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Reversal Reaction as a Manifestation of Immune Reconstitution Inflammatory Syndrome

Vinicius Menezes, Anna Maria Sales, José Augusto Nery, Ximena Illarramendi, Alice Miranda, Maria Clara Galhardo and Euzenir Sarno
Leprosy Laboratory, Oswaldo Cruz Institute, Oswaldo Cruz Foundation
Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation
Brazil

1. Introduction

Leprosy is a chronic infectious disease cause by the *Mycobacterium leprae*. The disease is found worldwide, especially, in countries situated in tropical and subtropical regions. According to the reports of the World Health Organization (WHO) the global registered prevalence of leprosy at the beginning of 2010 stood at 211,903 cases, whereas the number of new cases detected during 2009 was 244,796 (World Health Organization [WHO], 2010). Although there has been a declining trend in prevalence and detection of new cases, leprosy is still a public health problem in Brazil. In 2009, the prevalence rate of the disease was 1.99 per 10,000 habitants and 37,610 new cases of leprosy were detected in the entire country (Brazilian Ministry of Health, 2011). On the other hand, the Human deficiency Virus (HIV) infection is one of the greatest health problems of the world due to its pandemic nature and high morbidity and mortality rates. In the absence of treatment, the Acquired immunodeficiency syndrome (AIDS) usually leads to premature death. The World Health Organization estimates that 33.3 million people were living with HIV in the end of 2009 around the globe and 2.6 million people became HIV infected in 2009 (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2010). In Brazil, the AIDS epidemic has been maintained stable in the last few years. In 2009, the incidence rate was 20.1 per 100,000 habitants and 38,538 new cases of AIDS were registered in the country (Brazilian Ministry of Health, 2010). Although the prevalence rate of coinfected individuals has never been estimated neither in Brazil nor worldwide, leprosy and the HIV infection seem to overlap in a number of countries, mainly in Africa and Asia continents.

As observed with others Mycobacterial infections, it has been speculated that HIV and *Mycobacterium leprae* coinfection could exacerbate the pathogenesis of leprosy lesions and/or could lead to increased susceptibility of leprosy. However, up to date, HIV infection has not seemed to modify the epidemiology and the natural course of leprosy (Ustianowski et al., 2006). In contrast, initiation of anti-retroviral treatment has been reported to be associated with activation of sub-clinical *M. leprae* infection and exacerbation of existing leprosy lesions (Menezes et al., 2009).

It is well known that highly active anti-retroviral therapy (HAART) in HIV patients is associated with dramatic reduction of HIV viral load and subsequent increase in CD4 T lymphocytes and immune function. While the recovery of the immune system results in clinical benefits and decrease in the incidence of opportunistic diseases and death, a subset of patients experience clinical deterioration after HAART is initiated. This phenomenon is termed immune reconstitution inflammatory syndrome (Muller et al., 2010). This entity describes a collection of different inflammatory disorders which is associated with paradoxical worsening of symptoms and signs related to sub-clinical or preexisting infectious as well as of non infectious processes following HAART introduction (Hirsch et al., 2004). IRIS seems to result from dysfunction of some aspects of the immune system that affect the restoration of pathogen specific immune response and/ or immune regulation (French, 2009). The immunopathology of IRIS is poorly understood but it seems to be highly determined by the provoking pathogen. In this way, inflammation in Mycobacterial infections is often associated with characteristics of a TH1 immune response (French et al., 2009). The sudden clinical deterioration associated with IRIS can be at times fatal and needs prompt intervention (Murdoch et al., 2007). The incidence of IRIS is not well know but it has been described ranging from less than 10% to more than 50%(Muller et al., 2010).

Some evidences suggest that antiretroviral therapy can accelerate the onset of leprosy symptoms. In a retrospective cohort study, Sarno et al has demonstrated that in those individuals who initiated HAART the length of time covered up to leprosy diagnosis was significantly shorter than in those not receiving HAART (p=0,01) (Sarno et al., 2008). In another study, in the Amazon region of Brazil, seven patients out of 25 presented leprosy as manifestation of IRIS (Talhari et al., 2010). One study, in French Guyana, has observed that the incidence of leprosy was higher in HIV patients receiving HAART for less than 3 months than in HIV untreated patients (13 against 0,7 per 1,000 person-year, p=0,02) (Couppié et al., 2009). Another study, in India, has found a high incidence of leprosy of 5.22 per 1,000 person-year in HIV patients on HAART (Vinay et al., 2009). Several case reports of leprosy associated with IRIS have been published in the literature (Martiniuk et al., 2007; Chow et al., 2009), including one of histoid leprosy case (Bumb et al., 2010).

Currently, it is widely accepted that the reconstitution of the immune function observed in HIV patients on HAART can trigger leprosy reaction. Leprosy reactions are immune-inflammatory events that complicate the disease. The frequency of reaction has been reported to range from 2.6% to 20% of PB patients (Becx-Bleumink & Berhe, 1992) and from 15% to 60% of MB cases (Bwire R & Kawuma HJ, 1994; Nery JAC et al., 1998). It is broadly accepted that reaction is the result of a shift in the patient´s level of inflammation and/or cell- mediated immunity which, in turn, leads to accelerated nerve damage and serious physical disabilities (Sarno et al., 2008). It is frequently observed during multidrug therapy (MDT), but it may be developed before or after leprosy treatment. These reactional states are classified as type 1 (Reversal Reaction) or Type 2 (Erithema Nodosum Lepromatosum) reaction depending on the clinical characteristics of the acute episode and its immune background. Strong evidences currently indicates that reversal reactions are the result of an enhancement of cellular immunity and delayed hypersensitivity to *M. leprae* antigens, but both the precipitating factors and the physiopathological mechanisms involved remain ill-defined (Scollard et al., 2006). Reversal reaction is clinically characterized by the worsening of previous leprosy lesion or appearance of new infiltrated, erythematous plaques. It may be accompanied by neuritis or systemic symptoms such as fever, malaise, arthralgia, or edema.

Since HAART for AIDS treatment has become available in countries where leprosy is endemic, around 41 cases of leprosy reaction associated to IRIS have been described in the literature (Tables 1 and 2) (Pavie et al., 2009). It is worth to notice that the majority of the patients were paucibacillary (65,8%) and most of them (90,2%) developed reversal reaction with only 4 cases of Erythema nodosum leprosum published (Tables 1 and 2). The mean time that patients developed reaction after initiation of HAART was 18.95 (4-172) weeks (median:8, Mode:8, standard deviation:31,1)(Tables 1 and 2). Twenty three (56.09%) of the cases were from Brazil (Pereira et al., 2004; Visco-Comandini et al., 2004; Trindade et al., 2005; Talhari et al., 2007; Caruso et al., 2007; Batista et al., 2008; Deps et al., 2008 & Menezes et al., 2009), 13 (31.7%) from India (Narang et al., 2005; Singal et al., 2006; Kharkar et al., 2007; Kar et al., 2009 &Vinay et al., 2009), 3 (7.31%) from Haiti (Couppié et al., 2004 & Pavie et al., 2009), 1 (2.43%) from Uganda(Lawn et al., 2003) and 1(2.43%) from French Guiana(Couppié et al., 2004). Thirty one (75.6%) patients were man and 10 (27.3%) women. Twelve (27.3%) cases presented neuritis associated to reaction (Tables 1 and 2).

References	Leprosy/ Reaction Types	Weeks on HAART	CD4 Cell/µl		Viral load/Ml	
			HIV	IRIS	HIV	IRIS
(Lawn et al., 2003)	BT + RR	4	10	70	120,000	1,000
(Couppie et al., 2004)	BB + RR	6	87	257	19,000	650
	BT + RR + N	8	130	278	40,701	68
	BT + RR + N	12	31	171	62,700	50
(Pereira et al., 2004)	BT +RR	8	73	270	NA	NA
	BT +RR	24	35	100	NA	NA
(Visco-Comandini et al., 2004)	BT + RR	8	7	90	NA	NA
(Narang et al., 2005)	BT + RR	8	125	280	150,000	1,750
(Trindade et al., 2005)	BB+ RR	24	87	NA	<80	NA
	BB+ RR+N	4	223	NA	NA	NA
	BT+ RR	8	430	NA	NA	NA
(Singal et al., 2006)	I +RR	8	NA	NA	<400	NA
	BL + RR+N	4	108	224	NA	NA
(Kharkar et al., 2007)	BT + RR	12	299	504	NA	NA
	BT + RR	8	114	184	NA	NA
(Talhari et al., 2007)	BT + RR+N	12	92	426	NA	8,300
(Caruso et al., 2007)	BT+ RR	16	NA	57	NA	< 80
(Batista et al., 2008)	BT + RR+N	8	14	172	21,300	69,000
	BT + RR+N	8	104	235	NA	<80
(Deps et al., 2008)	BT + RR	10	33		6,310	NA
	BT + RR	4	170		9,230	NA

Table 1. Characteristics of 21 cases of leprosy reactions associated with immune reconstitution inflammatory syndrome published in literature until 2008:
Abbreviations: BT= Tuberculoid borderline; BB= Borderline borderline; BL= Lepromatous borderline; RR= Reversal reaction; N= Neuritis; NA= Not available.

References	Leprosy/ Reaction Types	Weeks on HAART	CD4 Cell/µl		Viral load/Ml	
			HIV	IRIS	HIV	IRIS
(Menezes et al., 2009)	BT+ RR	4	142	499	300	<80
	BB+ RR	4	37	200	53,000	2,200
	BT+ RR	8	NA	226	NA	<80
	BT+ RR	10	62	226	NA	<80
	BT+ RR + N	4	85	190	5,700,000	140
	BB+ RR	8	179	271	39,000	<80
	BB+ RR	4	160	140	77,204	4,880
	BT+ RR	16	76	215	180,000	<80
	BB+ RR	4	NA	408	NA	<80
	BT+ RR	16	NA	171	14,000	<80
(Kar et al., 2009)	BT+RR	7	125	333	NA	NA
(Pavie et al., 2009)	MB+RR+N	40	25	110	100,000	<80
(Vinay et al., 2009)	MB+ENL	172	177	892	NA	NA
	MB+RR+N	32	75	170	NA	NA
	PB+RR+N	24	85	251	NA	NA
	MB+ENL	8	99	99	NA	NA
	MB+ENL	112	124	239	NA	NA
	MB+ENL+N	16	31	144	NA	NA
	PB+RR	64	331	374	NA	NA
	PB+RR	20	174	436	NA	NA

Table 2. Characteristics of 20 cases of leprosy reactions associated with immune reconstitution inflammatory syndrome published in literature in 2009. Abbreviations: BT= Tuberculoid borderline; BB= Borderline borderline; BL= Lepromatous borderline; RR= Reversal reaction; N= Neuritis; ENL= Erithema nodosum lepromatosum; NA= Not available.

In the present series, the highest casuistic published so far, 12 cases of leprosy reaction as manifestation of IRIS are thoroughly described in order to establish clinical and immunological parameters of definition.

2. Subjects and methods

2.1 Study design and inclusion criteria

The Leprosy Laboratory and the Evandro Chagas Clinical Research Institute (IPEC), FIOCRUZ, Rio de Janeiro, have been evaluating coinfected HIV/*M. leprae* patients since 1989. Both institutions are reference centers in Rio de Janeiro for these diseases and so far, a total of 100 patients have been followed.

For the purpose of this study, we have reviewed the charts of all patients coinfected with *M. leprae* and HIV who were referred to the Leprosy laboratory/Fiocruz and the IPEC between 1997 and 2010. Inclusion criteria were based on the definition criteria proposed by French et al (French et al., 2004). Thus, reversal reaction as a manifestation of IRIS was defined as the presence of reaction any time during the first 6 months of HAART associated to decrease >1 log in HIV-1 viral load. In addition, it was defined in HAART naïve patients with no previous laboratory tests data (Viral load or CD4 lymphocytes

count), if reaction was present during the first 6 months after initiation of HAART associated to undetectable HIV-1 viral load.
Since the introduction of HAART for AIDS treatment by the Brazilian government in 1997 until the year of 2010, 33 patients had leprosy reaction under HAART, 12 of which were diagnosed with IRIS and were grouped into the case series presented in the present study.
Case reports of 10 of these patients have been published (Menezes et al., 2009) but additional data was obtained and as they are part of the cohort studied they were maintained to compose the present case series.

2.2 Definitions and clinical routine

All patients followed the clinic routine dermatological and neurological evaluation. For diagnostic purposes, skin biopsies were obtained by punch. Samples were routinely processed, paraffin embedded, and stained with hematoxylin and eosin (H&E) and Wade's modification of the Ziehl-Nielsen method for detection of acid-fast bacilli (2 sections of each staining). Slit skin smears were obtained from six body sites (one from each earlobe, one from each elbow, one from a lesion and one from the contra-lateral knee). The smears were stained for acid-fast bacilli (AFB) by Ziehl-Neelsen techniques. The bacilloscopic index (BI) was calculated using the Ridley & Jopling logarithmic scale (Ridley & Jopling, 1966), based on analysis of 100 fields. The lepromin test was measured 30 days after the intradermal injection of 0.1 mL of heat-killed *M. leprae* in the anterior forearm. The result was either scored as negative if <5 mm, or positive if ≥5 mm. Leprosy was then diagnosed and classified according to Ridley-Jopling criteria(Ridley & Jopling, 1966). The diagnosis of reversal reaction was histophatologically defined on the presence of epithelioid cells granuloma. In this study we identified two main patterns of reversal reaction depending on the severity of the tissue inflammatory changes (Ridley 1969):

- mild acanthosis and exocytosis; well developed cohesive epithelioid granulomas intermingled with few lymphocytes; blood vessels, arrector pili muscles, adnexa and nerve bundles; sparse multinucleated cells and small foci of red blood cell extravasation.
- Exuberant changes as moderate to severe acanthosis, spongiosis and exocytosis; epithelial apoptosis and basal epidermal erosion; severe dermal inflammatory infiltration, including granulomas dissociated by marked edema or centered by necrosis, as well as numerous giant cells and red blood cell extravasation.

All the patients were treated for leprosy with multidrug therapy. Reversal reaction was treated following recommendations of the Brazilian Ministry of Health, with a daily morning dose of prednisone, starting with 1mg/kg for 1 month, followed by a 10mg/month progressive reduction.
Diagnosis of HIV infection followed the Brazilian Ministry of Health regulations, which include the performance of two tests; the immune-enzymatic method (ELISA) plus immune-fluorescence or Western Blot (National STD/AIDS program of Brazil, 2008). The CD4 cell count and viral load were determined around the time of HIV diagnosis and again around the time of leprosy diagnosis (defined as the first time the patient visited a health center with signs of leprosy). HAART was started at CD4 cell count of less than or equal to 200 cells/μL or if an opportunistic infection was diagnosed (National STD/AIDS program of Brazil, 2008). To control the HIV infection, the patients were submitted to periodical clinical evaluation and routine laboratory tests. The exchange of information related to the

evolution of both infections is a routine at the Units, and remained under the responsibility of the professionals involved in the study.

2.3 Data collection and statistical analysis

Pertinent data were collected from the patient charts at both institutions. All analysis were performed using SPSS 16.0. The difference of the CD4 lymphocytes count and HIV viral load before and at the onset of reversal reaction associated with IRIS was analysed by the Wilcoxon test.

2.4 Ethical concerns

The study was approved by the ethics committee of the Oswaldo Cruz Institute and the IPEC.

3. Results

Among the total 33 patients experiencing leprosy reversal reaction under HAART, 12 (36.3%) met the predetermined IRIS criteria. Demographic, clinical and laboratory data of these 12 patients are presented in Table 3 (Figure 1). Ten patients were initially diagnosed with HIV infection. Significantly, HAART induced reaction in nine patients who had not been diagnosed with leprosy. All but one patient received standard treatment for reaction with a daily oral dose of prednisone. Five patients needed prolonged use of prednisone for up to 12 months (Table 3).

Case	Age/Sex	Leprosy/ reaction types	Lesion number/ complication	Lepromin test (mm)	BI	Time in prednisone (months)
1	48/M	BT/RR	2/ none	12	0	0
2	33/F	BB/RR	>20/ ulcer	10	0.5	9
3	39/M	BT/RR	>10/ulcer	6	0	12
4	34/M	BT/RR	>20/none	0	0	8
5	28/M	BT/RR + N	>20/none	0	0	10
6	46/M	BB/RR	1/none	12	0.57	11
7	22/M	BB/RR	>20/none	0	2.25	
8	28/M	BT/RR	1/ulcer	9	0	6
9	22/F	BB/RR	2/none	0	0.5	2
10	54/M	BT/RR	>20/none	0	0	0
11	27/M	BT/RR	>20/ulcer	NA	0	6
12	M	BB/RR	>10/none	10	0.57	9

Table 3. Clinical and epidemiological data of 12 patients with defined IRIS.BT= Borderline Tuberculoid, BB= Borderline Borderline, RR= reversal reaction; N=Neuritis

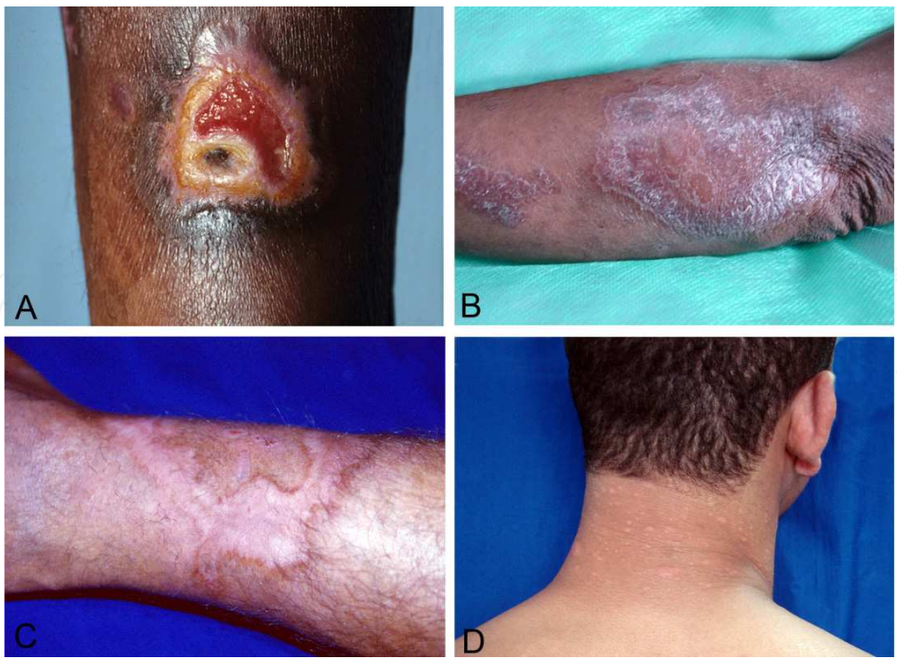

Fig. 1. Clinical pattern of reversal reaction skin lesions.
1A - Clean, ulcerated plaque with well-defined borders. 1B - Infiltrated and erythematous plaques with a scaly surface and irregular borders. 1C – Erythematous, queloid-like plaque with small central ulcerations. 1D - Disseminated urticariform lesions of various sizes.

The clinical or laboratory findings of all patients showed immune suppression prior to reversal reaction diagnosis. However, only 5 patients had opportunistic infection, namely pneumocistosis, esophageal candidiasis, neurotoxoplasmosis and disseminated tuberculosis. Moreover, by the time reaction occurred during HAART treatment, most of the patients had an increase of the CD4/CD8 T lymphocyte rate, mainly due to increase of CD4 cell count mean of 204.5 cells/μL (92-446cells/μL) (Table 4) (Figure 2). Nine patients had an undetectable viral load when reaction developed and three had a mean viral load reduction of 2.4 log (1.4 - 4.6 log) (Table 4) (Figure 2). All patients were treated for HIV with regimens containing two nucleoside reverse transcriptase inhibitors in combination with a protease inhibitor (8.33%), a boosted protease inhibitor (33.33%), or a nonnucleoside reverse transcriptase inhibitor (58.33%) (Table 4). The mean time the patients presented reversal reaction after starting HAART was 7.8 weeks (Table 4).
All patients presented erythematous infiltrated plaques and were in the borderline spectrum of leprosy. Four patients had complicated ulcerated lesions (figure 1A & 1C) (Table 3). The histopathological features observed in all the skin biopsies were fulfilled the patterns described for the diagnosis of reversal reaction with tissue severity (figure 3), ranging from heavy infiltration, foci of necrosis and extensive involvement of the epidermis (figure 3C & 3D), to moderate cellular infiltration with well-formed granulomas (figure 3A & 3B) (Table 5). There was evidence of fragmented acid-fast bacilli in 6 skin biopsies (Table 5). Two samples (cases 1 and 11) showed unusually extensive multinucleated cells permeating the granulomas (Table 5). The biopsy of patient 2 had heavy dermal edema and marked inflammatory infiltration, including some polymorphonuclear leukocytes and many foci of necrosis. Initially, these features led to a mistaken diagnosis of *erythema nodosum leprosum*.

After a clinical and histopathological review, reversal reaction superimposed to a multibacillary background was established.

Case	HAART regimen	Weeks on HAART	CD4 Cell/µl		Viral load/Ml	
			HIV	IRIS	HIV	IRIS
1	AZT+3TC+NFV	4	142	499	300	<80
2	AZT+ DDI+EFVZ	4	37	200	53,000	2,200
3	AZT+ DDI+EFVZ	8	NA	226	NA	<80
4	D4T+ 3TC+ NVP	10	62	226	NA	<80
5	D4T+3TC+LPV/ RTV	4	85	190	5,700,000	140
6	AZT+3TC+LPV/ RTV	8	179	271	39000	<80
7	TDF+ 3TC+ATV/ RTV	4	160	140	77,204	4880
8	AZT+ 3TC+EFVZ	16	76	215	180,000	<80
9	AZT+3TC+LPV/ RTV	4	NA	408	NA	<80
10	D4T+ 3TC + EFVZ	16	NA	171	14000	<80
11	AZT+3TC+EFVZ	12	03	173	407,800	<80
12	AZT+3TC+EFVZ	4	125	571	321,560	<80

Table 4. Laboratory data of the 12 patients with reversal reaction and defined IRIS
Abreviations: NA= not available. AZT= Zidovudine; 3TC= Lamivudine; D4T= Stavudine; DDI= Didanosine; TDF: Tenofovir, NVP= Nevirapina; EFVZ= Efavirenz, NFV= Nelfinavir; ATV/RTV= Atazanavir/ Ritonavir; LPV/RTV= Lopinavir/Ritonavir.

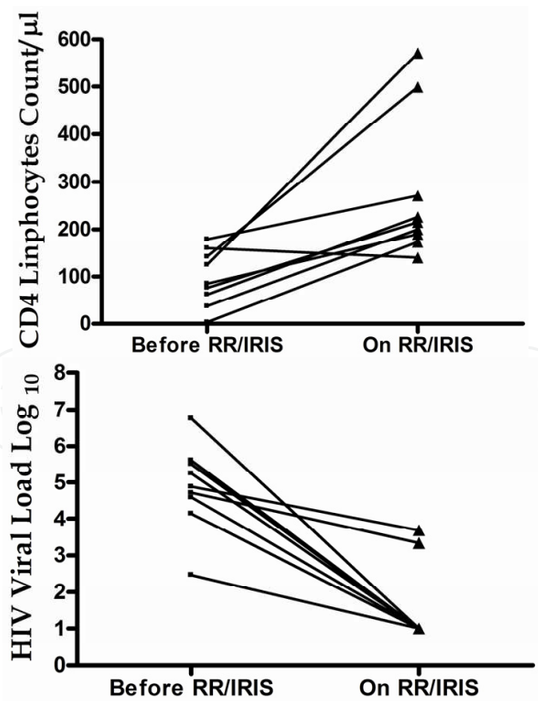

Fig. 2. Longitudinal analysis of CD4 lymphocytes count and HIV viral load before and at the onset of reversal reaction/IRIS. The mean increase of the CD4 cells count and the mean decrease of the HIV viral load were significant (p=0,007 and p=0,003, respectively).

Case	AFB (ILB)	Granuloma Giant cells [a]	lymphocyte	necrosis [b]	Severeness
1	0	+++	20%	+	Severe
2	2.6	++	20%	++	Severe
3	0	+	15%	+	Severe
4	1	-	30%	+	Severe
5	3	-	20%	-	Mild
6	0	+	30%	-	Mild
7	2.8	+	20%	-	Mild
8	0	+	20%	-	Mild
9	0	+	20%	++	Severe
10	1.9	++	19%	+	Severe
11	0	+++	25%	++	Severe
12	1	++	20%	-	Severe

Table 5. Histopathological data of the 12 patients with reversal reaction and defined IRISpatients. In relation to control. Symbols: a) + = few, ++ = several, +++ = many, -=not observed; b) + = little, ++ = moderate, -=not observed.

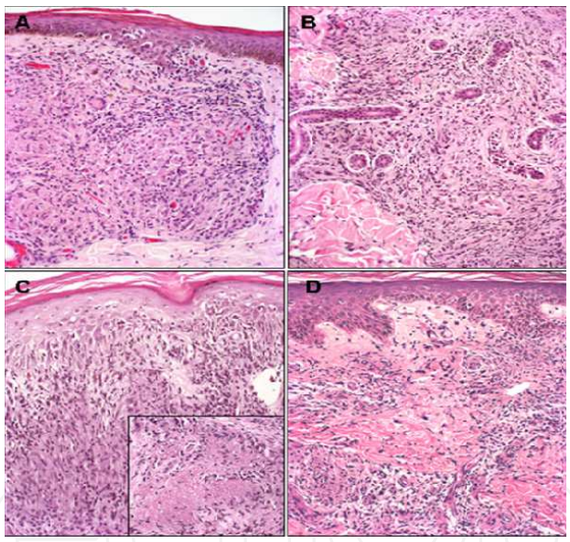

Fig. 3. Histopathological patterns of skin lesions in IRIS patients
A. Epidermis with intraepithelial lymphocytes and apoptosis; dermis showing cohesive tuberculoid granulomas with multinucleated giant cells in RR (pat. 6); *B.* Angled epithelioid granuloma dissociating adnexa in RR(pat. 5); *C, D.* Severe epidermal changes, dermal edema, and epithelioid granulomas with foci of necrosis (inset) in RR type D (pat. 9 and 2, respectively; H&E, original magnification, X200).

4. Discussion

As observed in the present case series, in the HAART era, leprosy reaction associated with IRIS appears to be a frequent event in coinfected patients. The 36% reversal reaction rate in coinfected patients undergoing HAART is similar to that estimated for tuberculosis as a

manifestation of IRIS (French., 2009). Interestingly, HAART triggered reversal reaction in 88% of the patients not previously known to have leprosy. As likewise seen in the literature (Table 1 and 2), most of the present IRIS cases associated to leprosy had the predominantly borderline-tuberculoid form. The borderline forms are considered the most unstable in that the immunological capability of the patient to restrain the infection is only partial. During reversal reaction, high amounts of inflammatory cytokines such as interferon gamma and tumor necrosis factor are produced, reflecting the immune activation characteristics of skin lesions with a tuberculoid pattern (Nery et al., 2000).

Although the moment of infection for either HIV or leprosy is difficult to establish, most of the patients were first diagnosed with HIV. In the present case series the period of time elapsed between HAART introduction and leprosy reaction was variable but similar to previously described in the literature, which ranges from 4 to 24 weeks (Hirsch et al., 2004). In HIV negative individuals, reversal reaction usually occurs during the initial months of multidrug therapy. As recently reported, the diagnosis of leprosy is associated with improved immune status in HIV infected individuals (Sarno et al., 2008). The appearance of clinical signs of *M. leprae* infection in the form of reversal reaction observed in this series and in published case reports is not a manifestation of immune suppression but rather of immune reconstitution. This is further supported by the presence of a positive lepromin test in some of the multibacillary patients.

Among the risks factors associated to the development of IRIS, male gender (Shelburne et al., 2005), young age (Ratnam et al., 2006), and immune suppression (Shelburne et al., 2005; Ratnam et al., 2006) were also observed in the present series. Other risk factors, such as short interval between initiating treatment for opportunistic infection (OI), a rapid fall in HIV-1 RNA after HAART, and being ART naïve at the time of OI diagnosis were observed in most of the patients(Shelburne et al., 2005). Additional significant predictors include a lower baseline CD4 cell percentage, a lower CD4 cell count at ART initiation, and a lower CD4 to CD8 cell ratio at baseline were observed in a few cases (Ratnam et al., 2006). In the same way, a higher baseline CD8 cell count is associated with IRIS as CD8 cell counts represent the presence of immune activation[29, 36, 37] (Ratnam et al., 2006) (Robertson et al., 2006) (Cianchetta-Sivori et al., 2007). In a case control study, the nadir CD4 T count of less than 100 cells was independently predictive of development of IRIS as well as the absolute drop in viraemia positively correlated with increasing risk for IRIS (Manabe et al., 2007). In this series, 5 cases had less than 100 CD4+ cells/μL.

Absolute CD4 T cell increase was observed in most patients, but in 1 patient a cell count decrease was observed. As recently described, absolute CD4 T cell increase is not present in all cases of IRIS (French et al., 2004; Shelburne et al., 2006). Approximately 10% of IRIS complicated MAC infection occurred in the absence of an increase of CD4 T cells count(Manabe et al., 2007). Robertson *et al* suggested to remove an increase CD4 cell count as a sole criterion of IRIS, because CD4 lymphocyte plasma levels do not necessary reflect function(Robertson et al., 2006). Immune responses may be restored before a rise in plasma CD4 cell count is detected. They proposed that an increase in CD4 T cell count should be viewed as supportive of diagnosis rather than required for it.

Manabe *et al* suggested that the use of the most potent regimens (boosted protease inhibitors [BPIs] and/or non-nucleoside reverse transcriptase inhibitors [NNRTIs]) is an independent risk factor for the development of IRIS (Manabe et al., 2007). In particular, the use of BPIs was associated with IRIS. All of the patients but one, in the present series, were using either one or more of these drugs. In addition, HAART induced reduction of 2.5 logs RNA levels has shown the highest risk of IRIS (Manabe et al., 2007). In the present study, a similar log reduction was observed in the cases with viral load data.

The pathogenesis of IRIS remains speculative. Current theories involve the combination of underlying antigen burden, the degree of immune restoration, as well as the host genetic susceptibility (Price et al., 2001). According to Murdoch, the antigenic stimulus can be intact, "clinically silent" organism or dead or dying organism and their residual antigens (Murdoch et al., 2007). A common feature of the cases of IRIS is that clinical presentation of the opportunistic infection is often atypical compared with that usually observed in HIV-1 infected patients (French et al., 2004). On the other hand, the pathogenesis of reversal reaction is still not completely understood. Restoration of the *M. leprae* specific immune response has been claimed, but convincing data are lacking. During reversal reaction, high amount of inflammatory cytokines are produced reflecting the immune reactivation of the skin lesions with tuberculoid pattern (Sampaio et al., 1995; Krutzik et al., 2005).

Among the various risk factors described for reversal reaction are concomitant infections, immunization, and pregnancy (Nery JA et al., 1998). In addition, in the present case series, HAART triggered reversal reaction in 88% of the patients not previously known to have leprosy. Different from initially expected HIV infection *per se* did not modify the course of the disease, but immune restoration by HAART does appear to worsen reversal reaction. In the present series, some patients had numerous lesions and ulcers and needed extended corticoid therapy, demonstrating a more intense inflammatory process. Such pattern could explain the profound scars left by the reversal reaction lesions that are not observed in non HIV patients. This type of presentation with numerous skin lesions and ulcerations is more usually seen in type II leprosy reactions which are more frequent in multibacillary patients and was never referred in the context of IRIS. On the other hand, patients with tuberculoid forms which display strong cellular response to *M. leprae,* usually have neuritis. Surprisingly, only one patient in this series was diagnosed with neuritis. The histological findings observed in all patients were typical of reversal reaction (Ridley & Radia,1981) even in those presenting AFB+ biopsies. Disorganized and disperse granulomas could be seen in some cases, thus rending difficult to classify those patients according to the leprosy spectrum (cases 2, 5 and 9). The presence of necrosis only occurred in severe reactions, either in small foci or causing liquefaction of the granuloma, followed by fibrosis as in case 3, leaving profound scars. In some other cases, however, the granulomas take typical tuberculoid characteristics, with cohesive epithelioid cells surrounded by a lymphocytic halo. The presence of low number of AFB has already been described in borderline tuberculoid lesions (Ridley & Jopling, 1966).

Treatment of complications due to IRIS in other coinfections is frequently necessary to minimize short-term morbidity but in the long-term follow-up, outcome appears to be good (Murdoch et al., 2007; Riddell et al., 2007). In the present series the patients were treated with prednisone as standard for reversal reaction, and had a favorable evolution in spite of the severity of disease or the need of a short extension of the use of corticoids. Prednisone is the drug of choice for treating reversal reaction because it reduces nerve edema, exerts an immunosuppressive effect, and decreases post-inflammatory scar formation (Naafs 1996; Andersson et al., 2005). Thus, no modification of the standard therapy for reversal reaction is needed in case of IRIS in leprosy patients.

5. Conclusions

The present is the largest case series of reversal reaction associated with IRIS in coinfected patients described in the literature. In countries like Brazil, where both epidemics overlap

and HAART has been broadly administered, leprosy reaction associated to IRIS is prone to occur. It might be posited, therefore, that the appearance of clinical signs of *M. leprae* infection in HIV-infected individuals is not a manifestation of immunosuppression but rather of immune reconstitution. In the present series, the patients treated with prednisone as standard reversal reaction therapy had a favorable evolution despite disease severity. Thus, the results of this study clearly indicate that no modification of the standard reversal reaction therapy appears necessary in the case of leprosy patients with IRIS. However, there is still need of prospective studies to evaluate the association of leprosy reactions and IRIS in order to better characterize the pathology and immunology of the coinfection.

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7. References

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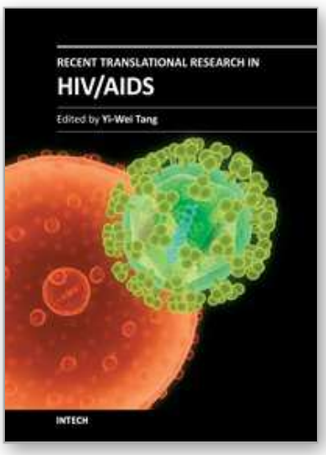

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The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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