

AIDS-Related Lymphomas: The Rhode Island Experience

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The majority of HI-infected persons in Rhode Island receive care at the Samuel and Esther Chester Immunology Center located at The Miriam Hospital in Providence, Rhode Island. The Immunology Center provides HIV care for approximately 1100 patients. The Center provides multiple services onsite including free HIV counseling and testing (rapid blood and/or saliva testing), onsite counseling and social work, medical care, clinical trials, limited psychiatric care, viral hepatitis treatment, substance abuse referral system, and adherence nursing. In 2006, the average age of the Immunology Center patient was 44 years; 65% of patients were male and 35% female. Thirty-one percent had private medical insurance, 51% public insurance, and 19% were uninsured. Fifty-two percent have been diagnosed with AIDS and three quarters are taking highly active antiretroviral therapy, of whom 61% have achieved full viral suppression on therapy. Thirty-two percent have concomitant hepatitis C infection, and 5% have chronic hepatitis B infection.

According to the Rhode Island Department of Health (HEALTH),¹ in 2006 there were 1,467 Rhode Islanders living with AIDS, mostly in greater Providence. Between 2000 and 2006, the percentage of women diagnosed with AIDS increased from 24% to 34%. People diagnosed with AIDS were more likely to be in the 40-49 year age group (39%) in 2006. Whites represented almost 43% of the new AIDS cases in 2006, African Americans 30%, and Hispanics represented 22% of new AIDS cases. Between 2000 and 2006, 981 individuals were diagnosed with HIV infection but did not have AIDS.

At this time, three conditions are considered AIDS-defining malignancies: B-cell non-Hodgkin lymphoma (NHL) of intermediate or high-grade histology, Kaposi sarcoma (KS) and invasive cervical cancer.² KS is the most common malignancy in HIV-affected individuals, but its incidence is decreasing secondary to the use of HAART. B-cell NHL is the second most common HIV-associated malignancy. In the absence of HAART, patients with HIV infection have 60 to 100 times increased risk of devel-

oping ARL when compared to the general population. Up to 90% of the ARL are diffuse large B-cell lymphoma (DLBCL) or Burkitt/Burkitt-like lymphoma (BL/BLL). The risk of developing low-grade B-cell NHL, Hodgkin disease (HD) and T-cell NHL is also increased in HIV-infected patients.^{3,4} The World Health Organization (WHO) recently classified ARL in a comprehensive manner. (Table 1) ARL, with an incidence of 5% as an AIDS-defining illness, accounts for up to 23% of the mortality in patients infected with HIV.⁵

This report describes the experience of hospital-based Immunology clinic in regards to ARL epidemiology, diagnosis and management from 1996 to 2006.

MATERIALS AND METHODS

Our primary objective is to describe the epidemiological, histological and clinical features of ARL in the post-HAART era. The population consisted of HIV-positive male and female patients of our Center, age 18 to 60, who were diagnosed with ARL from the year 1996 to present. The following diagnoses of lymphoma were included: B-cell NHL (DLBCL, BL/BLL, primary effusion lymphoma [PEL], and PCNSL), T-cell NHL and HD. Subject population was identified through direct physician communication and search of medical records database by the criteria listed above.

This report will include data on duration of HIV infection prior to diagnosis,

most likely route of transmission of HIV, use of HAART, CD4 count and plasma HIV RNA levels on diagnosis, clinical features, histological type, staging and therapy used for ARL and final outcome. Our long-term objective was to add to the current body of knowledge of the clinical features and treatment of ARL, with particular attention to the impact of HAART.

RESULTS

Twenty-two cases of ARL were diagnosed at our Institution. (Tables 2 and 3)

The median age at presentation was 43 years with a range of 28 to 60 years. Men predominated, 6.3:1. Patients had an average of 7.7 years, ranging from less than a year to 22 years, since the initial diagnosis of HIV infection. The most common HIV transmission route was male-to-male sexual contact (36%) followed by intravenous drug use (23%) and heterosexual contact (14%); other routes of transmission include transfusions, blood-borne and unknown (27%). The mean CD4 count at ARL presentation was 207 cells per cubic millimeter. Patients diagnosed with ARL had an average of 1.4 years since institution of HAART; all the patients were exposed to HAART at some point during their disease. At diagnosis, 50% of the patients were receiving HAART. From the patients who were not on HAART at the time of diagnosis, 64% started HAART during treatment, and 36% started HAART after the treatment for ARL was finished.

Table 1. WHO Classification of HIV-Associated Lymphomas

Lymphomas also occurring in immunocompetent patients

- Burkitt/Burkitt-like lymphoma
- Diffuse large B-cell lymphoma+
- Peripheral T-cell lymphoma
- Hodgkin lymphoma

Lymphomas occurring more specifically in patients who are HIV positive

- Primary effusion lymphoma*
- Plasmablastic lymphoma of the oral cavity*

Lymphomas occurring in other immunodeficiency states

- Polymorphic B-cell lymphoma

+ Includes primary CNS lymphoma * Subtypes of diffuse large B-cell lymphoma

Table 2. General characteristics of the subject population

Mean age in years (range)	43 (28-60)
Sex	
Male	19 (96.4%)
Female	3 (13.6%)
Mean duration of HIV infection in years (range)	
Most likely route of HIV transmission	
Male-to-male	8 (36.3%)
IV drug use	5 (22.7%)
Heterosexual	3 (13.6%)
Others/Unknown	6 (27.2%)
Mean CD4 count at presentation in cells/m m3 (n=21)	207
CD4 count for NHL (range)	165 (4-518)
CD4 count for HD (range)	337 (12-1155)
Mean duration of HAART in years (range)	1.4 (<1-9)
Institution of HAART	
Prior to ARL diagnosis	11 (50%)
During therapy for ARL	7 (31.8%)
After finishing therapy for ARL	4 (18.2%)

Table 3. ARL-associated characteristics of the subject population

Lymphoma type	
DLBCL	10 (45.5%)
BL/BLL	5 (22.7%)
NHL, NOS	1 (4.5%)
TCL	1 (4.5%)
HD	5 (22.7%)
ARL stage (n=10)	
I and II	3 (30%)
III and IV	7 (70%)
B symptoms	
Yes	14 (63.6%)
Lymphoma location	
Extranodal	11 (50%)
Nodal	11 (50%)
Therapy	
Chemotherapy	16 (72.7%)
Radiation therapy	2 (9.1%)
Multimodality	1 (4.5%)
Outcome	
Expired	6 (27.3%)
Alive	11 (50%)
Lost to follow-up	5 (22.7%)
Survival (months)	46 (0-139)
DLBCL	42
BL/BLL	24
HD	57

From the ARL standpoint, there were 15 cases of B-cell NHL; the most common histology was DLBCL (32%) followed by BL/BLL (23%); other histological types were also observed, such as PEL, PCNSL and unspecified NHL (18%). T-cell NHL was observed in one patient (5%) while HD was diagnosed in 5 patients (23%). More than 60% of the patients with ARL presented clinically with B symptoms (unexplained weight loss, fever or drenching night sweats) and 70% of them presented with Ann Arbor stages III or IV. As expected, 50% of the patients presented with extranodal disease affecting bone marrow, liver, CNS, stomach, jaw and nasal cavity.

Sixteen patients received chemotherapy, radiation therapy alone was used in 2 patients, one patient with PCNSL was treated with a multimodal approach (surgery followed by chemotherapy), and 3 patients had an unknown type of therapy. Patients diagnosed with NHL were treated with cytotoxic chemotherapy in 75% of the

cases; the most commonly used regimens were CHOP (cyclophosphamide, daunorubicin, vincristine and prednisone) and EPOCH (etoposide, daunorubicin, vincristine, cyclophosphamide and prednisone). Rituximab, an anti-CD20 monoclonal antibody, was used in 3 cases; two cases received rituximab along with CHOP and one patient received rituximab as a single agent. Patients diagnosed with HD were treated with ABVD (daunorubicin, bleomycin, vinblastine and dacarbazine) in 80% of the cases; the remainder case received radiotherapy alone. The only case of T-cell NHL was treated with radiotherapy alone.

At the time of this report, 6 patients had died, 5 patients were lost to follow-up, and the remaining 11 were still alive; from the latter group, 73% were in remission. The overall survival was 46 months and the median survival of the patients who died was 36 months. Patients with DLBCL and HL had longer survival time than patients with BL/BLL (57 months, 42 months, and 24 months, respectively).

DISCUSSION

ARL has been reported to affect mainly young HIV-positive male individuals; in our series the median age of presentation was 43 years old and there was a clear male predominance. The route of HIV transmission does not seem to play an important role in the incidence of these malignancies, but we have a small case series. As mentioned, ARL is the second most common malignancy observed in HIV-positive individuals. Antiretroviral therapy has become very effective in decreasing infectious complications and has decreased the incidence of KS;⁶ although HAART has also shown to decrease the incidence of ARL,^{7,8} it has done so to a lesser degree, hence the relative increase in the incidence of this malignancy in HIV patients.⁶ Furthermore, the incidence of some types of lymphoma, such as BL/BLL, has not been greatly affected by the use of HAART.⁹

ARL may be observed in HIV patients either as an initial presentation, as in 6 patients from our series, or at any time during the course of their disease; in our report, one patient was diagnosed with ARL 22 years after his initial diagnosis of AIDS. Some types of ARL are more likely to be seen in patients with lower CD4 counts (PCNSL and DLBCL), while others are likely to develop in the presence of higher counts, like BL/BLL and HD.

The most common ARL subtype is aggressive B-cell NHL: it accounts for 80% to 90% of the cases. In our series, DLBCL and BL/BLL accounted for 70% of the cases. HIV-infected patients have an increased risk of developing other non-AIDS-defining lymphomas; the risk of developing TCL and HD has been reported increased 15-fold and 5 to 9-fold, respectively.^{3,4} The pathogenesis of ARL is incompletely understood, but HIV seems to play an indirect role through immunodeficiency, cytokine deregulation of the microenvironment and chronic antigenic stimulation by HIV antigens. Functional and quantitative defects in T-cells and NK-cells are part of the many immune abnormalities induced by HIV. IL-6 and IL-10, which are produced inherently by HIV-infected cells, will promote a B-cell hyperactivation state.¹⁰ This state of generalized hyperproliferation and immunosuppression favors EBV infections; EBV-infected immortalized clones possess a constitutional genetic instability that allows the development of genetic rearrangements (MYC gene activation is observed in 75% of B-cell ARL) permitting the development of malignant lymphoma.¹⁰ Clinically, ARL tend to present with B symptoms and at advanced stages; involvement of the bone marrow and the CNS exemplifies the predilection of these lymphomas for extranodal sites.

The most extensive data regarding treatment exist for DLBCL. At this time, CHOP is the most commonly used regimen [11], but EPOCH [12] and CDE (cyclophosphamide, doxorubicin and etoposide) [13] have achieved good response and survival rates. In this setting, CNS prophylaxis should be considered in patients with testicular, epidural, paranasal and bone marrow involvement. HIV-associated BL/BLL patients with good immune status ($CD4 > 100$ cells per mm^3) have been treated with more intensive therapies with good response and survival [14, 15]. For those BL/BLL patients with lower CD4

counts, CHOP could be considered; CNS prophylaxis is mandatory in this setting but there is no clear consensus about the best regimen to use. For HIV-associated HD, regimens like ABVD [16] and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) [17] have been tried with success. In general terms, our patients with ARL are being treated more like their immunocompetent counterparts with better results, which are in part due to improved supportive care and better anti-infective therapies. All the previous regimens have been used along with HAART, growth factor support, and PCP and HSV prophylaxis using trimethoprim-sulfamethoxazole or pentamidine and acyclovir, respectively. Regarding HAART, most drugs have been used safely along with cytotoxic chemotherapy but zidovudine should be avoided given its bone marrow suppressing effects. The role of rituximab in combination with chemotherapy in the management of ARL is still debatable but it seems to be safer and beneficial in patients with CD4 counts higher than 100 cells per mm^3 [18-20].

CONCLUSIONS

ARL is likely to affect patients in their early forties who have CD4 counts less than 200 cells per mm^3 . ARL can develop at any time during HIV infection and no environmental factor seems to play an important role in its development. A better understanding of the multiple pathogenetic mechanisms for the development of ARL is needed to improve the current therapeutic approaches. The patients in our series responded well to standard chemotherapeutic regimens despite their HIV status. Early use of HAART, G-CSF and prophylactic antibiotics appear to have eased the management of these malignancies. ARL patients are likely to benefit from rituximab, although its role needs to be further elucidated.

The data from the Miriam Hospital Immunology Clinic for the last 10 years is similar to that reported from other parts of the developed world. Infections are still the most common AIDS-defining illnesses but because highly effective antiretroviral therapy improves the long-term outlook for patients infected with HIV, the incidence of malignancies, particularly ARL, may be increasing.

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The authors have no financial interests to disclose.

Off-label use of medication: Rituximab has not been approved for AIDS lymphomas.

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