LEADING ARTICLE

Peripheral T-cell lymphomas in HIV-infected individuals: a comprehensive review

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INTRODUCTION

The incidence of non-Hodgkin's lymphoma (NHL) was noted to be increased early in the human immunodeficiency virus (HIV) epidemic [1]. By 1987, aggressive forms of B-cell lymphoma (NHL) were classified as AIDS-defining illnesses [2]. Currently, lymphomas are considered the second most common malignancy in patients infected with HIV, and AIDS-related lymphoma (ARL) is the most lethal complication in this population [3]. The incidence and outcome of ARL in HIV-infected individuals has changed considerably with the use of highly active antiretroviral therapy (HAART). Antiretroviral use has resulted in a decrease in the incidence and an improvement in prognosis of systemic ARL [4,5].

In contrast to B-cell ARL, HIV-associated peripheral T-cell lymphomas (HIV-PTCL) have been reported less frequently. Single case reports of HIV-PTCL were first published in the 1980s [6–14]. However, evidence supporting a link with HIV continues to accumulate [15–58]. In general, PTCL are uncommon, biologically diverse, vary significantly based upon geographic region and racial population, and have a poor prognosis. Cytological atypia and immunophenotypic markers (e.g. CD30) are less helpful in classification compared with B-cell lymphomas and they do not necessarily correlate with clinical behaviour. Owing to their rarity and biological heterogeneity, success in therapy for PTCL has lagged behind that of aggressive B-cell lymphomas. To date, there has been no comprehensive review on this topic. As PTCL have become an emerging problem in the HIV-infected population, they deserve special attention from the medical community involved in the care of HIV-infected population. This article provides an extensive updated review on HIV-PTCL.

METHODS

Published articles of PTCL in patients with HIV infection were reviewed using MEDLINE. From January 1980 to December 2008, all articles that included the keywords 'T-cell lymphoma', 'NK-cell lymphoma', 'NK/T-cell lymphoma', 'HIV' and 'AIDS' were reviewed. Both case reports and larger case series with sufficient clinical details and concomitant pathological, immunohistochemical and/or molecular confirmation of HIV-PTCL were included. A total of 85 cases were included in the present analysis. Data were tabulated by considering the following variables: epidemiology (country or region of report), patient demographics (age, gender), HIV status (CD4 cell count, HIV viral load at time of PTCL diagnosis, presence of opportunistic infections and other AIDS-defining cancers), clinical presentation, pathology [NHL subtype based on the World Health Organization (WHO) classification of lymphoproliferative disorders, immunophenotype, molecular profile], presence of viral co-infection [Epstein–Barr virus (EBV), human herpesvirus 8 (HHV8), human T-lymphotrophic virus type-1 (HTLV-1)], lymphoma stage (Ann Arbor classification, nodal or extranodal sites of involvement), prognostic factors [lactate dehydrogenase (LDH) level, performance status], type of treatment, final outcome, survival times and cause of death. Descriptive statistics were used to analyse the aforementioned data elements. Survival analyses by age, sex, CD4 cell count, use of HAART, PTCL subtype, EBV expression, clinical stage, serum LDH level, extranodal disease and bone marrow involvement were performed using Kaplan–Meier estimates, which were compared using the log-rank method. All reported *P*-values are two-sided.

RESULTS

CLINICOPATHOLOGICAL FINDINGS

The median age at diagnosis for HIV-PTCL cases was 37 years (range 1–66 years). The majority of cases (99%) were under 60 years of age. There was a male predominance (81%) with a male to female ratio of 4:1. With regard to HIV status, the median CD4 cell count at diagnosis (available in 53 patients) was 130 cells/mm^3 (range 15–1578 cells/mm^3). The average HIV viral load at diagnosis was 279,185 copies/mm^3 (range undetectable–600,000 copies/mm^3). Opportunistic infections were present in 41 cases (73%), including *Candida* (22%), *Mycobacterium* tuberculosis (15%) and *Pneumocystis* pneumonia (12%). Kaposi's sarcoma was also reported in a subset (15%) of cases. The use of HAART was reported in 21 out of 59 cases (36%). The various subtypes of PTCL reported in these publications are shown in Table 1. T-cell receptor gene rearrangement studies were positive in 25 out of 26 evaluated cases (96%).

The majority (80%) of HIV-PTCL cases presented with advanced lymphoma stage (III or IV). Data on the primary site of NHL involvement were available in 65 patients, and showed that 11 cases (17%) were purely nodal at

Table 1: Subtypes of published HIV-associated peripheral T-cell lymphoma (PTCL)

PTCL subtype	Number of cases	Percentage
PTCL unspecified (PTCL-U)	36	42
Anaplastic large cell lymphoma (ALCL)	24	28
NK/T-cell lymphoma (NKTCL)	6	7
T-cell primary central nervous system lymphoma (PCNSL)	6	7
Adult T-cell leukaemia/lymphoma (ATLL)	4	5
Angioimmunoblastic T-cell lymphoma (AITL)	4	5
T-cell primary effusion lymphoma (PEL)	3	4
Enteropathy-like T-cell lymphoma (ELTL)	1	1
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	1	1

presentation while 54 (83%) had extranodal involvement. The most common extranodal sites of involvement included bone marrow (31%), head and neck (23%), lungs (15%), gastrointestinal tract (14%), skin (9%) and CNS (9%). Other extranodal sites noted were muscle, bone, kidneys, heart and the adrenal glands (Figure 1). Serum LDH levels reported in 16 cases showed an average level of 684 mg/dl (range 155–5635 mg/dl). Performance status was reported in only two cases.

Viral co-infection

EBV expression was detected in 21 of 36 (58%) reported cases in which infection for EBV was investigated. Methods to detect EBV were immunohistochemistry for LMP1 (50%), EBV-encoded RNA (EBER) *in situ* hybridisation (38%) and a PCR technique (12%). The presence of HHV8 was evaluated in eight cases, only three (62%) of which were positive. These three HHV8-associated NHL were all T-cell primary effusion lymphomas (two classic and one solid variant PEL), although T-cell receptor rearrangement was demonstrated in only one of the three cases (33%). HTLV-1 was found in three of the four adult T-cell leukaemia/lymphoma (ATLL) cases (75%). The single ATLL case that was negative for HTLV-1 expressed HIV genome in lymphoma cells.

Therapy and outcome

Data on therapy were available in 80 cases. Chemotherapy alone was used in 40 cases (50%), radiotherapy alone in five (6%), chemoradiotherapy in four (5%), and three (4%) patients underwent surgery. As many as 26 (33%) patients did not appear to receive any form of therapy (in only five cases therapy was not specified). Of the 50 individuals who had chemotherapy alone, 27 (68%) received CHOP-like regimens (i.e. containing cyclophosphamide, doxorubicin, vincristine and prednisone). Outcome data were available in 69 cases and showed that 51 (74%) patients died, with a median survival time of 6 months (Figure 2). Causes of death in persons with HIV-PTCL included lymphoma progression in 18 cases (41%), opportunistic infections in 11 (25%), other infectious complications in 11 (25%) and multi-organ failure in four (9%) patients.

Survival analysis results

In the survival analysis by PTCL subtype, PTCL-unspecified (PTCL-U) cases had the longest median survival at 9 months, followed by anaplastic large cell lymphoma (ALCL) at 6 months and primary CNS lymphoma (PCNSL) at 2.5 months. The shortest median survival time was observed in NK/T-cell lymphoma (NKTCL) cases at 1.5 months (Figure 3). The use of HAART and the presence of EBV co-infection in tumour cells were associated with improved survival (Figures 4 and 5, respectively). Advanced stage was associated with a worse survival (Figure 6). Age, sex, CD4 cell count, extranodal disease, LDH level and bone marrow involvement did not appear to be associated with survival in this analysis, although a trend towards a worse survival was observed for CD4 cell count less than 50 cells/mm^3 and a diagnosis of PCNSL (Table 2).

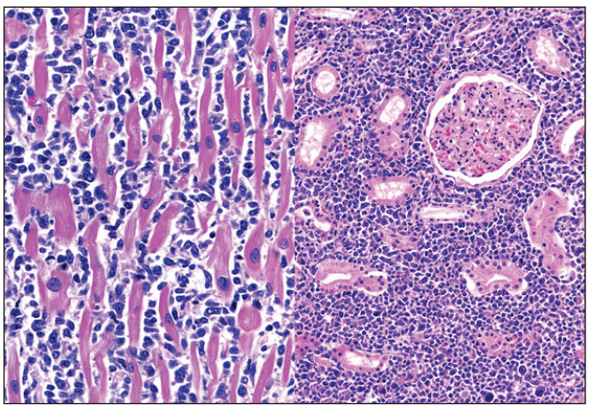

Figure 1: HIV-associated anaplastic large cell lymphoma involvement of (A) the myocardium and (B) kidney. Reproduced with kind permission from [87].

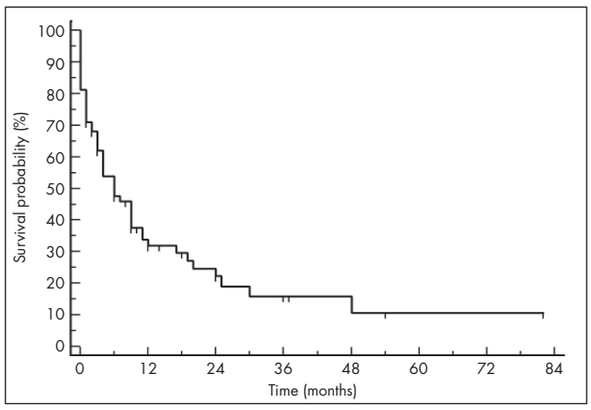

Figure 2: Overall survival for 69 cases of HIV-PTCL

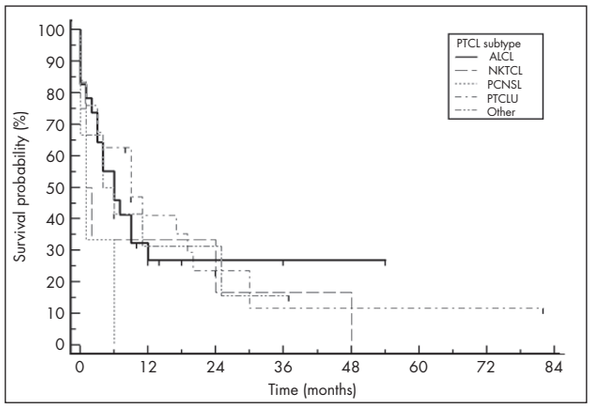

Figure 3: Overall survival by lymphoma subtype in 69 cases of HIV-PTCL

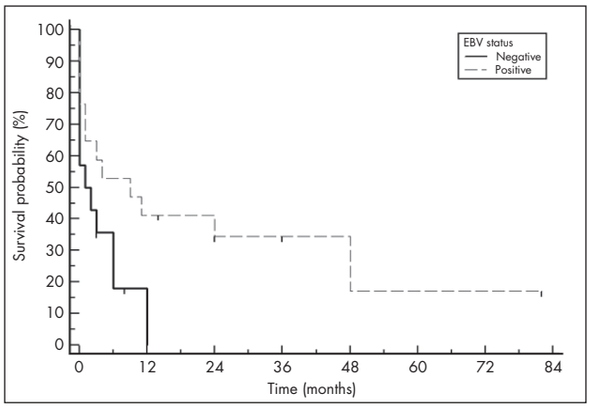

Figure 5: Overall survival by EBV status in 31 cases of HIV-PTCL

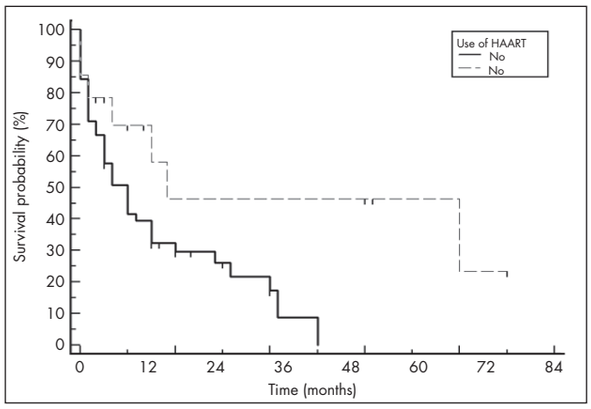

Figure 4: Overall survival by use of HAART in 59 cases of HIV-PTCL

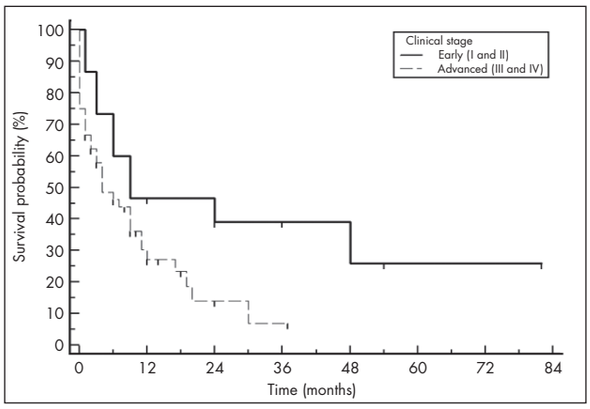

Figure 6: Overall survival by clinical stage in 63 cases of HIV-PTCL

Discussion

Epidemiology

Early registry data demonstrated that the risk of developing B-cell NHL was markedly increased in AIDS patients when compared to the general population [59]. Certain lymphomas, such as primary CNS lymphoma, were associated with a particularly high risk in AIDS patients [60]. The relative risk (RR) of developing HIV-PTCL is similarly increased [relative risk (RR): 15; 95% confidence interval (CI): 10–21.7] when compared with the general population [61]. In this USA-based study, in which data were gathered from 11 states or metropolitan areas between 1978 and 1996, of the 6788 cases of ARL identified, 96 (1.4%) were of T-cell origin [61]. Although these researchers showed that the RR was increased for all PTCL subtypes, they reported a particularly increased incidence of ATLL. ATLL has a strong relationship to HTLV-1, and is usually endemic in areas of Japan, the Caribbean, South America and Africa [62]. However, geographic data and HTLV-1 serology status in this study were not reported. Most available epidemiological data are retrospective and potentially underpowered. The exact incidence of HIV-PTCL may thus be underreported, partly confounded also by the known difficulty in diagnosing and classifying this group of lymphomas.

Pathogenesis

Failure to prove the presence of HIV genome or associated proteins in transformed B-cells by different methods does not support a direct role of HIV in the pathogenesis of most ARL [63]. Current evidence indicates that HIV probably contributes indirectly to lymphomagenesis, through immunological derangements and chronic antigenic stimulation. Oncoviruses are associated with approximately half of systemic ARL [64], implying that other mechanisms (i.e. viral oncogenes) may also play an important role in AIDS lymphomagenesis. Shiramizu and colleagues [65] reported four cases of non-B-cell ARL in which HIV p24 was detected in transformed T-cells. Others have also reported finding the HIV genome in tumour cells in ATLL [15] and NKTCL [22]. This suggests that HIV may play a more direct role in the pathogenesis of HIV-PTCL.

EBV is a well-known oncovirus associated with several lymphoproliferative disorders. Particular PTCL subtypes, such as angioimmunoblastic T-cell lymphoma (AITL) and NKTCL seem to have a strong association with EBV infection [66]. In a previous report, EBV was present in 78% of HIV-PTCL, including cutaneous T-cell lymphoma (CTCL) [67]. The role of EBV in this setting is incompletely understood, but seems to be related to selective immunosuppression and cytokine dysregulation via infection of B- and T-cells [68]. There is accumulating

Table 2: Univariate analysis of clinicopathological factors in HIV-associated PTCL

Factor	*P*-value	Hazard ratio	95% confidence intervals
Age >60 years	0.04	0.005	<0.001–0.74
Male gender	0.24	1.72	0.7–4.21
CD4 cell count <50 cells/mm^3	0.07	0.47	0.20–1.06
Diagnosis of PCNSL	0.06	0.22	0.04–1.09
Use of HAART	0.03	2.25	1.09–4.64
EBV positivity	0.04	2.77	1.03–7.46
Advanced lymphoma stage	0.04	0.5	0.26–0.98
Extranodal disease	0.74	1.2	0.42–3.45
Elevated LDH level	0.17	0.38	0.09–1.55
Bone marrow involvement	0.72	0.85	0.36–2.04

evidence that HHV8 is directly lymphomagenic. HHV8-encoded products such as LANA1 and viral IL-6 have been shown to inactivate p53 transcriptional activity, cause chemokine derangements and promote angiogenesis [69]. Like B-cell PEL, all cases of T-cell PEL in the present study were reported to be positive for HHV8 [25, 33]. HTLV-1 and HTLV-II co-infection have also been reported in patients with HIV-PTCL and in a few of these cases, the viral genome was found in lymphoma cells of HIV-ATLL and CTCL [7,12,70].

Pathology

The WHO lymphoma classification [71] divides ARL into three categories: (1) lymphomas also occurring in immunocompetent patients, like PTCL; (2) lymphomas occurring more specifically in HIV-positive patients, like PEL of T-cell immunophenotype; and (3) lymphomas also occurring in other immunodeficiency states. Based upon our review of the available literature, a wide variety of mature PTCL of unspecified and specified subtypes have been documented in HIV-infected persons (Table 1). PTCL-U was the most common subtype of HIV-PTCL encountered in our review. Even in the HIV-negative population, PTCL-U represents the largest PTCL subtype in North America. PTCL-U includes a heterogeneous group of T-cell NHL, with multiple morphologies, and a poor outcome using standard chemotherapy. ALCL appear to represent 28% of all HIV-PTCL reported to date. These lymphomas are identified by a highly pleomorphic appearance, propensity to invade lymph node sinuses, and exhibit uniform expression of CD30 (Ki-1) on lymphoma cells. ALK-negative cases are known to present at an older age with advanced stage, elevated LDH, frequent B symptoms, and extranodal involvement. While T-cell PCNSL and T-cell PEL were identified in our review of the literature, these subtypes are relatively rare when compared with their B-cell counterparts that are commonly seen in HIV-positive individuals. Extranodal NKTCL are EBV-associated CD56-positive lymphomas that demonstrate angiocentric invasion, vascular destruction, and necrosis. Despite frequent localised disease to nasal and extranasal sites (e.g. skin, soft tissue, gastrointestinal tract and testis) NKTCL are aggressive lymphomas. Distinguishing AITL from PTCL-U is difficult. Pathological features favouring AITL include prominent vascularisation by arborising venules, expansion of follicular dendritic cell networks, and the identification of CD10 as phenotypic marker of neoplastic T-cells. Other uncommon PTCL seen in the HIV population include ATLL, enteropathy-like T-cell lymphoma (ELTL) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL) **(AQ: OK to change abbreviation??)**. ELTCL usually complicate an established history of gluten-sensitive enteropathy or occur even following a short history of coeliac disease and/or dermatitis herpetiformis. ATLL, associated with infection by HTLV-1, frequently contains malignant cells with a distinct cloverleaf appearance. SPTCL is the least well-defined and rarest subtype of PTCL. Many aggressive B-cell NHL seen in HIV patients, especially those with plasmacytic differentiation, often lack CD20 and exhibit aberrant T-cell antigen expression [72]. These lymphomas may falsely lead to an impression of T-cell lymphoma, and could thereby skew the published data reported.

Clinical features

In one case series of HIV-PTCL [73], individuals more frequently affected were found to be younger men (median age 33 years) with a CD4 cell count of 101 cells/mm^3. Our results were very similar, as the majority of cases included in our review were also male patients with a median age of 37 years and comparable low median CD4 cell count (130 cells/mm^3). A South American case series also reports similar results [74], with 78% of their HIV-positive cases being male, with a median age of 36 years and CD4 cell count of 124 cells/mm^3. The majority of cases in our review and these other series [59,60] present with B symptoms and were classified as stage IV. Reported sites of extranodal involvement include, in order of frequency, bone marrow, head and neck region, lungs, gastrointestinal tract, skin and CNS.

Therapy

CHOP-type chemotherapy has been the mainstay of therapy for PTCL. In the present study, most patients were treated with CHOP-like regimens. Generally, treatment approaches are similar among the PTCL subtypes. One exception is limited-stage nasal NKTCL, where involved-field radiation without chemotherapy appears to be the key treatment modality. Patients with more widespread PTCL may be treated with a combination of chemotherapeutic agents, including anthracycline-based regimens, which carry variable response rates and high rates of relapse [75]. NKTCL nasal type, for example, appears to have an inherent resistance to conventional systemic therapy that may be related to expression of P-glycoprotein resulting in multidrug resistance. Because both local and systemic relapse remain problematic, new therapeutic approaches are needed.

Moreover, ARL in general also tend to have an aggressive clinical course and poor prognosis [76]. Combination chemotherapy with concurrent or delayed HAART has shown to be of benefit in ARL [77] demonstrating, almost uniformly, a benefit in overall survival at the cost of increasing the toxicity in patients with severe immunodeficiency. Further study is needed, including the role of high-dose chemotherapy, stem-cell transplant and novel treatment approaches (e.g. nucleoside analogues, histone deacetylase inhibitor, and immunotherapy) in HIV-PTCL.

Prognosis

In general, the prognosis for most B-cell ARL has improved considerably in the post-HAART era [78,79]. With the notable exception of ALK-positive ALCL, the outcome for PTCL despite therapy has been uniformly disappointing. Our review shows that up to 72% of patients diagnosed with HIV-PTCL died, with a median survival time of only 6 months. The shortest median survival times were observed with PCNSL and NKTCL cases. Most individuals died because of lymphoma progression or infection. Attempts have been made to define biologically distinct subgroups of PTCL based upon clinical, biological and molecular prognostic factors. The International Prognostic Index (IPI) score is a prognostic tool widely used to risk-stratify aggressive B-cell lymphomas by utilising age, LDH level, clinical stage, performance status and extranodal involvement as prognostic factors [80]. A recent prospective study validated the IPI score as a prognostic tool in ARL [81], and a smaller retrospective study validated its prognostic value in PTCL [82]. While most of the patients in our study presented with advanced AIDS, the prognostic value of a low CD4 cell count remains debatable [83]. A Prognostic Index for PTCL-U (PIT) score has been validated in immunocompetent patients. The PIT score uses age, performance status, LDH levels and bone marrow involvement as prognostic factors [84]. Unfortunately, the paucity of data on LDH level and performance status in the present review did not permit us to evaluate the PIT score in HIV-PTCL.

Data from our survival analysis demonstrated that the use of HAART and the presence of EBV co-infection in tumour cells were associated with improved survival of HIV-PTCL. The beneficial use of HAART on survival of patients for B-cell ARL is well known [78]. However, the overall survival for HIV-PTCL continues to be poor, at 6 months. Although the present study shows an association between EBV-positive status and improved prognosis in HIV-PTCL (9 versus 1.5 months; $P = 0.04$), there are equivocal data on the role of EBV status as a prognostic factor in PTCL. Dupuis and colleagues [85] showed in a retrospective study that EBV in lymphoma cells was associated with worse prognosis in patients with nodal PTCL. On the other hand, Lee and colleagues [86] did not find an association between EBV positivity and survival in Korean AITL patients. Potential explanations for our findings include a selection bias of cases, site specific and subtype of NHL, and type of EBV latency expression. Although the univariate analysis showed age older than 60 as a poor prognostic indicator, only one patient in our series was actually older than 60, thus limiting further conclusions. Finally, in the multivariate analysis, only 23 cases had usable data and no variables were retained in the model. Therefore, further research is warranted to identify reliable prognostic factors in HIV-PTCL.

Conclusion

Compared to B-cell ARL, there is a paucity of literature on HIV-PTCL. HIV-PTCL appears to be a highly aggressive disease developing mainly in males with AIDS. Mechanisms of lymphomagenesis in this heterogeneous group of ARL differ from those responsible for B-cell lymphomas and include race, geography and novel oncoviruses (e.g. HTLV-I). Although PTCL in this setting is associated with chemotherapy resistance and poor survival, the role of HAART is promising. Further research is needed to improve the diagnostic, prognostic and therapeutic approaches for HIV-PTCL.

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