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# Clinical profiles of human immunodeficiency virus-associated lymphoma in Hong Kong

## 香港本土與人類免疫缺乏病毒相關的淋巴瘤患者之臨床狀況

**Objective.** To identify the clinical and prognostic features of human immunodeficiency virus-associated lymphoma in the local population with a view to designing more effective treatment strategies.

**Design.** Retrospective review.

**Setting.** Referral hospital, Hong Kong.

**Subjects and methods.** All patients (n=10) with human immunodeficiency virus-associated lymphoma managed at Queen Elizabeth Hospital from January 1995 to December 2001.

**Results.** All patients were men with a median age of 39 years. The median CD4 cell count at the time of diagnosis of lymphoma was  $0.056 \times 10^9/L$ . All tumours were diffuse large B-cell lymphomas, with the exception of one systemic Burkitt-like lymphoma. Systemic lymphoma was diagnosed in seven patients and three had primary central nervous system lymphoma. Combined antiretroviral therapy was continued or given to five of the six patients who received some form of chemotherapy or radiotherapy treatment. Of the two patients with primary central nervous system lymphoma who received whole brain irradiation therapy, one patient survived 41 months in clinical remission after diagnosis and the other patient died of sepsis while in partial remission 19 months after diagnosis. The four patients with systemic lymphoma who received standard- or reduced-dose chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone had a median survival of 3 months.

**Conclusion.** The clinical profiles of these patients were similar to those of patients with human immunodeficiency virus-associated lymphoma in western countries. The overall survival of patients was poor with conventional chemoradiotherapy. Other innovative treatment approaches should be investigated to prolong the survival of this patient group.

### Key words:

Case management;  
 Epidemiology;  
 Hong Kong;  
 Human immunodeficiency virus;  
 Lymphoma, AIDS-related

### 關鍵詞：

病例管理；  
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**目的：**確定本地人口中，患上與人類免疫缺乏病毒相關的淋巴瘤患者的臨床預兆特徵，以設計更有效的治療策略。

**設計：**回顧性總結。

**安排：**轉介醫院，香港。

**對象與方法：**在1995年1月至2001年12月期間，於伊利沙伯醫院接受治療的所有(n=10)患上與人類免疫缺乏病毒相關的淋巴瘤患者。

**結果：**所有患者為男性，中值年齡為39歲。在診斷淋巴瘤時的CD4細胞中值數為 $0.056 \times 10^9/L$ 。除了一宗廣泛性Burkitt-like淋巴瘤病例外，全部腫瘤為彌漫性大細胞型淋巴瘤。七名患者被診斷出患有廣泛性淋巴瘤，三名患有原發性中樞神經系統淋巴瘤。曾接受化學治療或放射治療的六名患者中，有五名接受了「抗愛滋病雞尾酒藥物治療」。接受全腦放射治療的兩名原發性中樞神經系統淋巴瘤患者中，一名患者在診斷後於臨床緩解期存活了41個月；另一名患者在診斷後19個月的局部緩解期間死於細菌感染。四名患者接受標準或減劑量化學治療配以環磷酰胺、阿霉素、長春新鹼及強的松；他們的存活期中值數為3個月。

**結論：**本研究分析的患者，其臨床狀況與西方國家患上與人類免疫缺乏病毒相關的淋巴瘤患者類似。接受常規化學治療的患者，其總存活期並不理想，應該研究新的治療方法以延長患者的存活期。

## Introduction

Systemic high- or intermediate-grade non-Hodgkin's lymphoma (NHL) has been an AIDS-defining disease since 1985.<sup>1</sup> Human immunodeficiency virus-associated lymphoma (HIV-L) is usually a late manifestation of infection by HIV. The lymphoma is commonly associated with widespread, extranodal disease; central nervous system (CNS) involvement; and poor prognosis.<sup>2,3</sup> Such cases of NHL can be classified as being systemic, primary CNS lymphoma (PCNSL), or primary effusion lymphoma (PEL). As is the case for other individuals with impaired cell-mediated immunity, the incidence of NHL is markedly increased in patients with HIV infection, with the risk of NHL in this setting being approximately 100-fold that observed in the general population.<sup>4</sup>

Over time, the epidemiological and demographic characteristics of AIDS have changed in western countries.<sup>5</sup> The widespread use of highly active antiretroviral therapy (HAART) has influenced the natural history of the disease,<sup>6,7</sup> with a resulting significant decrease in AIDS-defining opportunistic infections, the incidence of Kaposi's sarcoma (KS) and PCNSL,<sup>8</sup> and mortality.<sup>9</sup> Multiple studies have shown no impact of HAART on the incidence of AIDS-related systemic NHL, however.<sup>5,10</sup> Importantly, patients with HIV-L often present with multiple features associated with a poor prognosis, including significant tumour burden, an advanced state of immunosuppression, and concurrent opportunistic infections. Strategies to manage such complex cases have had disappointing results to date. Prospective therapeutic studies have shown no difference in complete remission rates or overall survival between patients treated with low-dose or standard-dose chemotherapy.<sup>11,12</sup>

Since the first diagnosis of AIDS in Hong Kong in 1984 to December 2001, the cumulative incidences of HIV

infection and AIDS were 1755 and 560 cases, respectively. Nineteen cases of HIV-L have been reported and managed at Hospital Authority hospitals. Six of these patients were diagnosed before 1995 and 13 after 1995, when HAART became standard therapy. As a main referral hospital for the in-patient care of patients with AIDS in Hong Kong, 10 patients with HIV-L were managed at the Queen Elizabeth Hospital (QEH) from January 1995 to December 2001. Three other patients were diagnosed and managed in other local hospitals during this period. This study describes the epidemiological and clinical features, and treatment outcomes of the 10 patients with HIV-L managed at QEH.

## Subjects and methods

A retrospective review of the 10 patients with HIV-L diagnosed and treated at QEH between January 1995 and December 2001 was undertaken. All patients were HIV-seropositive by enzyme-linked immunosorbent assay, with confirmation by Western blot test, and had biopsy or cytologically proven NHL staged prior to treatment, using the Ann Arbor staging system.

History, physical examination, and routine blood investigations were performed at the time of diagnosis. Routine staging was performed for all patients and, where possible, included chest X-ray; computed tomography scans of the brain, chest, abdomen, or pelvis; lumbar puncture with cerebrospinal fluid (CSF) analysis; and bone marrow biopsies and aspirates. All patients underwent bilateral bone marrow aspiration and biopsy. Lumbar puncture with CSF analysis was completed for six patients. Computed tomography scanning was performed for all patients according to site of presentation. In situ hybridisation studies for Epstein-Barr virus (EBV) early RNAs (EBERs) were routinely completed for patients with PCNSL but not for those with systemic lymphoma. Hospital records, bone marrow

**Table. Clinical profiles and outcomes for human immunodeficiency virus-infected patients with lymphoma (n=10)**

Histology	Age (years)	Risk	HIV→HIV-L*	Stage	Extranodal involvement
<i>Systemic lymphoma</i>					
Diffuse large cell lymphoma	37	Heterosexual route	5 months	IVB <sup>§</sup>	Lung, liver
Diffuse large cell lymphoma	41	Heterosexual route	AIDS-defining illness	IVB	Suprarenal, liver
Diffuse large cell lymphoma	18	Haemophilic	5 years	IVB	Liver
Burkitt-like lymphoma	51	Heterosexual route	AIDS-defining illness	IVB	Lung, bone marrow
Diffuse large cell lymphoma	43	Heterosexual route	2 months	IVB	Nasopharynx, central nervous system
Diffuse large cell lymphoma	59	Heterosexual route	AIDS-defining illness	IA <sup>  </sup>	-
Diffuse large cell lymphoma	64	Heterosexual route	3 months	IVB	Liver
<i>Primary central nervous system lymphoma</i>					
Diffuse large cell lymphoma	32	Heterosexual route	AIDS-defining illness	-	No leptomeningeal involvement
Diffuse large cell lymphoma	29	Homosexual route	AIDS-defining illness	-	No leptomeningeal involvement
Diffuse large cell lymphoma	31	Heterosexual route	6 months	-	No leptomeningeal involvement

\* Time from diagnosis of HIV infection to the development of HIV-associated lymphoma

† ECOG performance score

‡ CD4+ cell count at diagnosis of HIV-associated lymphoma

§ IVB stage IV with systemic symptoms

|| IA stage I without systemic symptoms

¶ This patient was found to be HIV-seropositive after receiving four cycles of CHOP (100%) chemotherapy

\*\* CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone

pathology reports, laboratory data, treatment regimens, and response to therapy were reviewed. All patients underwent standard pathologic review.

The treatment modalities used to treat the seven patients with systemic lymphoma and the three patients with PCNSL are summarised in the Table. Combined antiretroviral therapy—comprising one protease inhibitor plus one or two nucleoside reverse transcriptase inhibitors (NRTIs) or non-NRTIs—were given to five of the six patients who received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-based combination chemotherapy or radiotherapy treatment. Whole brain irradiation (WBI) therapy was given to two of the three patients with PCNSL and was administered to a total dose of 40 to 45 Gy in 2 Gy daily fractions.

## Results

The clinical profiles and outcomes for the 10 patients with NHL treated at QEH between January 1995 and December 2001 who were HIV-seropositive are summarised in the Table.

### Patient characteristics

All patients were men with a median age of 39 years (range, 18-64 years). Nine patients were Chinese and one was Indian. Risk factors for HIV infection included heterosexual transmission for eight patients, male-to-male sexual transmission for one patient, and blood product transfusion for one patient with haemophilia. None of the patients was an intravenous drug user. Six patients presented with HIV-L as the primary AIDS-defining illness (ADI). Four patients presented with HIV-L as a subsequent ADI, with three having a history of *Pneumocystis carinii* pneumonia and one of disseminated mycobacterium avium-intracellulare infection. All except the patient with haemophilia had their HIV-seropositive status identified after presentation with the ADI.

For the four patients with HIV-L as a subsequent ADI, the median duration of presentation with HIV-L was 4 months (range, 2-6 months) after the primary ADI. None of the patients had a history of KS. The median CD4 cell count at the time of diagnosis of lymphoma was  $0.056 \times 10^9/L$  (range,  $0.003-0.081 \times 10^9/L$ ). Combined antiretroviral therapy was continued or initiated at QEH for five of the six patients who received chemotherapy or radiotherapy treatment. The other four patients died soon after the diagnosis of HIV-L (median survival, 22 days; range, 8-60 days) without receiving chemotherapy or radiotherapy because of their poor clinical state and rapidly progressive disease.

### Characteristics of lymphoma at diagnosis

Systemic lymphoma was diagnosed in seven patients and PCNSL was diagnosed in three patients. None of the patients presented with PEL. All patients had diffuse, large B-cell lymphomas, apart from the Indian man who had a systemic Burkitt-like lymphoma. No patient had Hodgkin's lymphoma. For patients with systemic lymphoma, six were at stage IV (with systemic symptoms) and one was at stage I (without systemic symptoms). The three patients with PCNSL showed no evidence of leptomeningeal involvement. Six of the patients with systemic lymphoma had extranodal lymphomatous disease, with specific sites including the liver (n=4), lung (n=2), brain (n=1), kidney (n=1), and nasopharynx (n=1). Four patients had more than one involved extranodal site. Bone marrow involvement was only noted in the one patient with Burkitt-like lymphoma. Nine patients had a serum lactate dehydrogenase (LDH) level higher than 400 U/L (reference range, 50-200 U/L), with results ranging from 300 to 2205 U/L at diagnosis of HIV-L. A significant proportion (40%) of patients had a haemoglobin level below 100 g/L (range, 71-144 g/L; reference range, 140-175 g/L), and 20% of patients had a platelet count of less than  $140 \times 10^9/L$  (range,  $24-697 \times 10^9/L$ ; reference range, 150-450  $\times 10^9/L$ ). All three patients with PCNSL showed EBERS

Epstein Barr virus status	Performance score <sup>†</sup>	CD4+ ( $\times 10^9/L$ ) <sup>‡</sup>	Prior AIDS-defining illness	Treatment	Outcome—median survival
+	3	0.04	<i>Pneumocystis carinii</i>	-	2 months, progressive disease
Not done	3	0.05	-	CHOP** (75%)	2 months, progressive disease
-	4	0.081	-	-	1 month, progressive disease
Not done	3	0.081	-	CHOP (50%)	3 months, progressive disease
+	4	0.056	<i>Pneumocystis carinii</i>	-	8 days, progressive disease
-	2	Not done <sup>¶</sup>	-	CHOP (100%)	5 months, progressive disease
-	3	0.08	<i>Pneumocystis carinii</i>	CHOP (75%)	2 months, sepsis
+	2	0.009	-	Whole brain irradiation, surgery	19 months, partial remission
+	2	0.06	-	Whole brain irradiation	pulmonary tuberculosis, sepsis
+	4	0.003	Disseminated mycobacterium avium-intracellulare infection	-	41 months, complete remission
					5 days, progressive disease, sepsis

positivity. This positivity was also demonstrated in two of the five patients with systemic lymphoma who had *in situ* hybridisation for EBERS completed.

### **Survival**

Of the two patients with PCNSL who received scheduled WBI therapy, one patient had survived 41 months after the diagnosis of lymphoma and remained in clinical remission (CR) at the time of writing. The other patient died of sepsis in partial remission 19 months after diagnosis. All four patients with systemic lymphoma (three stage IV with systemic symptoms, and one stage I without systemic symptoms) who received standard- or reduced-dose CHOP combination chemotherapy died due to disease progression ( $n=3$ ) or sepsis ( $n=1$ ) at a median of 3 months (range, 2-5 months). The patient with PCNSL, who survives in CR, continues to take HAART consisting of lamivudine, zidovudine, and indinavir. His most recent CD4 cell count was  $0.418 \times 10^9/L$ .

### **Discussion**

#### ***Clinical presentation and epidemiology***

The presentation of HIV-L may be systemic, may primarily involve the CNS as PCNSL, or may be localised in the body cavities as PEL. Systemic lymphoma is the most common presentation, accounting for approximately 80% of all cases. The histology is usually diffuse large cell, immunoblastic, or small non-cleaved cell lymphoma (Burkitt's lymphoma), and is usually of B-cell phenotype; low-grade histology is rare.<sup>2,3,13</sup> Burkitt's lymphoma tends to occur in patients with a relatively high CD4 cell count (median,  $0.150 \times 10^9/L$ ) compared with diffuse large cell or immunoblastic types (median,  $0.05 \times 10^9/L$ ).<sup>13</sup> Extranodal involvement occurs in approximately 80% of patients, with the most commonly involved sites being the bone marrow, gastrointestinal tract, meninges, and liver. Unusual sites have also been reported, including the anorectum, gingiva, heart, common bile duct, muscles, and the placenta and products of conception.<sup>13</sup>

Most patients with PCNSL (approximately 20% of all patients with HIV-L) are profoundly immunosuppressed and typically have a CD4 cell count below  $0.050 \times 10^9/L$ . Approximately two thirds or more have an ADI prior to the development of PCNSL.<sup>14,15</sup> The lesions are typically few in number (1-3), large (2-4 cm), and contrast enhanced on magnetic resonance imaging and computed axial tomography in approximately 50% of patients.<sup>16</sup> Lesions are most commonly sited in the cerebrum, but also frequently occur in the cerebellum, basal ganglia, and brain stem, and are nearly always found to be multifocal at autopsy.<sup>17</sup> The lymphoma cells tend to be distributed along vascular channels as perivascular cuffs, are of B-cell origin, display large cell and immunoblastic histologies, and uniformly exhibit EBV-associated DNA.<sup>18</sup>

Primary effusion lymphoma is uncommon, accounting for no more than 3% of HIV-L cases.<sup>19</sup> These patients

exhibit a unique constellation of clinical, morphological, immunophenotypic, and molecular characteristics, and thus represent a distinct clinicopathological entity.<sup>20</sup> The lesions present in the pleural, pericardial, or peritoneal cavities as lymphomatous effusions, usually in the absence of a tumour mass. Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8 sequences are a consistent finding.<sup>21</sup>

The natural history of HIV infection has been changed by HAART, which improves immune function in HIV-infected individuals.<sup>22</sup> While HAART therapy has been associated with a significant decline in the incidence of various opportunistic infections and KS,<sup>9,23</sup> such a major and significant decline has not yet been uniformly described with regard to systemic HIV-L. Recent data suggest that the incidence of PCNSL and systemic lymphoma has decreased with the widespread use of HAART.<sup>23,24</sup> However, the decline in lymphoma is far less impressive than that observed for opportunistic infections and KS, resulting in a proportionate increase in lymphoma as the initial ADI. In this study, the incidence of HIV-L in the AIDS population was 3.4%, with 60% presenting with HIV-L as the primary ADI, and the remaining patients presenting with HIV-L only 4 months (range, 2-6 months) after their primary ADI.

At present, there are some inconsistencies in the literature regarding potential effects on the clinical or pathologic characteristics of patients with HIV-L arising from the widespread use of HAART. These reported inconsistencies may relate to different populations, differences in access to HAART, or other unknown factors. Levine et al<sup>5</sup> reviewed records of 369 patients diagnosed with AIDS-related lymphoma at a single institution from 1982 to 1998 and compared these data to population-based information from the County of Los Angeles. Significant changes in the demographic characteristics of HIV-L occurred in both populations, with the latter time period characterised by a statistically significant increase among women, Latino/Hispanic individuals, and those who acquired HIV through heterosexual contact. There was a decrease in small non-cleaved (Burkitt's or Burkitt-like) lymphoma over time, while the prevalence of diffuse large B-cell lymphoma increased. Despite changes in the use of antiretroviral therapy and chemotherapy, the median survival did not appreciably change.<sup>5</sup> In a recent study, characteristics that were found to be statistically associated with development of HIV-L on multivariate analysis included a lower CD4 lymphocyte count (both at baseline and at nadir), older age, and lack of HAART therapy.<sup>10</sup>

Clinical features that contribute to a poor prognosis include lymphoma-specific factors (that is, aggressive histology, extranodal disease, and advanced stage) and HIV-specific factors (that is, poor bone marrow reserve, CD4 lymphopenia, and opportunistic infection). Clinical features that have been consistently associated with a poor outcome include a low CD4 lymphocyte count, prior opportunistic infection, and poor performance status.<sup>25</sup> The AIDS

Clinical Trials Group<sup>26</sup> (ACTG) developed a prognostic model based upon four variables that were associated with worse survival on multivariate analysis. These included CD4 cell count less than  $0.1 \times 10^9/L$ , patient age greater than 35 years, intravenous drug use, and stage III/IV disease.<sup>26</sup> In their prognostic model, median survival was 46 weeks for patients with none or one adverse factor compared with 18 weeks for those with three or four adverse factors. Several groups have reported that the International Prognostic Index is predictive for survival for patients with lymphoma and HIV infection.<sup>27</sup> In this study, all patients were men and most (80%) had acquired HIV infection through heterosexual contact. All except the Indian patient had a diffuse large B-cell lymphoma. Patients with systemic lymphoma presented at an advanced stage with elevated serum LDH and extranodal site involvement. Five of the seven patients with systemic HIV-L had at least three adverse factors as suggested by the ACTG. The overall survival of these patients was thus likely to be short regardless of whether or not they received standard- or reduced-dose CHOP-based chemotherapy.

### **Chemotherapy treatment strategies**

Four different strategies with respect to chemotherapy treatment have been studied and reported. These include the use of standard-dose, low-dose, and infusional chemotherapy regimens, and high-dose therapy (HDT) with autologous stem cell transplantation (ASCT).

### **Standard-dose versus low-dose chemotherapy**

Low-dose therapy was first evaluated in 35 patients with HIV-L and a mean CD4 lymphocyte count of  $0.15 \times 10^9/L$ .<sup>11</sup> These patients were treated with a modification of the standard methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) regimen, in which the cyclophosphamide dose was reduced to  $300 \text{ mg/m}^2$  and the doxorubicin dose to  $25 \text{ mg/m}^2$ . Complete remission was observed in 16 of the 35 (46%) individuals, and the median survival was 6.5 months. These results were not significantly different from those previously reported using a variety of more standard chemotherapeutic regimens. However, they were achieved with significantly less haematological toxicity; only 10% of chemotherapeutic cycles were complicated by an absolute neutrophil count of less than  $0.5 \times 10^9/L$  (reference range,  $1.8\text{--}7.8 \times 10^9/L$ ). It is noteworthy, however, that when a similar regimen was used in a group of individuals with a median CD4 count of  $0.035 \times 10^9/L$ , only 19% achieved CR and the median survival was only 3 months.<sup>28</sup> These observations highlight the strong relationship between immune function and clinical outcome.

At the same time, other studies demonstrated that full-dose chemotherapy could be safely administered if granulocyte-macrophage colony-stimulating factor (GM-CSF) was also administered. When standard-dose CHOP was administered and patients were randomly assigned either to receive concurrent therapy with GM-CSF or no further adjunctive treatment, those receiving GM-CSF had significantly

reduced haematological toxicity and a significantly lower incidence of admission to hospital for febrile neutropenia.<sup>29</sup>

The standard- and low-dose approaches to chemotherapy were directly compared in the ACTG 142 study, a large multicentre randomised clinical trial designed to address the importance of chemotherapy dose intensity in determining the clinical outcome following treatment for HIV-L.<sup>12</sup> In this study, 198 patients were randomly assigned to receive either the standard-dose m-BACOD regimen described earlier with adjunctive administration of GM-CSF, or the same low-dose m-BACOD regimen with GM-CSF administered only as required for management of neutropenia. The results of this trial demonstrated no significant difference in response rate or survival time. However, toxicity was more severe in those patients assigned to standard-dose therapy, particularly with respect to the occurrence of grade 4 neutropenia.

### **Infusional chemotherapy**

Another, more recent, approach has been the use of continuous infusion chemotherapy. Sparano et al<sup>30,31</sup> developed and tested a 96-hour continuous infusion regimen of cyclophosphamide, doxorubicin, and etoposide (CDE) in patients with newly diagnosed, systemic HIV-L. A large, multi-institutional Eastern Cooperative Oncology Group (ECOG) trial involving 107 patients received a 4-day infusion, with 48 patients receiving concomitant antiretroviral therapy with didanosine (ddI), and 59 patients receiving HAART regimens.<sup>31</sup> For the group as a whole, the rate of CR was 44%, with partial responses in 11% of patients. While there was no difference in CR rate, among patients who received HAART versus ddI, the median survival was longer for those patients who received combination antiretroviral therapy. This series of trials would indicate that while response rates to infusional CDE appear to be similar to those achieved with either low-dose or standard-dose m-BACOD, survival appears to be superior for patients who receive concomitant HAART. Furthermore, since failure-free survival was also noted to improve with CDE plus HAART, the increase in overall survival may reflect better control of the lymphoma.

### **High-dose therapy and autologous stem cell transplantation**

The use of HDT and ASCT has been shown to improve survival in patients with high risk and relapsed chemosensitive systemic NHL, without HIV.<sup>32</sup> This approach has not been routinely used for patients with lymphoma and HIV infection primarily because of concern over the increased risk of haematological and infectious complications. However, since patients with systemic HIV-L are at an advanced disease stage, with extranodal involvement, and are thus regarded as high-risk, HDT with ASCT should be considered if long-term survival is expected. Krishnan et al<sup>33</sup> studied the use of ASCT in patients with HIV-L. Nine patients with HIV-L were mobilised with a median of  $10.6 \times 10^6$  CD34+ cells/kg and engrafted after ASCT.

CD4 counts recovered to pre-transplantation levels and HIV viral loads were controlled in patients who complied with antiretroviral therapy. Seven of the nine patients remained in remission from the lymphoma at a median of 19 months after transplantation. Thus, these authors concluded that ASCT was feasible for selected patients with HIV-L receiving antiretroviral therapy, and that prolonged lymphoma remission could be achieved without significant compromise of immune function.<sup>33</sup> Furthermore, the potential application of gene therapy to the harvested stem cells may enhance the resistance of proliferating stem cells to HIV infection.

### ***Optimal treatment for primary central nervous system lymphoma***

Radiation therapy has generally been the mainstay of treatment for PCNSL, whether associated with HIV infection or not. Patients with HIV infection generally have a median survival of approximately 3 months, and fewer than 10% survive for 1 year—a treatment result that is clearly inferior to that achieved for PCNSL occurring in immunocompetent individuals.<sup>34</sup> Features associated with a favourable outcome include good performance status and no prior history of opportunistic infections. Studies combining chemotherapy with radiation therapy have failed to demonstrate an advantage for combination modality therapy.<sup>35</sup> The impact of HAART for patients with HIV-associated PCNSL is unclear. Spontaneous regression of PCNSL has been reported after HAART therapy in the absence of other systemic or radiation therapy for the lymphoma, however.<sup>36</sup> In this study, two of the three patients with PCNSL survived for longer than 1 year, and the remaining patient was still alive and in CR 41 months after the diagnosis of PCNSL, with a recent CD4 cell count of  $0.418 \times 10^9/L$ . It has been considered that spontaneous regression may have contributed to the long period of survival for this patient.

### **Conclusion**

The clinical profiles of the patients with HIV-L in this study are similar to those reported in western countries, with most patients contracting the infection via the heterosexual route and most having advanced stage diffuse large B-cell lymphoma. Given the increasing number of patients presenting with lymphoma as the primary ADI and their non-specific presentation, a high index of suspicion for HIV-L is required by clinicians caring for patients with HIV. In particular, this diagnosis should be considered for those patients who present with mass lesions, fever, or increased LDH. The overall survival of patients in this study was poor with conventional CHOP-based combination chemotherapy, although systemic lymphoma in patients without HIV infection is a potentially curable disease. Other innovative approaches to prolonging the survival of patients with HIV-L should be investigated, including the concomitant use of combination chemotherapy and HAART, and the use of more intensive chemotherapy with HDT and ASCT.

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