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## Non-Hodgkin's lymphoma as a rare manifestation of immune reconstitution disease in HIV-1 positive patients

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### Summary

Combination antiretroviral therapy (cART) can improve immune system function through suppression of HIV-1 replication. However, paradoxical immune response may develop in some patients as a result of effective therapy followed by immune restoration. The phenomena is known as IRS, immune reconstitution syndrome/immune recovery syndrome. IRS can develop within weeks to months after cART is commenced and the time is related to the type of the disease. There are but scant reports concerning IRS-NHL (non-Hodgkin's lymphoma) in HIV-1 positive subjects. We observed 4 (33%) cases of IRS-NHL out of 12 patients in whom NHL was diagnosed. As a result of potent cART they reached viral suppression in a mean time of 15 weeks followed by a rise in CD4(+) T cells within 16.5 weeks. The diagnosis of NHL was established at a mean time of 36 weeks after cART was introduced and 20 weeks after the CD4 T cell increase was achieved. This may indicate that the immune reconstitution as a result of cART was a predisposing factor for the development of NHL in our patients. There was prompt progression of the disease and the outcome was fatal in all cases. IRS-NHL should be suspected in any case of lymphadenopathy, generalized or limited to the abdomen or periphery, which develops after immune recovery due to potent cART within a few months.

#### Key words:

**HIV infection • immune reconstitution disease • NHL**

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## INTRODUCTION

Combination antiretroviral therapy (cART) can improve immune system function through suppression of HIV-1 replication [5,10,15]. However, in some patients the rise in CD4 T cells is accompanied by the development of an atypical clinical picture of opportunistic infections or other inflammatory or neoplastic diseases because of the deteriorated immune response [1–3,6,7,12,15]. These symptoms are known as IRS (immune reconstitution syndrome/immune recovery syndrome) or IRD (immune restoration disease) [1,13,15]. There are some predisposing factors, such as long-lasting HIV-1 infection, severe immunodeficiency, rapid immune restoration, immune dysregulation during immune reconstitution, subclinical infection before commencing cART, and genetic susceptibility [1,3,6,8]. IRS can develop within weeks to months after cART is commenced and the time is related to the type of the disease [1,2,6,7,12]. For example, Graves's disease can occur as IRS even after 2-3 years [6]. IRS-opportunistic infections (IRS-OIs) are observed earlier after cART is initiated (within weeks) [1,3,7,8,12,13]. The association of HIV-1 infection, cART, and non-Hodgkin's lymphoma (NHL) following deteriorated immune recovery has been reported [2], although the idea of IRS-NHL as a result of potent cART may be controversial. Well known is the fact that the incidence of NHL declines after commencing ART, but the rate of decline is slower than for OIs [5,8,14]. If cART is initiated, more virulent opportunistic infections no longer develop, the patient is kept alive, and NHL is allowed time to develop into a clinical disease. Thus NHLs are observed despite effective cART. On the other hand, different mechanisms of immune deterioration following potent ART that influence the development of NHL cannot be excluded, as the phenomena of IRS is observed in many OIs and several autoimmune diseases [2,4,6].

We report four cases of HIV-1 positive patients receiving cART who developed NHL which was probably related to deteriorated immune restoration following effective ART. The clinical data and therapy are presented in Tables 1–3.

## CASE REPORTS

### Patient 1

A 26-year old woman had been HIV-1 positive, without AIDS, for eight years before NHL developed. Initiation of antiretroviral therapy had been delayed due to the patient's decision. Her CD4<sup>+</sup> T-cell count was very low at the beginning of cART (see Table 1) Thirty-six weeks after cART was initiated, NHL (stage III) was diagnosed. The first symptoms resembled peritonsillar abscess and delayed the diagnosis of NHL. During the next four weeks the symptoms of a generalized neoplastic disease with enlargement of the cervical and retroperitoneal lymph nodes were observed. The times of viral suppression, immune reconstitution, and NHL development were similar, i.e. 36 weeks (see Table 3).

### Patient 2

A 59-year-old woman had been HIV-1 infected for 12 years before NHL was diagnosed. She had not suffered from

AIDS before. She had not visited the department of infectious diseases for many years and started cART when her CD4<sup>+</sup> T-cell count was 125 cells/ $\mu$ l (see Table 1). After six weeks of antiretroviral therapy, viral suppression was seen, followed by an increase in the CD4<sup>+</sup> T-cell count within the next six weeks. The first symptoms suggesting NHL were observed 32 weeks later. NHL (stage IV) was recognized at autopsy after 44 weeks. The proper diagnosis was difficult to establish because of the abrupt onset, rapid progression, and atypical presentation of the disease (ascites, leg edema, weight loss, weakness, hypoalbuminemia, moderately increased aminotransferases and GGT levels) suggesting liver cirrhosis as a result of alcohol abuse. Peripheral lymph nodes were not enlarged. No other diagnostics (except abdomen ultrasonography (USG), without any significant changes at the examination) was performed. She died within 16 weeks after the onset of the symptoms. At autopsy, NHL changes were observed in the lymph nodes, liver, spleen, kidney, pancreas, and suprarenal glands (histopathological confirmation) (see Table 3).

### Patient 3

HIV-1 infection was found in a 34-year-old man in July 2001. At presentation, no symptoms of AIDS were observed. He had started cART in Oct 2001. Viral suppression was achieved after 3 weeks and a rise in CD4<sup>+</sup> T cells within the next 11 weeks. The diagnosis of NHL (stage IIB) was established 18 weeks after immune restoration. Symptoms of generalized neoplastic disease with enlargement of the retroperitoneal lymph nodes developed. Initially, extrapulmonary tuberculosis or atypical mycobacteriosis was suspected. There was a temporal relationship between viral suppression, increase in the CD4<sup>+</sup> T-cell count, and the manifestation of NHL.

### Patient 4

A 45-year-old man was found to be HIV-1 infected in May 2002 when he developed a low-grade fever, weight loss, fatigue, and a generalized peripheral lymphadenopathy up to 2 cm in size; the right axillary lymph node was 4 cm in diameter. On the second of May he commenced cART. Eight days later, severe *Pneumocystis carinii* (jiroveci) pneumonia developed. The patient improved after three weeks of therapy with co-trimoxazole. Within the next two weeks he complained of high-grade fever, wasting, fatigue, and abdominal pain. Hepatosplenomegaly and enlargement of the peripheral lymph nodes were observed. USG and CT scan of the abdomen revealed numerous enlarged lymph nodes, partially forming conglomerates, not seen before. Bone marrow biopsy and direct examination of the abdominal lymph node disclosed mycobacteria. Therapy for tuberculosis and atypical mycobacteriosis was started. During the treatment, the right axillary lymph node enlarged significantly, but the patient did not agree to its excision. His condition improved significantly during the next three months (antimycobacterial and antiretroviral therapy was continued). The peripheral lymph nodes decreased; only the right axillary lymph node was 4 cm in diameter. In December 2002, a painful, large right axillary tumor 30 cm in size developed. The diagnosis of Burkitt's lymphoma was established. The patient's condition worsened despite chemotherapy and he died five months later. No data on the

Table 1. Data concerning HIV-1 infection/AIDS

Patients, age	Mode of HIV infection	Date of diagnosis HIV AIDS	AIDS-defining conditions before NHL	CD4 <sup>+</sup> T-cell count [cells/ $\mu$ l]			Viral load at cART initiation	Date of beginning cART	Antiretroviral therapy
				nadir	at cART initiation	CD4T increase			
F 26 years	intravenous drug user	1990 12.1997	None	89	92	123	1,700,000	03.1997	ZDV, ddC, SQV
F 59 years	heterosexual	1987 08.1999	None	125	125	58	170,000	06.1998	d4t, ddl, NFV
M 34 years	homosexual	07.2001 05.2002	None	152	175	6	78,000	10.2001	ZDV/LMV, EFV
M 45 years	homosexual	05.2003 05.2003	pneumocystis carinii pneum. mycobacteriosis	5	5	90	535,000	05.2003	d4T, LMV, LPV/RTV

Abbreviations: PCP – *Pneumocystis carinii (jiroveci)* pneumonia; ZDV – zydovudine; ddC – zalcitabine; SQV – saquinavir; d4T – stavudine; ddl – didanosine; NFV – nelfinavir; EFV – efavirenz; LPV/RTV – lopinavir/ritonavir.

Table 2. Data concerning non-Hodgkin's lymphoma

Patients, age	Diagnosis		CD4 <sup>+</sup> T-cell count [cells/ $\mu$ l] at the diagnosis of lymphoma	Viral load [copies/ml]	Chemotherapy	Date of death
	type	date				
F 26 years	Immunoblastic diffuse B-cell lymphoma CD20(–) CD45RO(–)	12.1997	215	3000	5 × CHOP, DHAD, AMS, VP 01–07.1998	29.07.1998
F 59 years	Follicular B-cell lymphoma G3 LCA(+++) CD20(+++) CD43(–) Bcl(–) Ki67(15%)	08.1999	149	5156	None	09.08.1999
M 34 years	Peripheral T-cell lymphoma CD45RO(+) CD3(+) CD20(–)	05.2002	181	<50	6 × CHOP 06–09.2002	24.10.2002
M 45 years	Burkitt's lymphoma CD20(+) MIB1(++++)	12.2003	87	2600	CODOX/IVAC TPI 01–03.2004	20.05.2004

Table 3. Data concerning immune reconstitution and survival

Patients, age	Time (weeks) from beginning of HAART to:			Survival time from diagnosis		
	viral suppression	immune restoration	onset of lymphoma	HIV years	AIDS months	Lymphoma months
F 26 yrs	36	36	36	8	7	7
F 59 yrs	6	12	44	12	diagnosis at autopsy	diagnosis at autopsy
M 34 yrs	3	14	32	1.3	5	5
M 45 yrs	NA	4	32	1	12	5

time of viral suppression are available. NHL developed 28 weeks after immune restoration. However, the manifestation of PCP followed by mycobacterial lymphadenopathy and the lack of the patient's agreement to a axillary lymph node biopsy about 14 weeks earlier probably delayed the diagnosis of NHL and made it difficult.

## DISCUSSION

The use of combination antiretroviral therapy (cART) is associated with a significant decrease in plasma HIV RNA level and rise in the CD4<sup>+</sup> T cells count resulting in the decline of AIDS morbidity and mortality [4,9–11]. However, in some patients infectious diseases may develop as a manifestation of the immune restoration related to cART [1,3,7,8,12,13]. Sarcoidosis and autoimmune diseases as well as NHL are less common as IRDs [1,3,6,15]. IRS can develop within weeks to months after cART is commenced and the time is related to the type of the disease, though this is not yet well established [3,7,13,15]. For example, Graves's disease can occur as an IRS even after 2–3 years, while IRS-opportunistic infections are observed earlier (within weeks) [6].

We discuss here the occurrence of NHL as an occurrence of immune reconstitution syndrome in HIV-1 positive patients. Twelve individuals with AIDS-related lymphomas were identified. In all of them a very low CD4<sup>+</sup> T-cell count was seen at the time of HIV-1 diagnosis. In eight (67%) patients, NHL was found before cART was initiated. In the other four (33%) patients, NHL followed immune restoration, a result of antiretroviral therapy. At the beginning of cART, profound immune deficiency and very high viral loads were seen in them. There were no signs and symptoms of lymphomas (Table 1). A temporal relationship of viral suppression followed by an increase in the CD4 T cell count and then the appearance of NHL was observed. Significant inhibition of viral replication was achieved within a mean time of 15 weeks, followed by CD4<sup>+</sup> T cell increases within 16.5 weeks. NHL developed 36 weeks after cART was introduced, suggesting that immune reconstitution may have been a predictive factor for the development of NHL in our patients [2,15].

Collazos et al. also observed a temporal relationship between cART, viral load, and rise in CD4<sup>+</sup> T cells followed

by NHL and assumed that NHL in their patients could be a manifestation of IRS [2]. The difference between the appearance of NHL in our cases (10 months) and that reported by Collazos et al. (2 months) may be a result of the delayed time of diagnosis in some of our patients, but it can also indicate that IRS-NHL develops even after 11 months of potent cART and is dependent on the time of immune restoration. However, we cannot be absolutely sure that our four cases are true IRS manifestations. We realize that NHL is a malignant transformation due to severe degrees of immunodeficiency and takes time to manifest itself as a clinical entity. Nevertheless, IRS-NHL in our patients developed 20 weeks after the CD4<sup>+</sup> T-cell count increase. This means that the development of NHL probably coincided with the time of immune recovery. Moreover, the role of immune deterioration and aberrant cytokine production as a result of the restoration of the severely suppressed immune response, leading to the development of NHL, should be taken into account. NHL in our patients was characterized by abrupt onset, advanced disease at presentation, and prompt progression of the symptoms. A similar observation was reported by Collazos et al. The clinical presentation of the lymphomas in their three patients was abrupt, with the appearance of large, rapidly growing lymphomatous masses [2].

The diagnosis of NHL in our patients was difficult. Initially, peritonissillar abscess, liver cirrhosis, extrapulmonary tuberculosis, and atypical mycobacteriosis were suspected, indicating atypical presentation of IRS-NHL. Clinical evaluation of the patients a few weeks earlier did not reveal any disease. The antiretroviral therapy was effective in all four patients at the onset of the symptoms. That is why lymphomas were unexpected events.

**In summary**, NHL as an immune reconstitution syndrome may develop within a few months in severely immunosuppressed patients at the time of immune recovery/deterioration as a result of potent ART. IRS-NHL can be compared to the phenomena of IRS observed in many opportunistic infections and several autoimmune diseases. Similar predisposing factors are seen, such as long-lasting HIV-1 infection leading to severe immunodeficiency, rapid immune restoration as a result of potent ART, and immune dysregulation during immune reconstitution. Thus, although controversial and difficult to prove, IRS related to NHL cannot be excluded.

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