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Human immunodeficiency virus-associated anaplastic large cell lymphoma

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Abstract

Anaplastic large cell lymphoma (ALCL) is a distinct subtype of peripheral T-cell lymphoma (PTCL) characterized by the expression of CD30 in lymphoma cells. Like aggressive B-cell non-Hodgkin lymphoma, the risk of developing PTCL is also increased in the setting of HIV infection. To date, the occurrence of ALCL in HIV-positive individuals is limited to a few case reports and small case series. A total of 37 cases of HIV-associated ALCL were identified after reviewing the available published literature. Analysis of these cases showed that this group of HIV-infected patients was on average 38 years of age with a male-to-female ratio of 4:1, and a reported median CD4 cell count of 83 cells/mm^3. HIV-associated ALCL cells rarely expressed anaplastic lymphoma kinase. Epstein–Barr virus infection was associated with one-third of the cases. These lymphomas manifested almost exclusively with extranodal involvement and exhibited a very aggressive clinical course. The median overall survival was 5 months. The administration of chemotherapy and early stages at presentation were identified as good prognostic factors, while the use of HAART showed a statistical trend toward improved survival in HIV-associated ALCL.

Keywords: *Anaplastic large cell lymphoma, ALCL, ALK, HIV*

Introduction

Non-Hodgkin lymphoma (NHL) is at present the most common malignancy that occurs in human immunodeficiency virus (HIV)-infected patients [1]. NHL is also the most common cause of death, and accounts for up to 23% of the mortality in HIV-infected individuals [2]. As the HIV epidemic developed, aggressive forms of B-cell NHL such as Burkitt lymphoma and primary effusion lymphoma (PEL) became recognized as acquired immunodeficiency syndrome (AIDS)-defining illnesses. These HIV-associated B-cell lymphomas are characterized by an aggressive clinical course and high frequency of extranodal involvement. A large proportion of HIV-associated B-cell NHL demonstrate viral coinfection with Epstein–Barr virus (EBV) (e.g. 40–60% compared to 10–20% in non-HIV-associated NHL) [3] and human herpesvirus-8 (HHV-8) [4].

Despite the fact that the majority of HIV-associated lymphomas are of a B-cell phenotype, several peripheral T-cell lymphoma (PTCL) subtypes have also been documented in HIV-positive persons [5]. Based upon epidemiological studies, the risk of developing PTCL in HIV-positive individuals is 15 times higher than in the general population [6]. PTCL represents 12–15% of all NHL in HIV-seronegative Western populations [7]. Studies involving Asian and Latin-American populations have shown a slightly greater proportion of PTCL [8,9], related to an increased prevalence of viral infections such as EBV and human T-lymphotropic virus type 1 (HTLV-1) and/or genetic predisposition.

PTCL arises from mature, post-thymic T-cells, and, according to the clinical, pathological, molecular, and genetic features, is divided into specific subtypes. The most common PTCL subtypes encountered in the HIV-negative population, in order of

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frequency, are PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic lymphoma (AITL), and anaplastic large cell lymphoma (ALCL) [10]. A retrospective study involving 93 previously published cases of systemic and cutaneous HIV-associated PTCL similarly showed that PTCL-NOS (38%) and ALCL (18%) were the most common HIV-associated PTCL subtypes to be reported [11]. Another study focusing solely on HIV-associated systemic PTCL found that PTCL-NOS accounted for 42% of cases and ALCL for 28% [5].

ALCL is a T-cell lymphoma characterized by large anaplastic lymphoma (hallmark) cells containing abundant cytoplasm and pleomorphic, often horseshoe-shaped, nuclei that have a tendency to grow cohesively and invade lymph node sinuses [7]. Tumor cells are positive for CD30 and cytogenetic analysis shows a characteristic chromosomal translocation, t(2;5)(p23;q35), resulting in the fusion of the nucleophosmin (NPM) gene on chromosome 5q35 to a portion of the anaplastic lymphoma kinase (ALK) gene on chromosome 2p23, generating a chimeric mRNA molecule. Other less common translocations seen in ALCL pair the ALK gene with genes located in chromosomes 1, 2, 3, 17, 19, 22, and X [10]. These chromosomal aberrations lead to the activation of the ALK protein, a transmembrane receptor tyrosine kinase that belongs to the insulin receptor superfamily. ALK gene rearrangement is seen in 40–60% of ALCL cases [12]. ALK-positive ALCL carries a favorable prognosis, with a 5-year survival of 80%. On the other hand, ALK-negative ALCL portends a poor prognosis, with a 5-year survival of 33% [13].

In recent years, the number of publications reporting an association between HIV infection and the development of ALCL has increased [5,11]. However, complete data on HIV-associated ALCL are lacking. Therefore, the aim of this review is to describe the clinicopathological characteristics and outcome of HIV-associated ALCL as well as identify potential prognostic indicators for this aggressive T-cell lymphoma.

Methods

Published literature (PubMed/MEDLINE and article references) was searched from January 1985 to October 2009 for cases using the terms 'HIV or AIDS' and 'ALCL or anaplastic large cell lymphoma.' Only cases with morphological and/or immunohistochemical confirmation of systemic ALCL, according to the World Health Organization (WHO) Classification of Lymphoproliferative Disorders, in HIV-positive individuals were included. Cases with a negative or unknown HIV status, cases of primary cutaneous ALCL, and cases with anaplastic large cell morphology of a B-cell origin were excluded.

Data were tabulated according to the following extracted variables: patient age, gender, country or region of report, CD4 cell count, HIV viral load at the time of lymphoma diagnosis, use of highly active antiretroviral therapy (HAART), presence of opportunistic infections, immunophenotype, ALK expression, evidence of viral coinfection (EBV, HHV-8, HTLV-1), molecular studies (ALK and T-cell receptor [TCR] gene rearrangement), tumor location, bone marrow involvement, stage of lymphoma (Ann Arbor classification), lactate dehydrogenase (LDH) levels, treatment (e.g. chemotherapy, radiotherapy, etc.), final outcome, and cause of death. Descriptive statistics were used to report clinicopathological characteristics. Survival analyses were performed using Kaplan–Meier non-parametric estimates for incomplete observations. Survival curves were compared using the log-rank test. The threshold of significance was a p-value of less than 0.05. MedCalc software (Mariakerke, Belgium) was used to perform survival analyses and generate graphs.

Results

Search results

Our initial search resulted in 71 articles from which 29 manuscripts were finally included [14–42], which accounted for 37 cases fulfilling the abovementioned inclusion criteria of pathologically confirmed HIV-positive ALCL.

Clinical findings

The clinical characteristics of 37 patients with HIV-associated ALCL are summarized in Table I. The average patient age ($n = 35$) was 38.2 years, with a male:female ratio of 4:1, and a median CD4 cell count of 83 cells/mm^3. HIV viral load was not consistently provided ($n = 6$), but in those cases where these data were available the viral load ranged from 82 000 to 600 000 copies. HIV status was also evaluated according to the presence of prior AIDS-defining illnesses. There were 11 patients with a notable AIDS-defining illness, commonly due to an opportunistic infection. Of the patients reviewed, seven (21%) received HAART therapy while 26 (79%) did not. For the remaining four cases, no information regarding antiretroviral therapy was documented.

Lymphoma stage was provided for all patients ($n = 37$). Most cases (78%) presented with advanced lymphoma (i.e. stage III or IV). All (100%) patients had extranodal involvement. The most common extranodal sites were the lung, soft tissue, liver, and

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Table I. Clinical characteristics of HIV-associated anaplastic large cell lymphoma.

Patient features (n = cases with available data)	n/Mean	%/Range
Age, years (n = 37)	38	1–66
Sex (n = 35)		
Male	28	80
Female	7	20
CD4 count, cells/mm^3 (n = 22)	83	20–300
Prior AIDS-defining illness (n = 21)		
Mycobacterium avium complex	4	19
Candida sp.	3	14
Pneumocystis jiroveci	2	14
Toxoplasma gondii	2	10
Cryptosporidium sp.	2	10
Other*	2	10
No prior	10	48
Lymphoma location (n = 36)		
Nodal	10	28
Extranodal	36	100
Lung	9	25
Soft tissue	9	25
Liver and spleen	9	25
Skin	6	17
Bone marrow	6	17
Head and neck	4	11
Other sites†	7	19
Clinical lymphoma stage (n = 37)		
I–II	8	22
III–IV	29	78
LDH levels, mg/dL (n = 7)	1142	245–4275
Lymphoma therapy (n = 33)		
CHOP/CHOP-like regimen	13	39
Other chemotherapy regimens	6	18
Supportive or no therapy‡	14	42
Outcome (n = 33)		
Alive	10	30
Dead	23	70
Survival time, months (n = 32)	5	0–54
Cause of death (n = 16)		
Lymphoma progression	6	37
Opportunistic infection	5	31
Other infection§	4	25
Thyrotoxicosis	1	6

*Includes *Cytomegalovirus*, Kaposi sarcoma.
†Includes GI tract, heart, kidneys, adrenals, brain.
‡Includes radiotherapy alone and propranolol.
§Includes sepsis, pneumonia.

spleen; as an example of the potential of extranodal involvement in HIV-associated ALCL, Figure 1 depicts cardiac (A) and renal (B) involvement. Ten cases (28%) presented with concurrent nodal involvement. LDH levels were elevated in all the reported cases (n = 7).

In terms of therapy (n = 33), 58% of the cases received chemotherapy or chemoradiotherapy and 42% of the cases received supportive or no treatment. In the patients treated with chemotherapy (n = 19), the most common regimen used was standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; n = 9; 47%). CHOP-like regimens such as EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone; n = 2; 11%), COPE (cyclophosphamide, vincristine, prednisone, etoposide; n = 1; 5%), and CHOP/bleomycin (n = 1; 5%) were used in a few patients, methotrexate-containing regimens were used in three patients (16%), and the regimen was not specified in three (16%). Response was reported in 14 patients, from which 10 (71%) achieved a complete response, two (14%) achieved a partial response, and two (14%) did not show a response to chemotherapy, with or without radiation.

Patient outcome and survival were reported in 33 and 32 cases, respectively (Table I). The documented median overall survival (OS) was 5 months (Figure 2). At the time of this review, 70% of patients were deceased. The most common causes of death were lymphoma progression (37%) and opportunistic infections (31%).

Pathologic findings

The pathologic findings are summarized in Table II. Four cases stated a pathological diagnosis of ALCL but did not give further details on the morphology or immunophenotypic profile [22,23,25,30]. Similar to immunocompetent cases, HIV-positive ALCL presented with a broad spectrum of morphological features. Lymphoma cell size ranged from small to large, including anaplastic 'hallmark' cells. In all of the cases lymphoma cells were positive for CD30 expression, fulfilling the diagnostic criteria for ALCL. The most common T-cell antigens expressed in HIV-associated ALCL were CD45RO (88%), CD2 (83%), CD5 (78%), CD4 (75%), and CD43 (73%). Ki-67 was reported in five cases and in all the cases was higher than 60%. CD3 and CD8 were expressed in 61% and 9% of the cases, respectively. One of the most important findings was that ALK-1 immunohistochemical stains were positive in only two of the evaluated cases (11%) [19,33], although none of the eight evaluated cases for ALK gene rearrangement detected abnormalities [14,19,34,39,40]. TCR gene rearrangement was positive in 100% of the evaluated cases (n = 14). EBV coinfection was evident by means of positive EBV-encoded RNA (EBER) *in situ* hybridization in 33% of the cases, but latent membrane antigen-1 (LMP-1) immunoreactivity was seen in only 7% of cases. Coinfection with HTLV-1 and HHV-8 was not shown by polymerase chain reaction (PCR) in any of the tested cases.

Prognostic factors

The survival analyses were performed using available data from 32 cases of HIV-associated ALCL that

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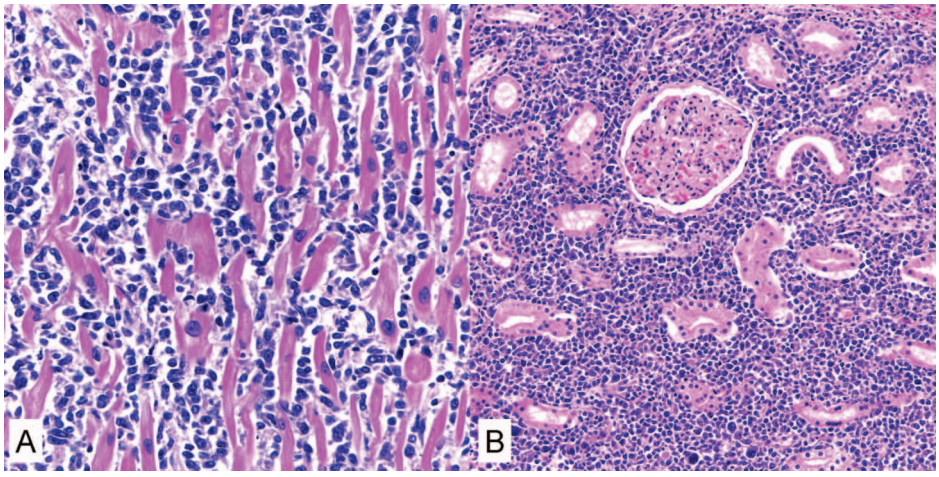

Figure 1. Involvement of (A) the myocardium (H&E stain, original magnification × 400) and (B) kidney (H&E stain, original magnification × 200) by HIV-associated anaplastic large cell lymphoma. Reproduced with kind permission from [36].

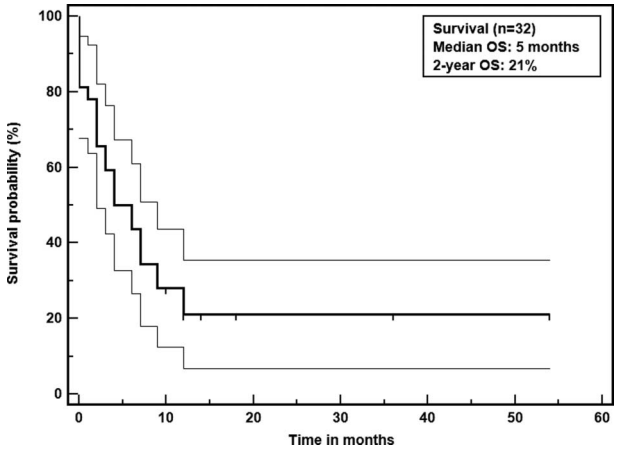

Figure 2. Kaplan–Meier survival estimates in 32 cases of HIV-associated anaplastic large cell lymphoma.

reported outcome. In the univariate analysis, we evaluated age, sex, CD4 cell count, use of HAART, lymphoma stage, EBV status, bone marrow involvement, and use of chemotherapy. Patients treated with chemotherapy ($n = 19$) had a median OS of 7 months, while untreated patients had a median OS of 2 months ($n = 13$) ($p = 0.0141$; Figure 3); cases with early-stage lymphoma did not reach a median OS, while patients with advanced stage lymphoma had a median OS of 4 months ($p = 0.0295$; Figure 4); and, in those patients treated with HAART, the median OS was 12 months, compared with 4 months in patients not treated with HAART ($p = 0.1011$; Figure 5). Clinical stage and use of HAART lost their statistical significance when evaluating survival estimates in chemotherapy-treated patients ($p = 0.06$ for both factors; data not shown).

The significance of the International Prognostic Index (IPI) or the Prognostic Index in PTCL-NOS (PIT) on prognosis could not be performed as there were insufficient published data on performance status ($n = 2$) and LDH levels ($n = 7$) in the reviewed studies.

Discussion

This is the first comprehensive review of HIV-associated ALCL. Limitations of this review are related to the retrospective nature of the study, with limited available data in some cases and potential selection bias. Accordingly, we have included peer-reviewed cases of ALCL in HIV-positive individuals, which could have potentially been misdiagnosed by their authors and, in turn, could have biased our data. Incomplete published data in some cases prevented us from performing further analyses for important prognostic features such as the IPI or the PIT scores.

ALCL is a mature T-cell lymphoma that has attracted much interest since the identification of ALK-positive and ALK-negative variants. The ALK-negative ALCL has been included as a provisional separate entity in the recent WHO classification of lymphomas [43]. In the general population, ALCL accounts for 3% of adult NHL and 10–20% of childhood lymphomas. Prior review of the literature showed that ALCL is the second most common PTCL subtype reported in HIV-positive individuals, accounting for 28% of all published HIV-associated PTCL cases [5,11]. This is higher than the distribution seen in PTCL of immunocompetent individuals. A recent study showed that ALCL, when including both ALK-positive and ALK-negative cases,

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Table II. Pathological characteristics of HIV-associated anaplastic large cell lymphoma.

Lymphoma features	Case number studied	Case number positive	%
Immunohistochemistry			
CD30	37	37	100
CD45	20	15	75
CD2	6	5	83
CD3	28	17	61
CD4	12	9	75
CD5	9	7	78
CD7	3	0	0
CD8	11	1	9
CD43	11	8	73
CD45RO	17	15	88
CD56	6	1	17
EMA	29	20	69
ALK-1	18	2	11
LMP-1 (EBV)	15	1	7
LNA-1 (HHV-8)	1	0	0
Molecular studies			
TCR gene rearrangement	14	14	100
ALK gene rearrangement	8	0	0
EBER *in situ* hybridization	18	6	33
HTLV-I PCR	3	0	0
HHV-8 PCR	1	0	0

EMA, epithelial membrane antigen; ALK-1, anaplastic lymphoma kinase 1; LMP-1, latent membrane antigen-1; EBV, Epstein–Barr virus; LNA-1, latent nuclear antigen-1; HHV-8, human herpesvirus 8; TCR, T-cell receptor gene rearrangement; EBER, EBV-encoded RNA; HTLV-1, human T-lymphotropic virus-1; PCR, polymerase chain reaction.

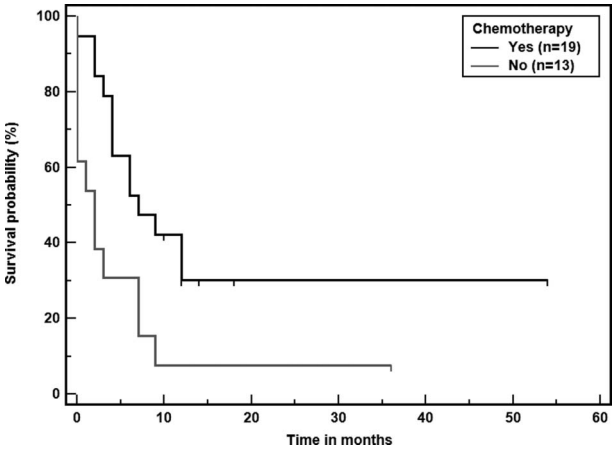

Figure 3. Kaplan–Meier survival estimates in 32 cases of HIV-associated anaplastic large cell lymphoma according to therapy received.

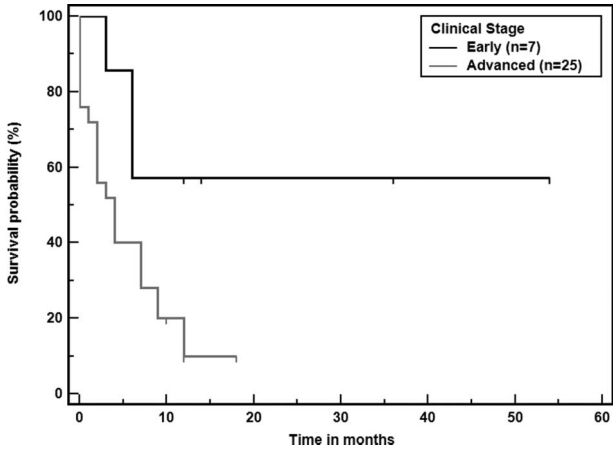

Figure 4. Kaplan–Meier survival estimates in 32 cases of HIV-associated anaplastic lymphoma according to clinical stage.

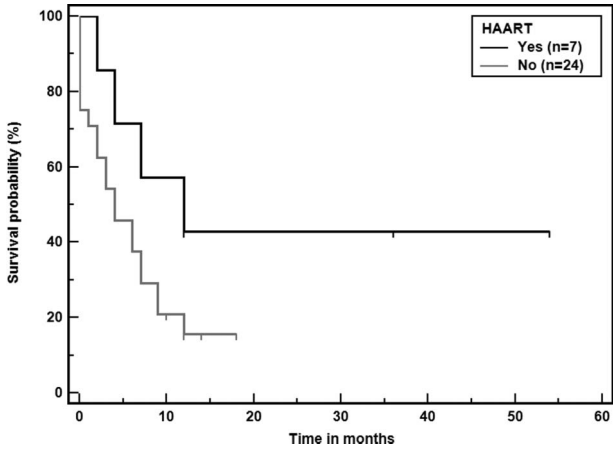

Figure 5. Kaplan–Meier survival estimates in 31 cases of HIV-associated anaplastic lymphoma according to use of highly-active antiretroviral therapy (HAART).

accounted for only 12% of cases, thereby representing the third most common PTCL subtype seen in the HIV-negative population [10]. The average patient age of our cases was relatively young (38 years), and included patients as young as 1 year of age. By comparison, in the HIV-negative population, the peak incidence of ALK-negative ALCL is in adults (40–65 years), unlike ALK-positive ALCL, which occurs most commonly in children and young adults [43]. The lack of ALK expression in HIV-associated ALCL could be a function of the characteristics of the population or the HIV status *per se*; this is unclear at the moment. The male predominance of ALCL in HIV-positive patients is similar to that reported in the general population. The effect of different ethnicities was not reviewed.

ALCL poses a diagnostic challenge, given its broad morphologic spectrum (e.g. anaplastic appearance, lymphohistiocytic pattern, small cell pattern, and Hodgkin-like pattern) and apparent null-cell immunophenotype due to the loss of several pan T-cell antigens [7]. ALCL needs to be distinguished from primary cutaneous ALCL, other T- or B-cell lymphomas with anaplastic features and/or CD30

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expression, and other anaplastic tumors seen in the setting of HIV infection (e.g. anaplastic plasmacytoma, germ cell neoplasia, poorly differentiated carcinoma). HIV-associated ALCL in reviewed cases appeared to present with similar morphological characteristics to those noted in immunocompetent patients, including the presence of hallmark cells and Reed–Sternberg-like cells. The overall immunophenotype of HIV-ALCL cases demonstrated consistent CD30 immunoreactivity, expression of one or more T-cell antigens, rare CD8-positive cases, and positivity for epithelial membrane antigen (EMA) in the majority of cases. The expression of CD3 in our cohort seems higher than that previously reported in immunocompetent cases of ALCL [7]; this could be explained by chance or a real difference seen in HIV-positive cases. However, other more useful markers such as CD2, CD4, and CD5 were also positive in a significant proportion of patients in this study. The most noticeable feature in these HIV-associated ALCL cases is the large proportion of cases that lacked ALK expression. This review identified only two ALK-positive cases, one of which lacked ALK gene rearrangement [19]. In the second ALK-positive case, ALK gene rearrangement was not performed [33]. In the HIV-negative (general) population, ALK-negative ALCL occurs predominantly in adults, involves mainly lymph nodes, and exhibits a poorer clinical outcome with conventional chemotherapy [43]. The preponderance of ALK-negative cases seen in our HIV-positive reviewed cases could certainly help explain the poor prognosis observed in this cohort of HIV-positive ALCL cases.

The development of HIV-associated ALCL in our series of published cases appears to be associated with marked immunosuppression. The median CD4 cell count was under 100 cells/mm^3, which is indicative of marked immunodeficiency. Many of the patients also had a history of AIDS. However, in many of these cases HIV infection was diagnosed concurrently at the time their ALCL was diagnosed. The large proportion of HIV-positive patients with significant immunodeficiency is likely related to the fact that the majority (79%) of these individuals did not receive HAART therapy. These findings are similar to the known association between HIV-associated immunodeficiency and the development of certain aggressive AIDS-related B-cell lymphomas, such as diffuse large B-cell lymphoma and plasmablastic lymphoma [44,45]. Of interest, HIV-associated Burkitt lymphoma and Hodgkin lymphoma tend to arise at comparatively higher CD4 cell counts (e.g. over 200 cells/mm^3) [45,46].

Latent infection with oncogenic gamma-herpesviruses such as EBV and HHV-8 plays a key etiologic role in HIV-related lymphomagenesis [4]. EBV is associated with the development of several HIV-associated lymphomas such as Burkitt lymphoma [47], plasmablastic lymphoma [44], primary central nervous system (CNS) lymphoma [4], and primary effusion lymphoma [4]. The exact role of EBV in PTCL is unclear. In certain subtypes of PTCL, such as AITL, evidence of EBV infection can be demonstrated in the reactive background comprising largely B-cells [48]. Both ALK-positive and ALK-negative ALCL in the general population have been reported to be consistently negative for EBV (i.e. EBER and LMP-1) [43]. Therefore, it is of interest that our review detected several cases in which EBV coinfection was reported (one LMP-1-positive case, six EBER-positive cases); it is currently unclear whether this is a real correlation or just the product of misdiagnosis. While some studies showed no correlation between EBV status and survival in immunocompetent cases of AITL [49], others found EBV status to be an adverse prognostic factor in immunocompetent cases with PTCL-NOS [50]. In the setting of HIV infection, demonstration of EBV coinfection appears to portend a better prognosis in HIV-associated PTCL [5]. In the present report, however, EBV did not correlate with survival in HIV-associated ALCL.

With the emergence of HAART, the efficacy of systemic chemotherapeutic regimens for managing HIV-associated lymphomas has improved. This is due, in part, to a decrease in the rate of opportunistic infections and improvement in host immunity seen in cases that respond to antiretroviral therapy [51–53]. HAART has clearly lowered the incidence of certain AIDS-related malignancies such as Kaposi sarcoma and primary CNS lymphoma [54,55]. With the absolute reduction in incidence of these AIDS-defining cancers that were previously frequently encountered in the pre-HAART era, a relative increase in other malignancies can be expected. Indeed, an increase in the incidence of Hodgkin lymphoma and other non-AIDS-defining cancers (e.g. anal cancer, lung cancer) has been reported in recent years (HAART era) [55,56]. Prospective studies examining AIDS-related lymphomas have noted that response to HAART correlates with a better survival [51,52]. HAART has previously also been shown to be associated with improved survival with HIV-associated PTCL [5]. Not surprisingly, in our review, the use of HAART in HIV-associated ALCL showed a similar trend toward better survival.

Advanced clinical stage in our review correlated with a poor survival. Multiple prognostic factors have been evaluated for ALCL in immunocompetent persons. In particular, the IPI score has proved to be a reliable prognostic tool for ALCL in HIV-negative cases [57–60]. The IPI score in patients with

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HIV-associated lymphomas has been recognized as a reliable prognostic indicator [61–65], as has CD4 cell count [66]. However, the vast majority of HIV-associated lymphoma cases in which the IPI score was studied were of B-cell origin. We were unable to evaluate the significance of the IPI or PIT score in cases of HIV-associated ALCL because of limited available published data.

In terms of treatment, patients with HIV-associated ALCL who were not treated with chemotherapy had a poor prognosis of approximately 2 months. Chemotherapy seems to be a very strong factor for survival. CHOP and CHOP-like regimens were used in the majority of the patients obtaining an 85% overall response rate. Despite this initial good response to therapy, the prognosis in chemotherapy-treated patients continues being poor at 7 months.

Conclusion

In summary, we provide the first large comprehensive review of HIV-associated ALCL. These data show that HIV-associated ALCL tends to manifest in young males with advanced lymphoma, exhibits an aggressive clinical course, and presents almost exclusively with extranodal disease. Poor patient outcome in these cases appears to be related to the lack of ALK expression, low patient CD4 cell counts, and the large proportion of individuals who do not receive therapy given their poor performance status and/or comorbid disease. Chemotherapy seems to play an important role in the management of this condition, although a standard of care has not been determined. HAART appears to be beneficial in the management of this aggressive HIV-associated PTCL. Further research is needed to improve the outcome of patients with HIV-associated ALCL.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References

1. Spano JP, Costagliola D, Katlama C, et al. AIDS-related malignancies: state of the art and therapeutic challenges. J Clin Oncol 2008;26:4834–4842.
2. Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol 2005; 34:121–130.
3. Shibata D, Weiss LM, Hernandez AM, et al. Epstein-Barr virus-associated non-Hodgkin's lymphoma in patients infected with the human immunodeficiency virus. Blood 1993;81: 2102–2109.
4. Carbone A, Cesarman E, Spina M, et al. HIV-associated lymphomas and gamma-herpesviruses. Blood 2009; 13:1213–1224.
5. Castillo J, Perez K, Milani C, et al. Peripheral T-cell lymphomas in HIV-infected individuals: a comprehensive review. J HIV Ther 2009;14:34–40.
6. Biggar RJ, Engels EA, Frisch M, et al. Risk of T-cell lymphomas in persons with AIDS. J Acquir Immune Defic Syndr 2001;26:371–376.
7. Fornari A, Piva R, Chiarle R, et al. Anaplastic large cell lymphoma: one or more entities among T-cell lymphoma? Hematol Oncol 2009;27:161–170.
8. Beltran B, Morales D, Quinones P, et al. Distribution and pathology characteristics of non Hodgkin lymphoma in Peru: a study of 1014 cases using WHO Classification of Lymphoid Neoplasm. Blood (ASH Annual Meeting Abstracts), Nov 2007; 110:4419.
9. Aozasa K, Takakuwa T, Hongyo T, et al. Nasal NK/T-cell lymphoma: epidemiology and pathogenesis. Int J Hematol 2008;87:110–117.
10. Swerdlow S, Campo E, Harris N, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. Lyon, France: International Agency for Research on Cancer; 2008.
11. Castillo J, Pantanowitz L. HIV-Associated NK/T-cell lymphomas: a review of 93 cases. Blood 2007;110(Suppl. 1): 1013a (Abstract 3457).
12. Amin HM, Lai R. Pathobiology of ALK+ anaplastic large-cell lymphoma. Blood 2007;110:2259–2267.
13. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008; 111:5496–5504.
14. Arber DA, Chang KL, Weiss LM. Peripheral T-cell lymphoma with Toutonlike tumor giant cells associated with HIV infection: report of two cases. Am J Surg Pathol 1999;23:519–522.
15. Arzoo KK, Bu X, Espina BM, et al. T-cell lymphoma in HIV-infected patients. J Acquir Immune Defic Syndr 2004;36: 1020–1027.
16. Baschinsky DY, Weidner N, Baker PB, et al. Primary hepatic anaplastic large-cell lymphoma of T-cell phenotype in acquired immunodeficiency syndrome: a report of an autopsy case and review of the literature. Am J Gastroenterol 2001; 96:227–232.
17. Beylot-Barry M, Vergier B, Masquelier B, et al. The spectrum of cutaneous lymphomas in HIV infection: a study of 21 cases. Am J Surg Pathol 1999;23:1208–1216.
18. Bozner P, Elkhalifa MY. Anaplastic large cell lymphoma of T-cell phenotype in acquired immunodeficiency syndrome. South Med J 1997;90:559–566.
19. Burke AP, Andriko JA, Virmani R. Anaplastic large cell lymphoma (CD 30+), T-phenotype, in the heart of an HIV-positive man. Cardiovasc Pathol 2000;9:49–52.
20. Cai G, Inghirami G, Moreira A, et al. Primary hepatic anaplastic large-cell lymphoma diagnosed by fine-needle aspiration biopsy. Diagn Cytopathol 2005;33:106–109.
21. Chadburn A, Cesarman E, Jagirdar J, et al. CD30 (Ki-1) positive anaplastic large cell lymphomas in individuals infected with the human immunodeficiency virus. Cancer 1993;72: 3078–3090.
22. Chow DC, SH Be, Eickhoff L, et al. Primary esophageal lymphoma in AIDS presenting as a nonhealing esophageal ulcer. Am J Gastroenterol 1996;91:602–603.
23. Diekman MJ, Bresser P, Noorduyn LA, et al. Spontaneous regression of Ki-1 positive T-cell non-Hodgkin's lymphoma

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in a patient with HIV infection. Br J Haematol 1992;82: 477–478.
24. Dunphy CH, Collins B, Ramos R, et al. Secondary pleural involvement by an AIDS-related anaplastic large cell (CD30+) lymphoma simulating metastatic adenocarcinoma. Diagn Cytopathol 1998;18:113–117.
25. Escobedo Palau JA, Rubio Felix SA, Gracia Nasarre M, et al. [Large T-cell (Ki-1) anaplastic lymphoma in a patient with human immunodeficiency virus infection, an exceptional association]. Rev Clin Esp 1995;195:126–127.
26. Fatkenheuer G, Hell K, Roers A, et al. Spontaneous regression of HIV associated T-cell non-Hodgkin's lymphoma with highly active antiretroviral therapy. Eur J Med Res 2000; 5:236–240.
27. Gonzalez-Clemente JM, Ribera JM, Campo E, et al. Ki-1+ anaplastic large-cell lymphoma of T-cell origin in an HIV-infected patient. AIDS 1991;5:751–755.
28. Hicks MJ, Flaitz CM, Nichols CM, et al. Intraoral presentation of anaplastic large-cell Ki-1 lymphoma in association with HIV infection. Oral Surg Oral Med Oral Pathol 1993;76:73–81.
29. Jhala DN, Medeiros LJ, Lopez-Terrada D, et al. Neutrophil-rich anaplastic large cell lymphoma of T-cell lineage. A report of two cases arising in HIV-positive patients. Am J Clin Pathol 2000;114:478–482.
30. Kottilil S, Fram R, Cortez K, et al. Hypercalcemia and T-cell lymphoma with acquired immunodeficiency syndrome: occurrence without human T-cell leukemia virus-I. South Med J 2000;93:894–897.
31. Mann KP, Hall B, Kamino H, et al. Neutrophil-rich, Ki-1-positive anaplastic large-cell malignant lymphoma. Am J Surg Pathol 1995;19:407–416.
32. Mira JA, Fernandez-Alonso J, Macias J, et al. Bone involvement and abcess formation by neutrophil-rich CD30+ anaplastic large-cell lymphoma mimicking skeletal infection in an AIDS patient. J Infect 2003;47:73–76.
33. Nagajothi N, Dham SK, Gelfand Y, et al. Treatment of AIDS-associated anaplastic large-cell lymphoma with dose-adjusted EPOCH chemotherapy. J Natl Med Assoc 2007;99:799–801.
34. Nava VE, Cohen P, Kalan M, et al. HIV-associated anaplastic large cell lymphoma: a report of three cases. AIDS 2008;22: 1892–1894.
35. Nosari A, Cantoni S, Oreste P, et al. Anaplastic large cell (CD30/Ki-1+) lymphoma in HIV+ patients: clinical and pathological findings in a group of ten patients. Br J Haematol 1996;95:508–512.
36. Pantanowitz L, Castillo J, Freeman JK, et al. Images in HIV/AIDS. Fatal HIV-associated anaplastic large-cell lymphoma. AIDS Read 2009;19:19–21.
37. Piira TA, Ries K, Kjeldsberg CR, et al. Anaplastic large-cell lymphoma presenting primarily in bone in a patient with AIDS. Hematol Pathol 1994;8:111–116.
38. Proca DM, De Renne L, Marsh WL Jr, et al. Anaplastic large cell lymphoma in a human immunodeficiency virus-positive patient with cytologic findings in bladder wash: a case report. Acta Cytol 2008;52:83–86.
39. Rowsell EH, Zekry N, Liwnicz BH, et al. Primary anaplastic lymphoma kinase-negative anaplastic large cell lymphoma of the brain in a patient with acquired immunodeficiency syndrome. Arch Pathol Lab Med 2004;128:324–327.
40. Rush WL, Andriko JA, Taubenberger JK, et al. Primary anaplastic large cell lymphoma of the lung: a clinicopathologic study of five patients. Mod Pathol 2000;13:1285–1292.
41. Samuels MH, Launder T. Hyperthyroidism due to lymphoma involving the thyroid gland in a patient with acquired immunodeficiency syndrome: case report and review of the literature. Thyroid 1998;8:673–677.
42. Willard CC, Foss RD, Hobbs TJ, et al. Primary anaplastic large cell (KI-1 positive) lymphoma of the mandible as the initial manifestation of acquired immunodeficiency syndrome in a pediatric patient. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:67–70.
43. Mason D, Harris N, Delsol G, et al. Anaplastic large cell lymphoma, ALK-negative. In: Swerdlow S, Campo E, Harris N, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. Lyon, France: International Agency for Research on Cancer; 2008. pp. 317–319.
44. Castillo J, Pantanowitz L, Dezube BJ. HIV-associated plasmablastic lymphoma: lessons learned from 112 published cases. Am J Hematol 2008;83:804–809.
45. Lim ST, Karim R, Nathwani BN, et al. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. J Clin Oncol 2005;23:4430–4438.
46. Bedimo RJ, McGinnis KA, Dunlap M, et al. Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: impact of immunosuppression. J Acquir Immune Defic Syndr 2009 Jul 16. [Epub ahead of print].
47. Hecht JL, Aster JC. Molecular biology of Burkitt's lymphoma. J Clin Oncol 2000;18:3707–3721.
48. Iannitto E, Ferreri AJ, Minardi V, et al. Angioimmunoblastic T-cell lymphoma. Crit Rev Oncol Hematol 2008;68:264–271.
49. Lee Y, Lee KW, Kim JH, et al. Epstein-Barr virus-positivity in tumor has no correlation with the clinical outcomes of patients with angioimmunoblastic T-cell lymphoma. Korean J Intern Med 2008;23:30–36.
50. Dupuis J, Emile JF, Mounier N, et al. Prognostic significance of Epstein-Barr virus in nodal peripheral T-cell lymphoma, unspecified: a Groupe d'Etude des Lymphomes de l'Adulte (GELA) study. Blood 2006;108:4163–4169.
51. Hoffmann C, Wolf E, Fatkenheuer G, et al. Response to highly active antiretroviral therapy strongly predicts outcome in patients with AIDS-related lymphoma. AIDS 2003;17: 1521–1529.
52. Tam HK, Zhang ZF, Jacobson LP, et al. Effect of highly active antiretroviral therapy on survival among HIV-infected men with Kaposi sarcoma or non-Hodgkin lymphoma. Int J Cancer 2002;98:916–922.
53. Wolf T, Brodt HR, Fichtlscherer S, et al. Changing incidence and prognostic factors of survival in AIDS-related non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy (HAART). Leuk Lymphoma 2005; 46:207–215.
54. Franceschi S, Maso LD, Rickenbach M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. Br J Cancer 2008;99:800–804.
55. Dal Maso L, Polesel J, Serraino D, et al. Pattern of cancer risk in persons with AIDS in Italy in the HAART era. Br J Cancer 2009;100:840–847.
56. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008;123:187–194.
57. Park SJ, Kim S, Lee DH, et al. Primary systemic anaplastic large cell lymphoma in Korean adults: 11 years' experience at Asan Medical Center. Yonsei Med J 2008;49:601–609.
58. Suzuki R, Kagami Y, Takeuchi K, et al. Prognostic significance of CD56 expression for ALK-positive and ALK-negative anaplastic large-cell lymphoma of T/null cell phenotype. Blood 2000;96:2993–3000.

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59. ten Berge RL, Oudejans JJ, Ossenkoppele GJ, et al. ALK-negative systemic anaplastic large cell lymphoma: differential diagnostic and prognostic aspects—a review. J Pathol 2003; 200:4–15.
60. Wang FH, Li YH, Zeng J, et al. Clinical analysis of primary systemic anaplastic large cell lymphoma: a report of 57 cases. Chin J Cancer 2009;28:49–53.
61. Lim ST, Karim R, Tulpule A, et al. Prognostic factors in HIV-related diffuse large-cell lymphoma: before versus after highly active antiretroviral therapy. J Clin Oncol 2005;23: 8477–8482.
62. Miralles P, Berenguer J, Ribera JM, et al. Prognosis of AIDS-related systemic non-Hodgkin lymphoma treated with chemotherapy and highly active antiretroviral therapy depends exclusively on tumor-related factors. J Acquir Immune Defic Syndr 2007;44:167–173.
63. Navarro JT, Ribera JM, Oriol A, et al. International prognostic index is the best prognostic factor for survival in patients with AIDS-related non-Hodgkin's lymphoma treated with CHOP. A multivariate study of 46 patients. Haematologica 1998;83: 508–513.
64. Rossi G, Donisi A, Casari S, et al. The International Prognostic Index can be used as a guide to treatment decisions regarding patients with human immunodeficiency virus-related systemic non-Hodgkin lymphoma. Cancer 1999;86: 2391–2397.
65. Tanaka PY, Pracchia LF, Bellesso M, et al. A prognostic score for AIDS-related diffuse large B-cell lymphoma in Brazil. Ann Hematol 2009 Jun 4. [Epub ahead of print].
66. Bower M, Gazzard B, Mandalia S, et al. A prognostic index for systemic AIDS-related non-Hodgkin lymphoma treated in the era of highly active antiretroviral therapy. Ann Intern Med 2005;143:265–273.

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