⁰ the diagnosis of VL in association with IRIS was inconclusive, as manifestations appeared shortly after the onset of HAART (6-10 days). In addition, both patients had leukopenia and thrombocytopenia prior to the onset of HAART, which may be due to the natural course of VL instead of IRIS. The largest series of cases of VL in association with IRIS was reported in Ethiopia; however, scarce clinical data were presented regarding these patients. In these cases, IRIS was diagnosed 3 months after the onset of HAART, based solely on positive serology for *Leishmania*, or due to the presence of *Leishmania* spp in splenic aspirate. All these patients previously had negative serology for *Leishmania*.⁸ It is known²⁷ that 50% of HIV/*Leishmania* co-infected individuals have negative serology for *Leishmania*, especially those with CD4 counts of less than 100 cells/mm³. Therefore, perhaps VL as a manifestation of IRIS was an uncertain diagnosis in this series of cases reported in Ethiopia. Moreover, in a prospective study conducted by de la Rosa et al,²⁸ VL in association with IRIS was not observed in 11 patients with the subclinical form of the disease, who were treated with HAART during 29 months of follow-up. Four patients with active VL who started HAART during the clinical manifestation of VL presented a regression of symptoms.

A total of 10 cases of PKDL were reported in association with IRIS.^{7,13,15,17,19,22-26} Post-kala-azar dermal leishmaniasis

was diagnosed between 1 and 111 months after the onset of HAART. In only 1 patient, the previous diagnosis of VL was unconfirmed. Following the onset of antiretroviral treatment (ART), CD4 counts increased in all 10 cases. Furthermore, skin lesions appeared only after HAART was initiated, characterizing a new event related to a preexisting *Leishmania* infection. Taken together, these findings suggest a stronger association between PKDL and IRIS compared to VL in association with IRIS.

Regarding the 5 reported cases of cutaneous leishmaniasis associated with IRIS, *Leishmania* infection was commonly disseminated. In 1 case in Brazil, the dissemination of lesions occurred during CD4 count recovery,¹⁶ whereas in the case described by Kerob et al,¹¹ several nodules containing *Leishmania* appeared following combined ART and amphotericin B treatment.

Sinha et al¹⁰ reported a case of DCL in association with IRIS in 1 HIV-positive individual on ART. In contrast to classical DCL, which is an anergic form of leishmaniasis characterized by disseminated non ulcerating skin lesions, this patient had fever, weight loss, diarrhea and splenomegaly. In addition, *Leishmania chagasi* was isolated from this patient's lesions, which had not been previously reported in cases with DCL. In this case, PKDL should have been considered as a possible diagnosis due to the patient's clinical presentation.

Two cases of cutaneous leishmaniasis with mucosal involvement have been previously described.¹⁴ In both patients, mucosal damage occurred shortly after immune recovery following HAART in contrast to the classical course observed in uninfected individuals wherein mucosal damage occurs

later. Moreover, the species isolated in these 2 cases was *Leishmania braziliensis*, which is commonly associated with the mucosal form of leishmaniasis. Treatment with pentavalent antimony and amphotericin B resulted in the resolution of lesions in the 2 cases, although the authors did not specify the use of corticosteroids.

Uveitis as a manifestation of IRIS, resulting from *Leishmania* infection, was reported in 3 HIV-infected patients undergoing HAART. One patient had uveitis concomitantly with PKDL and was treated successfully with miltefosine.¹³ In 2 patients, uveitis resulted in blindness in the affected eye, despite treatment with high doses of corticosteroids.^{18,21} In these cases, as well as in the patient reported herein, the isolated species was *L braziliensis*, which is commonly associated with the mucosal form of leishmaniasis.

Discussion

The present study reviewed cases of severe leishmaniasis in HIV-infected individuals as a manifestation of IRIS. Common characteristics found in these patients were cutaneous involvement regardless of the *Leishmania* species isolated, onset of disease regardless of when the patients were infected with *Leishmania*, as well as a rapid progression to severe forms of the disease in association with a rapid CD4 count recovery following ART. The median CD4 count before the onset of HAART was over 50 cells/mm³ in almost all cases, in comparison with lower CD4 counts found in patients with other infectious diseases in association with IRIS.^{5,29} In the majority of the reviewed cases, the length of time between the onset of HAART and occurrence of IRIS was 6 months, similar to what was observed in other infectious diseases associated with IRIS. The only exception was a patient who developed PKDL and uveitis as a manifestation of IRIS 9 years after the onset of HAART. However, this patient was unsuccessfully treated¹³ during this period, and IRIS occurred following rescue therapy, when the CD4 count rose from 71 to 321 cells/mm³. This finding suggests that leishmaniasis as a manifestation of IRIS occurs largely as a result of immune response recovery, despite the length of the recovery period or the initial CD4 count. Gelanew et al⁷ reported on 3 HIV-infected patients with PKDL, in which a definitive IRIS diagnosis was impossible due to the absence of standardized clinical and laboratory criteria.⁷ However, PKDL in association with IRIS could be considered in one of these cases, since the onset of symptoms was concomitant with an increase in CD4 (from 40 to 93 cell/mm³) following HAART. A diagnosis of IRIS would be conceivable in several notable cases detailed in the literature, involving an aggressive co-infection with HIV/*Leishmania*.^{30,31} Yet, in most of these reports, the length of time between the initiation of HAART and the occurrence of leishmaniasis is incomplete or absent, and relevant information regarding CD4 counts and viral load, before and after HAART, is missing.

Two cases of patients infected with HIV and MCL as a manifestation of IRIS have been described.¹⁴ Common findings are

dissemination of lesions, frequently found on the arms, lower limbs, and feet. In addition, lesions are also observed in the nasal, oropharyngeal, and genital mucosa in these patients. Moreover, in the 2 patients reported by Posada-Vergara et al,¹⁴ the onset of leishmaniasis, in one case, and the worsening of leishmaniasis, in the other, occurred 1 month after the onset of HAART. It has been well established that mucosal damage in individuals with leishmaniasis who are not HIV positive is usually associated with an exacerbation of the cellular immune response and elevated production of proinflammatory cytokines. In this form of leishmaniasis, the Montenegro skin test is positive, indicating a positive delayed-type hypersensitivity response to *Leishmania* antigens.^{32,33}

In several reports, patients experienced rapid healing of lesions in response to combined amphotericin B and corticosteroid treatments.^{9,12} From an immunological point of view, a parallel could be established between IRIS and type 2 leprosy reactions. Leprosy is the prototype of granulomatous disease in which the immune response can result in a paradoxical exacerbation of a patient's lesions, which are typically characterized as erythema nodosum leprosum.³⁴ Treatment with anti-inflammatory immunomodulatory drugs, such as thalidomide, is required to control the exacerbation of leprosy.^{35,36} Further studies should be conducted to evaluate the effectiveness of combined ART and corticosteroid therapy during the first 6 months of treatment in HIV-infected individuals with severe immunosuppression, who are at potential risk for life-threatening immune restoration disease.

ART results in a decreased incidence of opportunistic infections and longer patient survival.¹ Viral loads markedly decrease in tandem with an increase in CD4 counts, resulting in the restoration of immune function in more than 70% of the affected individuals.^{1,6} Restoration of CD4 counts seems to take place in 2 phases: the first phase occurs 2 weeks after treatment and lasts for 3 months. There is a relatively rapid redistribution of sequestered memory T lymphocytes (CD4+CD45RO+) from the lymphoid tissues into the bloodstream following a decrease in viral load.^{37,38} The second phase starts 6 months after viremia control and is characterized by less profuse and more gradual expansion of naive T cells (CD45RA+CD62L+), persisting for 1 to 2 years.³⁸ The swift restoration of the T-cell repertoire may contribute to the development of IRIS, especially in individuals with high amounts of antigens caused by either the presence of killed microorganisms during previous infections or prior subclinical opportunistic infections.⁶ The immunological mechanisms involved in IRIS development remain unclarified. Elevated production of proinflammatory cytokines is frequently found during the course of IRIS, most notably high levels of interleukin 6, interferon gamma, and tumor necrosis factor- α .³⁹⁻⁴¹ The recovery of pathogen-specific T cells may play a role in the intensity of the inflammatory response, as evidenced by several reports which found an increase in T cells specific to *M tuberculosis*, *M avium*, and *Cryptococcus neoformans* in patients who developed IRIS in association with these diseases.^{42,43} However, the importance of specific T cells warrants further investigation, as

other studies found no association between the recovery of *M tuberculosis*-specific T cells and tuberculosis in association with IRIS.^{44,45} To date, the literature contains no reports linking the recovery of *Leishmania*-specific T cells with IRIS-associated leishmaniasis. It is also possible that other mechanisms could contribute to the intensity of inflammatory responses during IRIS, such as the excessive activation of innate immune cells³ or the impairment of a regulatory T-cell response.^{44,46}

In conclusion, leishmaniasis as a manifestation of IRIS may present as a new disease or as the progression of latent disease following the introduction of HAART and consequent restoration of immunity. Further studies should be conducted to clarify the immunological aspects involved in IRIS development as well as to establish relevant criteria to aid in the definitive and prompt diagnosis of IRIS.

Acknowledgment

We thank Andris K. Walter for his assistance in English revision.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this work was supported by UCSD Center for AIDS Research, NIH (grant P30AI036214).

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