Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2015 January ; 15(1): e23–e29. doi:10.1016/j.clml.2014.09.009.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)-ASSOCIATED BURKITT LYMPHOMA FOLLOWING COMBINATION ANTI-RETROVIRAL THERAPY IN HIV-INFECTED PATIENTS

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Abstract

HIV/AIDS-associated immune reconstitution inflammatory syndrome (IRIS) is defined as a paradoxical worsening or unmasking of infections and autoimmune diseases, following initiation of combination anti-retroviral therapy (cART). More recently, the case definition of IRIS has been broadened to include certain malignancies including Kaposi's sarcoma, and less frequently Hodgkin's and non-Hodgkin's lymphoma (NHL). Here in we describe 3 patients infected with HIV who began cART and within a median of 15 weeks each achieved non-detectable HIV viral loads, and yet within 6 months presented for medical attention with fevers, night sweats, weight loss and bulky lymphadenopathy. Laboratory studies included elevated lactate dehydrogenase and β -2 microglobulin levels and well preserved CD4⁺ lymphocyte counts in excess of 350 cells/ μ L. In each patient lymph node biopsies were diagnostic of Burkitt lymphoma (BL). Patients were managed with multi-agent chemotherapy in conjunction with cART. We also survey the medical literature of other cases of IRIS-associated BL. Although the pathogenesis of IRIS-associated BL is not well elucidated, chronic antigenic stimulation coupled with immune deterioration, followed by subsequent restoration of the immune response and aberrant cytokine expression may be a pathway to lymphomagenesis. IRIS-associated BL should be suspected in patients with normal or near normal CD4⁺ lymphocyte counts who develop progressive lymphadenopathy post-initiation of cART.

Keywords

Immune reconstitution inflammatory syndrome; HIV/AIDS; Burkitt lymphoma; combination anti-retroviral therapy; cancer

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INTRODUCTION

The introduction of combination anti-retroviral therapy (cART) has led to a dramatic improvement in morbidity and mortality for people living with HIV/AIDS (PLWHA).¹ With adherence to cART, most PLWHA can look forward to a lifespan which approaches that of the general non-HIV infected population. A significant contributor to this longevity is linked to the diminished risk of AIDS-related lymphoma (ARL) in the era of cART. The incidence of ARL in PLWHA has decreased to approximately 1–3 cases per 1000 person-years in the era of cART, representing nearly a 10-fold reduction from the pre-cART era.^{2,3} This was confirmed in a recent Swiss cohort study which showed that cART was not only associated with a significantly decreased incidence of ARL but that a diminished CD4⁺ lymphocyte count remained an important risk factor for lymphomagenesis.⁴

In PLWHA who begin cART, as many as 80%–90% will experience a rapid recovery in CD4⁺ lymphocyte counts and a concomitant decline in the HIV viral loads which can lead to a paradoxical ‘unmasking’ of occult opportunistic infections or other inflammatory or neoplastic processes. This phenomenon called immune reconstitution inflammatory syndrome (IRIS) may occur in 10%–37% of patients who begin cART.^{5–7} IRIS is attributed to a rapid yet dysregulated restoration of antigen specific immune responses associated with antiretroviral therapy. The heightened production of pro-inflammatory cytokines in the background of ineffective immune modulation may result in an unusually intense inflammatory response.⁸ While IRIS has been reported to occur as early as 2 days following the initiation of cART, it generally presents within a window of 3 months. IRIS is often self-limited, especially if the pre-existing condition is effectively treated, or if the inflammatory response is dampened with a brief course of corticosteroids.^{9,10} However, if the inflammatory condition is exuberant or is associated with a poorly controlled infection or malignancy, IRIS can be catastrophic.

New onset or sudden progression of preexisting Kaposi sarcoma within 3 months of initiation of cART is well described.^{11–14} ARL may also occur shortly after initiation of cART and has also been suggested as a rare manifestation of IRIS.¹⁵ The brisk anti-HIV response seen with the use of newer and better tolerated anti-retroviral agents in patients with severe immunosuppression, lower baseline CD4⁺ lymphocyte counts and higher HIV viral load at the time of initiation of cART have been implicated as likely contributors for IRIS-associated NHL.¹⁵

We describe 3 HIV-infected patients who shortly after beginning cART were diagnosed with IRIS-associated Burkitt lymphoma (BL). We also review the medical literature seeking to examine the clinical circumstances surrounding other cases of IRIS-associated BL and discuss the hypothesis for this rare but clinically significant condition.

CASE REPORTS

Patient 1

A 28-year old male was infected with HIV after unprotected sex with another man. His initial CD4⁺ lymphocyte count at the time of diagnosis was 180 cells/ μ L and the HIV viral

load was 130,000 copies/mL. He began cART consisting of emtricitabine, tenofovir, atazanavir and ritonavir. Within 3 months of beginning cART, the patient's HIV viral load had fallen to an undetectable level, but two months later he sought medical attention for evaluation of bulky right axillary lymphadenopathy. A core needle biopsy revealed findings consistent with BL with positive fluorescence *in-situ* hybridization (FISH) studies for MYC gene rearrangement. (Figure 1) A positron emission tomography (PET) - computed tomography (CT) scan showed intense fluoro-deoxy glucose (FDG) uptake corresponding to a 6 cm right axillary lymph node, along with abnormal glucose uptake in the left axillary, left para-aortic, mediastinal and right external iliac lymph nodes. (Figure 2) FDG uptake was also present at the right ilium and left T1 costovertebral region suggesting concomitant osseous involvement by the lymphoma. A bone marrow biopsy showed focal involvement by BL, but cerebrospinal fluid (CSF) was free of tumor contamination. The patient enrolled in an AIDS Malignancy Consortium (AMC) clinical trial of alternating cycles of cyclophosphamide, doxorubicin, vincristine and methotrexate (CODOX-M) and rituximab, ifosfamide, etoposide and high-dose cytarabine (R-IVAC).¹⁶ His chemotherapy course was complicated by grade 4 cytopenias and a single episode of *Staphylococcal* bacteremia. He achieved a complete response (Figure 2) and has remained in remission for the past 51 months.

Patient 2

A 43-year old male who has a history of unprotected sex with men, episodic intravenous drug abuse (crystal methamphetamine and cocaine) and untreated HIV infection began cART after receiving treatment for neurosyphilis. His CD4⁺ lymphocyte count was 443 cells/ μ L and the HIV viral load was 7,600 copies/mL when he began cART consisting of stavudine, lamivudine and efavirenz. He achieved a non-detectable HIV viral load, but 6 months later stopped antiviral therapy and remained off treatment for 6 additional years. He agreed to restart cART after he was once again diagnosed and then completed treatment of neurosyphilis. His HIV viral load was 121,242 copies/mL and his CD4⁺ lymphocyte count was 428 cells/ μ L. Three months after beginning Atripla® (efavirenz, emtricitabine and tenofovir), his HIV viral load had fallen to less than 40 copies/mL. However, 2 months later, the patient sought medical attention for drenching night sweats, hectic fevers, weight loss and problematic chin numbness. A CT scan showed moderately bulky bilateral axillary lymphadenopathy with the largest nodal mass in the left axilla measuring 5 cm in maximal diameter. A core biopsy from the left axilla showed findings consistent with BL with positive FISH studies for MYC and IgH gene rearrangement. (Figure 1) Magnetic resonance imaging of the brain and sampling of CSF did not show central nervous system (CNS) involvement by lymphoma but a bone marrow biopsy showed extensive marrow involvement by BL. The patient was treated off AMC protocol with alternating cycles of CODOX-M and R-IVAC with which he achieved a complete response and remains in remission 27 months post-completion of chemotherapy.

Patient 3

A 45-year-old male previously in good health but with a history of episodic intravenous drug abuse (crystal methamphetamine) and unprotected sex with men was diagnosed with HIV infection after seeking treatment for a community acquired bacterial pneumonia.

Laboratory assessment included a CD4⁺ lymphocyte count of 304 cells/ μ L and an HIV viral load of 238,000 copies/mL. He began cART consisting of Atripla®. Four months later, the patient's HIV viral load was 240 copies/mL and his CD4⁺ lymphocyte count was 350 cells/ μ L. Six weeks thereafter, he sought medical attention for right groin pain. His physical exam was notable for massive right inguinal lymphadenopathy and brawny lower extremity lymphedema. CT scan showed bulky lymphadenopathy above and below the diaphragm with an 11 cm right groin mass encasing the iliac and common femoral veins. (Figure 3) A Doppler study showed extensive thrombosis of the right leg involving the distal external iliac and femoral veins. CT angiogram of the chest showed diffuse bilateral pulmonary emboli. Core needle biopsy from a retroperitoneal node showed BL with positive FISH studies for MYC gene rearrangement. (Figure 1) EBER1-mRNA by *in-situ* hybridization (ISH) was positive. CSF and bone marrow studies did not reveal lymphoma. He was treated off AMC protocol with alternating cycles of CODOX-M and R-IVAC. He had an immediate and dramatic regression of right groin lymphadenopathy. Furthermore, with parenteral anticoagulants a follow up Doppler study 4 weeks later showed complete resolution of the right leg thrombosis. Just prior to cycle 2B of planned chemotherapy, the patient died suddenly while sleeping from a presumed cardiac arrest. A request for autopsy was declined by family members.

The clinical data and therapy of these 3 patients are summarized in Table 1.

DISCUSSION AND LITERATURE REVIEW

Lymphoma has been associated with HIV infection since the beginning of the AIDS epidemic. In 1983 the Center for Disease Control and Prevention (CDC) included certain types of intermediate and high-grade lymphomas in the catalog of AIDS-defining clinical conditions.¹⁷ Prior to 1996 and the advent of cART, ARLs were associated with a dismal prognosis, particularly in patients who had compromised performance status, advanced immune dysfunction and limited hematopoietic reserve.¹⁸ Since the introduction of cART, coupled with the use of granulocyte colony stimulants, appropriate opportunistic infection prophylaxis and use of rituximab in conjunction with combination chemotherapy, the survival of diffuse large B-cell lymphoma (DLBCL) patients has steadily improved and is now comparable to their HIV-negative lymphoma counterparts.¹⁹ Risk factors for ARL include lower CD4⁺ lymphocyte counts, cumulative years with HIV infection and a history of extended periods of uncontrolled HIV viremia, but these factors are heterogeneous across different NHL subtypes.^{20,21} For example, BL is often seen in patients with CD4⁺ lymphocyte counts greater than 200–300 cells/ μ L, while DLBCL is seen in patients with CD4⁺ lymphocyte counts less than 150 cells/ μ L, and certain human herpesvirus type-8 associated ARLs and primary CNS lymphoma (PCNSL) are diagnosed in patients with CD4⁺ lymphocyte counts less than 50 cells/ μ L.^{4,22–24}

Recently, several case reports and cohort studies have suggested an increased incidence of Hodgkin's lymphoma (HL) and ARL among PLWHA during the first 6 months following initiation of cART.²⁰ The occurrence or unmasking of a previously subclinical malignancy, as well as the progression of known cancers (e.g., Kaposi's sarcoma, ARL) in the setting of initiation of cART, has been described, though with much less frequency in comparison to

opportunistic infections.²⁵ A nested and matched case-control study from the CASCADE collaboration showed that most of the excess cancer risk in patients initiating cART reflects the immunodeficiency that most likely led to the use of cART.¹⁴

IRIS is most often encountered in patients who have low CD4⁺ lymphocyte counts at time of cART initiation, and whose CD4⁺ lymphocyte counts subsequently rapidly rebound. A complex range of contributing factors for IRIS include reconstitution of both the number and the function of immune cells, redistribution of lymphocytes, alterations in helper T lymphocyte profile with deficient regulatory function, modulation of apoptosis pathways, and the capacity to handle the antigenic load.²⁶

The restoration of CD4⁺ lymphocytes observed as a result of cART occurs in 2 phases. In an early phase, which begins within 1–2 weeks and persists for about 2–3 months after the initiation of the treatment, a rapid increase of CD4⁺ cell count occurs through redistribution and activation of existing memory CD4⁺ cells sequestered in lymphoid tissues.²⁷ The sudden boost in immunity with recovery of lost responses to specific preexisting antigens as well as recovered cytotoxicity and macrophage activating cytokine production targeted against these antigens, is likely responsible for the aberrant immune reaction characteristic of IRIS.²⁸ In the late phase, active proliferation of naïve CD4⁺ lymphocytes, which occur after several months of maintained suppression of viral replication, is likely due to re-establishment of thymic T-cell lymphocyte activity.²⁹ Based on these observations, a brisk immune recovery measured by increasing CD4⁺ lymphocytes could trigger IRIS, although an increase in CD4⁺ lymphocyte counts might not occur until after a significant drop in HIV viral load. Additional factors that may promote IRIS-associated ARL, other than those related to CD4⁺ lymphocyte dynamics and HIV viremia; include cytokine dysregulation leading to increased serum levels of IL-6 and IL-10.^{29–31}

The clinical characteristics of unmasking or IRIS-associated lymphoma are not well described. There is also a particular paucity of case reports which provide clinical details on the subset of these patients with IRIS-associated BL. Utilizing MEDLINE®/PubMed® search, with the key words “lymphoma”, “immune reconstitution inflammatory syndrome” and “AIDS-related non-Hodgkin lymphoma” and restricted to English language reports between the years 2000–2013, we identified 3 additional reported cases of BL in the context of IRIS. (Table 1) Like our cohort, all 3 were male patients with a median age of 45 years (37–57 years). Two patients manifested with IRIS-associated BL at 28 weeks after initiation of cART and 1 patient at 8 weeks. All 3 patients’ CD4⁺ cell count before initiation of cART was less than 200 cells/μL with a median of 128 cells/μL. The median viral load at initiation of cART was significantly lower in these 3 cases compared to our cohort: 39,394 copies/mL (range: 8,111 – 535,242 copies/mL) vs. 132,203 copies/mL (range: 121,242 – 238,000 copies/mL). Two of the 3 patients died within 6 months of diagnosis due to disease progression despite receiving systemic chemotherapy with multi-agent regimen, highlighting the poor prognosis associated with this disease entity.

To speculate on the frequency of unmasking lymphoma and IRIS-associated BL, one can extrapolate from a large HIV-associated lymphoma cohort in the United States. Between 1996 and 2011, 482 lymphoma patients were identified through the Centers for AIDS

Research Network of Integrated Clinical Systems (CNICS).³² Of these 48 (10%) fulfilled criteria for unmasking lymphoma which was defined as HL or NHL occurring within 6 months after cART initiation accompanied by a $0.5 \log_{10}$ copies/mL reduction in HIV RNA between values taken prior to ART and at lymphoma diagnosis. Of these unmasking lymphomas, 10 (21%) were HL, 19 (40%) DLBCL, 4 (8%) BL, 9 (19%) PCNSL, and 6 (12%) other NHLs. The median CD4⁺ cell count at lymphoma diagnosis among IRIS cases was 163 cells/mL (interquartile range, 67–302), and 54% had suppressed HIV RNA (<400 copies/mL). No significant differences were identified between IRIS-associated lymphoma and non-IRIS lymphoma, with the exception of possible earlier stage (47% stage I/II versus 24%, $p=0.03$), more frequent hepatitis B/C co-infection (31% vs. 19%, $p=0.05$), and more frequent prior AIDS illness (92% vs. 79%, $p=0.05$), as well as expected lower HIV RNA at lymphoma diagnosis likely resulting from the IRIS case definition. Additionally, no differences in cumulative mortality 5 years after lymphoma diagnosis were identified between IRIS and non-IRIS cases, although there was a suggestion of increased early mortality among IRIS cases.

BL, a clinically aggressive subtype of NHL, is rarely seen in immunocompetent individuals. It is disproportionally common in PLWHA with an estimated life-time incidence risk of about 10–20%.^{33,34} Unlike other ARLs, the incidence of BL appears to be largely unaffected by cART and is independent of CD4⁺ lymphocyte count.³⁴ This significant feature was also noted in the patients we describe. They were each diagnosed with BL shortly after beginning cART and in the context of a rapid and profound decrease in HIV viral load. This phenomenon raises the question of whether the degree and velocity of virologic response that is now achievable with use of novel anti-retroviral agents possibly facilitates an abnormal lymphoproliferative pathway.

Our case series serves to remind clinicians to maintain heightened vigilance for IRIS-associated NHL in those who begin cART. The occurrence of progressive lymphadenopathy and B symptoms in those with a well preserved CD4⁺ cell count and a rapidly falling HIV viral load should further raise the clinical specter of IRIS-associated BL. Additional clinical and epidemiological studies evaluating the causative mechanism in IRIS-associated NHL are needed.

Acknowledgments

This project was supported in part by the AIDS Malignancy Consortium award number U01CA121947 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the national Cancer Institute of Health

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Figure 1. HISTOPATHOLOGY AND IMMUNOPHENOTYPE OF BURKITT LYMPHOMA LYMPHOMA

H&E staining shows Burkitt lymphoma with uniform intermediate-sized tumor cells with small nucleoli, fine chromatin, and frequent apoptotic bodies. Immunohistochemistry shows strong homogenous staining for CD20, Ki67 (MIB1), CD10, BCL6, and MYC. Tumor cells are negative for BCL2. FISH studies for MYC using dual color break apart probes show one allele with colocalization of both probes (red and green) and one allele with segregation of both probes.

Figure 2. PRE & POST TREATMENT PET-CT SCAN SHOWING COMPLETE RESPONSE TO CHEMOTHERAPY

Pre-treatment positron emission tomography (PET) - computed tomography (CT) scan (A) shows intense fluoro-deoxy glucose (FDG) uptake corresponding to a 6 cm right axillary lymph node, along with abnormal glucose uptake in the left axillary, left para-aortic, mediastinal and right external iliac lymph nodes. A follow-up PET-CT scan (B) 3 months after starting chemotherapy shows a complete response.

Figure 3. RAPIDLY PROGRESSIVE LYMPHADENOPATHY

CT scan shows bulky right inguinal (A) and retroperitoneal (B) lymphadenopathy with an 11×8 cm mass encasing the iliac and common femoral veins (arrow).

TABLE 1

Clinical, immunologic and virologic characteristics among subjects diagnosed with Burkitt lymphoma after starting combination anti-retroviral therapy

	Patient 1	Patient 2	Patient 3	Patient 4 ¹⁵	Patient 5 ²²	Patient 6 ³⁵
Age	28 years	43 years	45 years	57 years	45 years	37 years
Sex	male	male	male	male	male	male
Race/ethnicity	white	white	white	Black	not reported	White
Year of HIV infection	2008	1996	2013	1983	2003	not reported
Hepatitis B/C co-infection	none	none	none	not reported	not reported	not reported
Prior anti-retroviral therapy	none	Stavudine, lamivudine and efavirenz	none	Tenofovir, lamivudine, lopinavir & ritonavir	None	None
cART	Emtricitabine, tenofovir, atazanavir & ritonavir	Atripla® (efavirenz, emtricitabine & tenofovir)	Atripla® (efavirenz, emtricitabine & tenofovir)	Raltegravir, tenofovir, emtricitabine, darunavir & ritonavir	Stavudine, lamivudine and efavirenz	Atazanavir, ritonavir, tenofovir & emtricitabine
Initiation of newer cART	February-2009	October-2011	March-2013	November 2007	May 2003	not reported
Time from cART initiation to onset of lymphoma	20 weeks	20 weeks	24 weeks	28 weeks	28 weeks	8 weeks
Symptoms of lymphoma	rapidly progressive lymphadenopathy	weight loss, night sweats & lymphadenopathy	rapidly progressive lymphadenopathy	Left upper extremity weakness, diplopia	weight loss, night sweats & lymphadenopathy	Left eye ptosis, left upper & lower extremity weakness, bone pain
CD4+ count (cells/ μ L)						
at cART initiation	255	428	304	128	5	169
at diagnosis of lymphoma	323	553	293	not reported	87	464
HIV viral load (copies/mL) at cART initiation	132,203	121,242	238,000	8,111	535,242	39,394
at diagnosis of lymphoma	undetectable	undetectable	240	not reported	2,600	Undetectable
CSF involvement	no	no	no	not reported	not reported	not reported
Chemotherapy	CODOX-M/IVAC-R	CODOX-M/IVAC-R	CODOX-M/IVAC-R	Yes*	CODOX-M/IVAC	EPOCH/R-CHOP/R-ESHAP***
Outcome	CR, NED at 51 months follow-up	CR, NED at 27 months follow-up	Died after 6 weeks of starting chemotherapy, likely due to cardiopulmonary event.	CR**	Primary chemorefractory disease; died at 5 months after diagnosis	Primary chemorefractory disease; died at 6 months after diagnosis due to disease

	Patient 1	Patient 2	Patient 3	Patient 4 ¹⁵	Patient 5 ²²	Patient 6 ³⁵
					due to disease progression	progression

* Regimen not described

** Duration of follow-up not available

*** EPOCH: Etoposide-prednisone-Oncovin-cyclophosphamide-hydroxydaunorubicin; R-CHOP: Rituximab-cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone; R-ESHAP: Rituximab-etoposide-steroid-cytarabine-cisplatin; CODOX-M/IV AC-R: cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine, rituximab; CR: complete remission; NED: no evidence of disease.