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CASE REPORT

Oral cavity and extra-oral plasmablastic lymphomas in AIDS patients: report of five cases and review of the literature

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Summary: Plasmablastic lymphoma (PBL) is a distinct disease entity of the diffuse large B-cell lymphoma which often occurs in human immunodeficiency virus-positive patients. The immunophenotype of this lymphoid neoplasm is characterized by the presence of plasma cell markers-associated VS38c and CD138 antigens and the absence of B-cell markers such as CD20 and CD45. The most frequent site of involvement is the oral cavity and the jaw, while several reports describe the development of PBL in extra-oral sites including the lymph nodes, the anal canal, the soft tissue, the skin and the gastrointestinal tract as less frequent. The Epstein–Barr virus is often associated with PBL pathogenesis and the neoplastic cells contain this virus genome. Here we review the epidemiological, clinical, immunological, histopathological and virological characteristics and the prognosis and outcome in a series of five patients with diagnosis of HIV/AIDS and PBL.

Keywords: plasmablastic lymphoma, AIDS, HIV, Epstein–Barr virus, herpes virus type-8

INTRODUCTION

Plasmablastic lymphoma (PBL) is a rare entity typically described in the oral cavity of human immunodeficiency virus (HIV)-infected patients.[1,2]

The World Health Organization (WHO) classified the PBL as a diffuse proliferation of large neoplastic cells in which the majority of the tumour cells show the immunophenotype of plasma cells (CD138 and VS38c positive).[3] However, a recent morphological and immunohistochemical (IHC) study has suggested that PBL may represent an heterogeneous group of neoplasms with different clinical and histopathogical characteristics, corresponding to different entities which include PBL, diffuse large B-cell lymphoma (DLBCL) with plasmablastic differentiation and extramedullary plasmablastic tumours associated with plasma cell myeloma anaplastic lymphoma kinase+ DLBCL and human herpes virus type-8 (HHV-8) (+) germinotropic lymphoproliferative disorder.[4–6] PBL immunophenotype is similar to myeloma; however, using genomic profiling, PBL seems closer to DLBCL.[4] The differential diagnosis between DLBCL and PBL is performed on a clinical, morphological and phenotypical basis. PBL accounts approximately for 3% of all HIV-related non-Hodgkin's lymphomas (NHL) and is strongly associated with the Epstein–Barr virus (EBV) in the pathogenesis.[7]

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In this article, we reviewed the epidemiological, clinical, histopathological, immunological, virological and the outcome of five adult patients with PBL and AIDS.

MATERIALS AND METHODS

We analysed the epidemiological, clinical, histopathological, immunological and virological findings and the outcome of five patients with AIDS and PBL assisted at a single reference hospital of infectious diseases in Argentina. The patients were clinically staged according to the Ann Arbor stage system. In all cases, diagnosis was confirmed by the histopathological examination of the biopsy smears. Physical examination, including performance status, complete blood cell counts, serum biochemistry counting lactate dehydrogenase (LDH) levels, and hepatitis B (HBV) and C (HCV) serology was performed in all the patients. In order to define the neoplasm extension, all patients underwent the following studies: bone marrow aspirate and trephine biopsy, chest X-ray and complete tomography scan of the brain, thorax, abdomen and pelvis. Histopathological diagnosis was made according to the criteria of the WHO classification.[7] The difference between PBL and anaplastic plasmacytoma or anaplastic myeloma was based on the clinical picture, high proliferation index, EBV association and the absence of maturation. IHC stains were applied in all cases including the analysis of Ki-67 index, a cell-cycle-specific marker (clone Ki67-DAKO) and the mouse monoclonal antibodies directed against CD20 (clone L26), CD45 (clone 2B11 + PD7/26), CD10 (clone: 56C6-Novocastra), CD138 (clone MI15), plasma cell marker (clone VS38c), MUM-1 (multiple myeloma oncogene 1, clone MUM1p) and BCL-6 (clone PG-B6p). The primary antibodies were from DAKO

Table 1 **Demographic findings in five cases of plasmablastic lymphomas from AIDS patients**

Gender	1 Male	2 Male	3 Female	4 Male	5 Female
Age	47	35	25	39	55
HIV/risk infection	Unprotected sexual contact	IVDUs	Unprotected sexual contact	IVDUs	Unprotected sexual contact
Clinical Stage	Advanced	Advanced	Advanced	Advanced	Early
HBV	(+)	(−)	(+)	(+)	(−)
HCV	(−)	(+)	(−)	(+)	(−)
LDH (U/L)	409	450	1186	1365	380
Bone marrow envolved	(+)	(−)	(−)	(+)	(−)

IVDUs, intravenous drug users; HBV, hepatitis B virus; HCV, hepatitis C virus; LDH, lactate dehydrogenase

Q2 Diagnostics. The definition of PBL was made on the basis of immunopathological findings, including a lack of expression of CD20 and plasmacytic differentiation such as CD38, CD138 and MUM-1.

The presence of EBV-associated latent membrane protein-1 (LMP-1) by IHC and EBV-encoded mRNAs (EBERs) by *in situ* hybridization (ISH) were analysed in biopsy smears. Based on the correct histopathological setting, a cut-off of 10% was adopted to consider EBER as positive. Detection of HHV-8 RNA in tissue obtained by biopsy smears was performed by reverse-transcriptase polymerase chain reaction (RT-PCR). We have also evaluated the chemotherapy regimens, the response to therapy and the outcome with relapse and the cause of death. Finally, we include the overall time of survival reported in months.

RESULTS

During the 10-year period, 82 HIV-infected patients were diagnosed with lymphoma. Fifty-four (65%) of them were NHL and
Q3 28 (35%) were Hodgkin's disease. Five (2.7%) of NHL were diagnosed as PBL and were included in this study. Three were men. The major route of HIV transmission was unprotected sexual contact and most of the patients were heterosexual (60%). The median of age was 39 years (range 25–55 years). In one patient of our series (patient 5) the diagnosis of PBL was concomitant with the seropositivity for HIV. Two patients had high levels of LDH, three had antibodies to HBV (60%) and two were HCV reactive (40%). Bone marrow biopsy showed the infiltration of atypical lymphoid cells in two patients (40%). Demographic findings are described in Table 1.

Only one patient presented an early clinical stage at the time of diagnosis; the other four had advanced clinical stage (3 or 4).

Three patients had tumours that involved the oral cavity (Figures 1 and 2); one was a primary PBL of the liver (Figure 3) and the other presented with several nodular skin lesions (Figure 4). The median of CD4 T-cell counts was 85 cells/μL (range 37–270 cells/μL). Two patients presented more than 200 cells/μL.

The diagnosis was definitive in all patients by histopathological and IHC methods. Histopathological examination of biopsy smears showed a diffuse proliferation of atypical lymphoid cells containing large-sized polygonal plasmablastic cells with abundant basophilic cytoplasm; large and eccentric nuclei with a prominent central nucleoli associated with marked mitotic and apoptotic findings. The ki67 index was >80% in all the patients of this series. IHC examination revealed that tumour cells expressed the plasma cell markers CD138, VS38c and MUM-1 (Figure 5). The EBV genome was detected by IHC and ISH (Figure 6) in four of four patients in whom this method was available (100%); RT-PCR for HHV-8 was detected in two patients (40%).

Follow-up was available in four patients; three patients received chemotherapy plus highly active antiretroviral

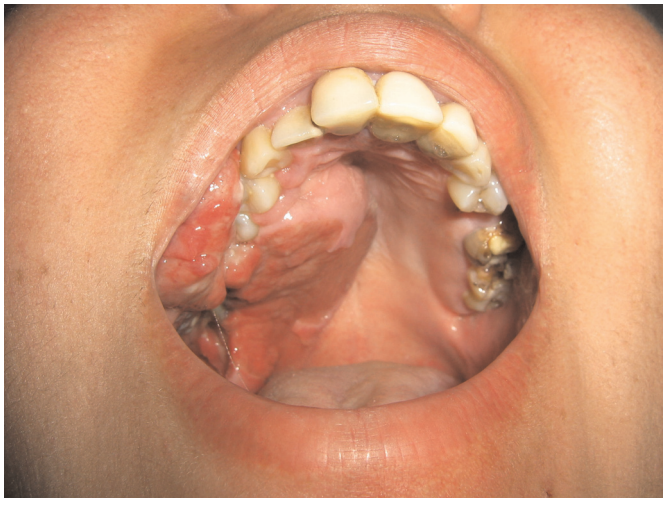

Figure 1 **A large and ulcerative lesion involving the gingiva and the palate in a case of a female with diagnosis of plasmablastic lymphoma of the oral cavity.**

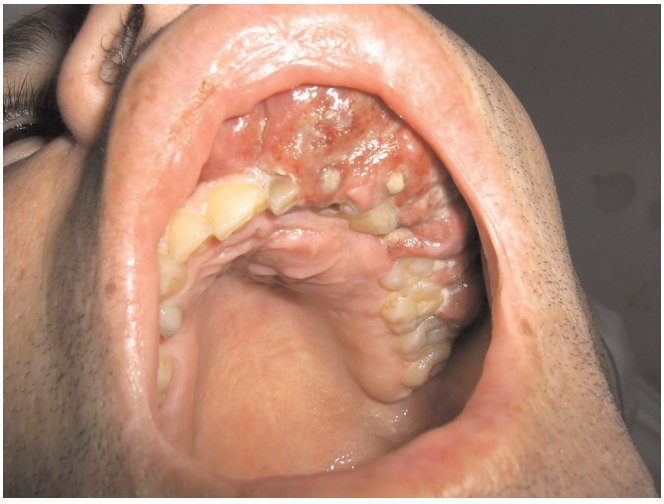

Figure 2 **A large tumour lesion corresponding to a man with a primary oral cavity plasmablastic lymphoma**

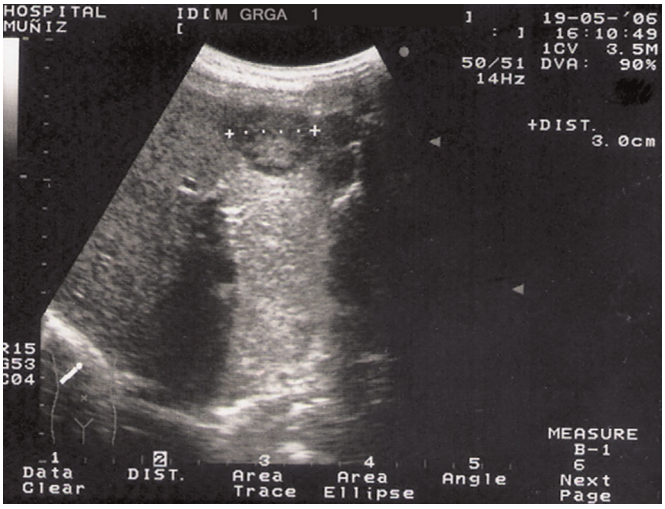

Figure 3 **Abdominal ultrasound showing a large single lesion in the left liver lobe in a patient with a primary plasmablastic non-Hodgkin's lymphoma**

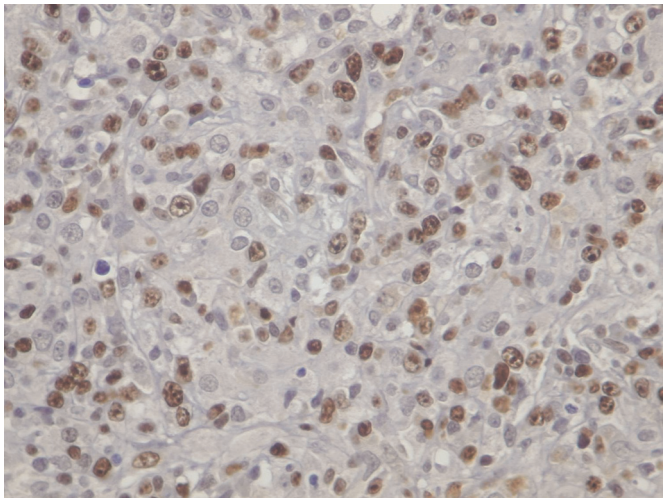

Figure 5 **MUM-1 expression in the neoplastic cells**

therapy (HAART) and the last patient of our series was treated with HAART alone. With regard to chemotherapy, all patients were treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and all received intrathecal prevention chemotherapy based on methotrexate at a dose of 12 mg on the 15th day of every cycle. The first three patients presented a partial response to chemotherapy and died with a median survival time of five months. One patient was not able to follow-up. The other one received HAART based on abacavir plus lamivudine plus efavirenz. Due to a good and fast clinical response only to HAART, she did not receive chemotherapy. In this case, a gradual decrease in the size of the oral cavity lesion was noticed before chemotherapy was initiated; after 10 months, only with HAART we could appreciate a complete remission of the lesion and the mucosa tissue appeared to be normal and without signs of lymphoid infiltration in a second biopsy (Table 2).

DISCUSSION

Patients infected with HIV are at increased risk to develop NHL.[8] The incidence of NHL including DLBCL, Burkitt's lymphoma and PBL is increased among HIV-seropositive patients and 16% of deaths in AIDS patients have been associated with lymphomas.[9] In HIV-positive patients, 3% of NHL is PBL. In our series, of 82 AIDS-associated lymphomas, 2.7% of NHL were PBL. These lymphomas are characterized by their rapid progression, frequent extranodal manifestation and poor outcome.

Although PBL is described almost exclusively in AIDS patients, Khurana *et al.*[10] and Fan Lin *et al.*[11] reported two **Q4** cases of nodal PBL in HIV-negative patients. AIDS-related PBL have a markedly predilection for the oral cavity involvement at the time of the neoplasm diagnosis. There have been a few reports in the medical literature of cases with extra-oral compromise as we could see in our series.[12–14] Within the oral cavity, the gingiva and the palate infiltration are characteristic of the PBL subtype.

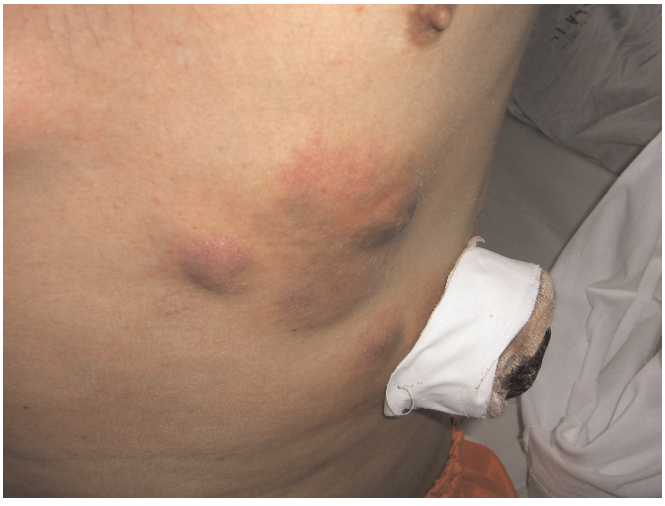

Figure 4 **Multiple subcutaneous nodules in a patient with diagnosis of primary plasmablastic cutaneous lymphoma**

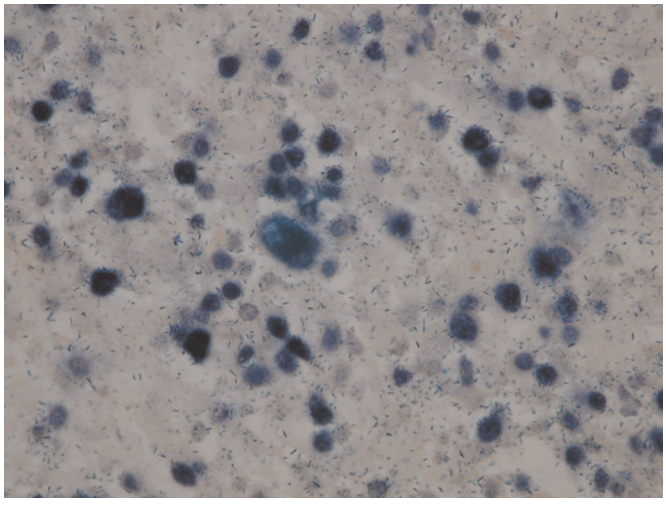

Figure 6 ***In situ* hybridization positive for Epstein–Barr virus genome in the atypical cells**

Table 2 **Immunological, histopathological and virological findings from AIDS patients with plasmablastic lymphomas**

Location	1 Liver	2 Skin	3 Oral cavity and skin	4 Oral cavity	5 Oral cavity
CD4 level	37	56	270	85	215
EVB (LMP-1 and EBERs) in biopsy samples	(+)	(+)	(+)	ND	(+)
HHV-8 in biopsy smears	(−)	(+)	(−)	(−)	(+)
Ki67	>90%	>90%	>80%	>80%	>90%
Survival	5 months	4 months	8 months	Unknown	10 months
Treatment	CHOP plus HAART	CHOP plus HAART	CHOP plus HAART	Unknown	HAART alone
Response	Partial	Partial	Partial	Unknown	Complete
Cause of death	Lymphoma progression	Lymphoma progression	Lymphoma progression	Unknown	Prolonged survival

EBV, Epstein–Barr virus; HHV-8, herpes virus type 8; HAART, highly active antirretroviral therapy; ND, not done; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; EBER, EBV-encoded mRNA; LMP-1, latent membrane protein-1

Gujral *et al.*[15] recently reported 34 cases of PBL and the authors emphasize the frequency of HIV-positive status and the preference for extranodal site of involvement, specially the oral cavity mucosa (25 cases) and the gastrointestinal tract (5 cases). Globally, in this series 31 cases (91%) were extranodal PBL. In our series, all patients presented with extranodal involvement.

In AIDS patients, viral infection, especially EBV infection, has been strongly associated with the pathogenesis of PBL.[12] HHV-8 is other oncogenic virus that has also been reported in association with PBL in AIDS patients.[16,17] Cioc *et al.*[2] examined five biopsy smears corresponding to oral cavity lymphomas from men with AIDS. Four of these tumours were PBL and the other was a DLBCL. Most of the neoplastic cells in these five lymphomas contained the HHV-8 RNA. The four PBL cases contained EBV. In our series, the four patients in whom this test was made present the EBV genome in the atypical cells. Using RT-PCR we found that two patients out of this four had the HHV-8 genome (40%). The role of HHV-8 in the pathogenesis of PBL remains unclear; nevertheless, a considerable number of relevant articles highlight the possibility of a participation of this virus in the pathogenesis of this entity.[2,18,19] The clinical background continues to be of relevance to rule out the diagnosis of Castleman's disease (CD) in the absence of peripheral lymphadenopathy. Although we detected HHV-8 in two patients of our series, the detection of HHV-8-associated PBL arising from CD is associated with distinct histopathological findings. Considering that WHO places PBL and PEL as different categories and the lack of expression of CD45 in our cases, we discarded the possibility of a diagnosis of extracavitary PEL.[20] The differential diagnosis between PBL and anaplastic plasmacytoma or anaplastic myeloma was based on the clinical picture, high proliferation index, EBV association and the absence of maturation, as we can see in the cases presented.

HCV should also have a role in the pathogenesis of lymphomas in patients co-infected with HIV. Durberg *et al.*[21] described that patients infected with HCV have a high risk to develop NHL in comparison with the general population. In our series, two patients (40%) were infected by HCV, probably related to the source of HIV infection.

The prognosis of PBL patients is usually very poor and it worsens by the presence of immunodeficiency associated with the HIV-infection. The clinical course is very aggressive and the majority of patients died in the first year after the neoplasm diagnosis. The refractory or relapsing disease rate is high and survival is generally short after neoplasm diagnosis. Guan *et al.*[7] performed a meta-analysis showed that HAART combined with chemotherapy and/or radiotherapy was the most effective treatment which improved the prognosis of PBL in comparison with just chemotherapy and/or radiotherapy. Three patients of our series, received chemotherapy plus HAART; they all died and the mean of survival was of five months. One patient had responded only to HAART before the treatment with chemotherapy was initiated and remained in remission during 10 months using no other therapy. The other patient was not available to follow-up.

The small number of patients included in our series has been a drawback to come to any statistical conclusion. In an extensive literature research using PubMed/Medline from January 1997 to September 2009, Castillo *et al.*[22] analysed 248 PBL cases, out of which 157 were HIV-seropositve patients. Seventy patients received chemotherapy and were considered appropriate for the study. Their median of age at the time of neoplasm diagnosis was 38.8 years and the male-to-female ratio was 4:1. The mean of CD4 T-cell count was 165 cell/μL and only 37% of patients received HAART. Extraoral involvement was found in 43% of the cases and the expression of EBERs was 86%. The overall survival in this series was 14 months. In the univariate analysis, early-stage clinical diagnosis and a complete response to chemotherapy were associated with prolonged survival. Similar to other aggressive lymphomas, in this series, PBL patients were treated with CHOP or CHOP-like regimens without any evidence of longer survival with more intensive chemotherapy.[22] The meta-analysis of Guan *et al.*[4] supports the hypothesis that the addition of HAART to chemotherapy improves the prognosis with these kinds of patients.

The clinical course of PBL is usually aggressive; however, spontaneous regression with HAART[23,24] and a prolonged and durable response to chemotherapy have been reported.[25]

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