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ORIGINAL RESEARCH

Non-Hodgkin Lymphomas of the Oral Cavity in AIDS Patients in a Reference Hospital of Infectious Diseases in Argentina: Report of Eleven Cases and Review of the Literature

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Abstract
Introduction Extranodal non-Hodgkin lymphoma (NHL) were commonly described in AIDS patients and are related with an atypical morphology and aggressive clinical course.
Materials and Methods In this single institutional study we evaluated the epidemiological, clinical, immunological, virological, histopathological and the outcome of eleven HIV/AIDS patients with oral cavity lymphomas (OCL).
Results Nine were males and seven intravenous drug abusers. The median of age was 33 years and the median of CD4 T cell counts at the time of diagnosis was 97 cell/μL. The majority of tumors presented as large and ulcerated masses involving the gingiva, the palate and the jaw. Six of these tumors were diffuse large B-cell lymphomas (DLBCL); three were Burkitt's lymphomas and the final case was a plasmablastic lymphoma. An association with Epstein-Barr virus (EBV) was found in three of the ten tested cases by in situ hybridization (EBER 1 and 2 probes) and immunohistochemistry (LMP-1). Human herpes virus-8 (HHV-8) was detected by polymerase chain reaction (PCR) in only one neoplasm. Six patients died without specific treatment; four received chemotherapy and highly active antiretroviral therapy (HAART) and three of them presented a prolonged survival.
Discussion Combination of HAART and chemotherapy should modify the poor prognosis of AIDS patients with OCL.

Keywords oral cavity lymphoma · AIDS · plasmablastic lymphoma · EBV · HHV-8

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Introduction

Non-Hodgkin's lymphoma (NHL) is an AIDS-defining neoplasm which is mostly a high-grade B cell lymphoma. Patients with HIV infection are at increased risk to develop NHL [1, 2]. These lymphomas are characterized by their rapid progression, frequent extranodal initial manifestations, and poor outcome [2]. Oral cavity is a rare site of presentation for NHL in AIDS patients and only 3% of them involve primarily the oral cavity [3, 4].

Here, we describe the epidemiological, clinical, immunological, virological, histopathological, and outcome in a series of 11 HIV-seropositive patients with lymphomas presenting with initial oral cavity involvement.

Material and Methods

We analyzed the epidemiological, clinical, immunological, virological findings, and the outcome in 11 HIV-positive patients with NHL of the oral cavity. The patients were

clinically staged according to the Ann Arbor system. Primary NHL of the oral cavity was defined as those lymphomas presenting with involvement of the oral soft tissue or the jaw as the predominant manifestation of the disease. All the diagnosis except one (patient 2 in which the diagnosis was done by cytology of fine needle aspiration smear) was performed by the histopathological examination of biopsy smears obtained from the oral lesions. In order to define the neoplasm extension, we performed, in all patients, complete blood cell counts, serum biochemistry including lactate dehydrogenase (LDH) levels, hepatitis B and C (HCV) serology, bone marrow aspirate and trephine biopsy, chest X-ray, ultrasonogaphy of the abdomen and pelvis, and complete tomography scan of the head and neck region. Histopathological diagnosis was made according to the criteria of the World Health Organization (WHO) [5]. We also included patients with other sites of further disease compromise. Additional immunohistochemical stains were applied in all cases. Immunohistochemistry examination of the oral cavity tumors included the analysis of Ki 67 (prolipherative) index and the mouse monoclonal antibodies directed against CD20, CD45, CD10, CD138, plasma cell clone VS38c, and BCL-6. The primary antibodies were from DAKO Diagnostics.

The presence of Epstein-Barr virus (EBV)-associated latent membrane protein-1 by immunohistochemical (IHC) and EBV-encoded mRNAs by in situ hybridization (ISH) were analyzed in biopsy smears. Detection of human herpesvirus-8 (HHV-8) RNA in oral tissue obtained by biopsy smears was performed by polymerase chain reaction (PCR).

Results

Eleven patients with AIDS and lymphomas located in the oral cavity were available for study. Demographic findings are described in Table 1 and immunological, histopathological and virological features are listed in Table 2. Nine patients were men and seven were intravenous drug users. The median of age at the time of tumor diagnosis was 33 years and the median of CD4 T cell count was 97 cell/μL. Serum levels of LDH were available from nine patients and they were elevated in all except one. Eight of the 11 patients were positive for HCV (Table 1). The majority of the tumors involved the gingiva, the palate, and the jaw (Figs. 1, 2, and 3). The most frequent clinical presentation was a large mass involving the gingiva extending to the palate and with osteolytic lesions of the upper or lower jaws. There were no cases with tongue involvement. Histopahological examination showed that the majority of the tumors (six) were diffuse, large B-cell lymphomas (DLBCL), expresses CD20 and were positive for the monoclonal antibody antiCD20

Table 1 Demographic findings in the cases of oral lymphomas from AIDS patients

	Patient number										
	1	2	3	4	5	6	7	8	9	10	11
Gender	Male	Male	Male	Male	Male	Male	Female	Female	Male	Male	Male
Age	31	26	32	44	38	51	25	24	43	35	38
HIV/risk infection	Hemophilia	IVDUs	IVDUs	IVDUs	IVDUs	IVDUs	Unprotected sexual contact	Unprotected sexual contact	IVDUs	Unprotected sexual contact	IVDUs
HCV	+	+	+	+	+	+	–	–	+	–	+
Bone marrow involved	–	–	–	–	–	–	–	–	+	–	–

Table 2 Immunological, histopathological and virological findings from AIDS patients with oral cavity lymphomas

	Patient number										
	1	2	3	4	5	6	7	8	9	10	11
Location	Cavum	Palate, jaw	Gingiva, palate	Gingiva palate, jaw	Gingiva, jaw	Cavum	Gingiva, palate, jaw	Gingiva	Palate, Gingiva	Tonsil	Gingiva
CD4 level	177	47	30	78	189	19	270	235	58	173	116
Phenotype	B	ND	B	B	B	B	B	B	B	B	B
Histopathology Subtype	DLBCL	ND	DLBCL	Burkitt	DLBCL	DLBCL	Plasmablastic	Burkitt	DLBCL	DLBCL	Burkitt
EVB	Negative	ND	Negative	Positive	Negative	Negative	Positive	Positive	Positive	Negative	NT
HHV-8	NT	NT	Negative	Negative	Negative	NT	Negative	Negative	Negative	Positive	Negative
Survival	>5 years	74 days	27 days	20 days	>3 years	2 months	7 months	15 months	NT	2 months	15 days

IVDUs intravenous drug users, *DLBCL* diffuse large B-cell lymphoma, *EBV* Epstein-Barr virus, *NT* not tested

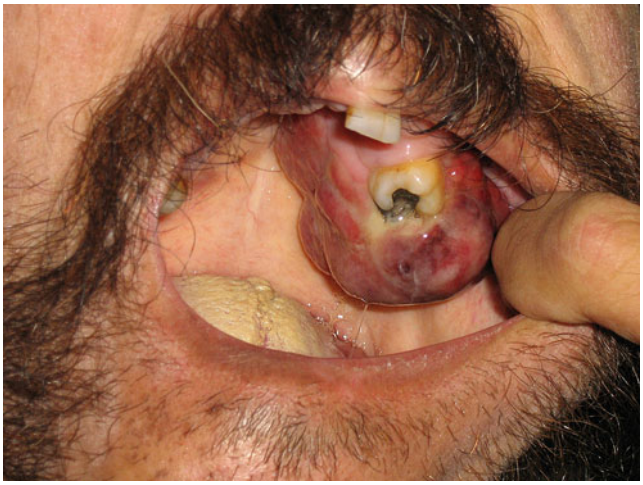

Fig. 1 Large and ulcerative tumor lesion of the oral cavity involving the gingiva and the left hard palate corresponding to a diffuse large B-cell lymphoma

(Fig. 4). Three neoplasms were Burkitt's lymphomas and only one express the plasma cell marker CD138, VS38c, MUM-1, and other markers of plasma cell proliferation which were classified as primary plasmablastic lymphoma of the oral cavity. In patient 2, the histopathological diagnosis was not available because the diagnosis method was only by the cytological aspiration. Bone marrow biopsy was negative for the detection of atypical cells in all the patients except one.

Two specimens of Burkitt's lymphoma and the plasmablastic lymphoma were positive for EBV RNA by ISH and IHC in the majority of the tumor cells (Figs. 5 and 6). One DLBCL located in tonsil-contained HHV-8 RNA in the tumor cells (Table 2).

Follow up were available in ten patients. Six patients died with a median survival of 43 days (range 15-74 days); none of them were available to receive chemotherapy

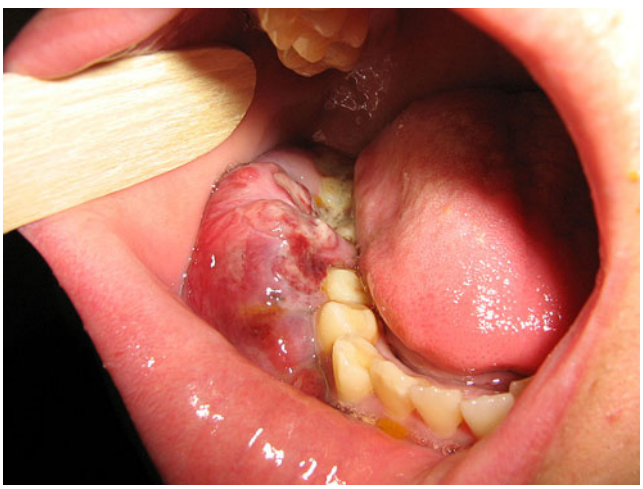

Fig. 2 AIDS-associated Burkitt lymphoma of the oral cavity presenting with a rapidly growing mass of the gingiva

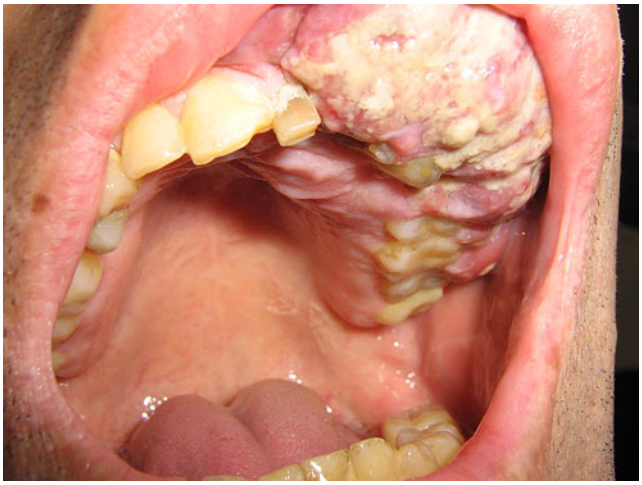

Fig. 3 A large tumor lesion of the palate and the gingiva corresponding to a plasmablastic lymphoma of the oral cavity

because of their poor clinical status. The other four started on chemotherapy plus highly active antiretroviral treatment (HAART). Three of them presented clinical, virological, and immunological improvement. Patients 1, 5, and 8 presented prolonged survival without neoplasm relapse. Patient 7 failed to respond to chemotherapy plus HAART and died after 7 months of having been diagnosed with resistant/relapse plasmablastic lymphoma (Table 2).

Discussion

AIDS-associated B-cell lymphomas were commonly described to have atypical morphology, extranodal involvement as primary manifestation and aggressive clinical course. Lymphomas of the oral cavity are a rare complication of advanced HIV/AIDS disease. In a series of 543

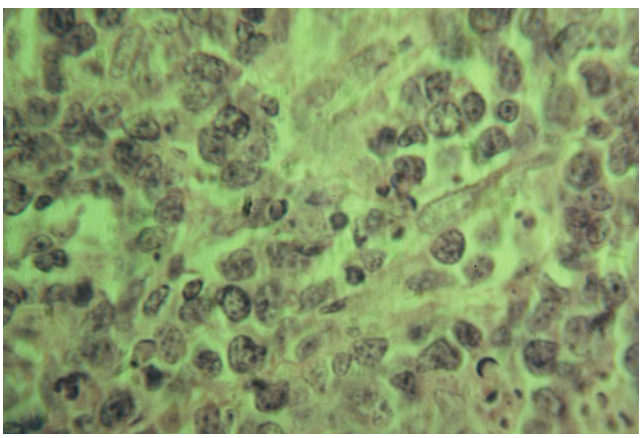

Fig. 4 Oral biopsy demonstrating the existence of an atypical infiltrate with medium-sized with round nuclei, multiple nucleoli and clumped chromatin cells consistent with the diagnosis of high-grade non-Hodgkin lymphoma

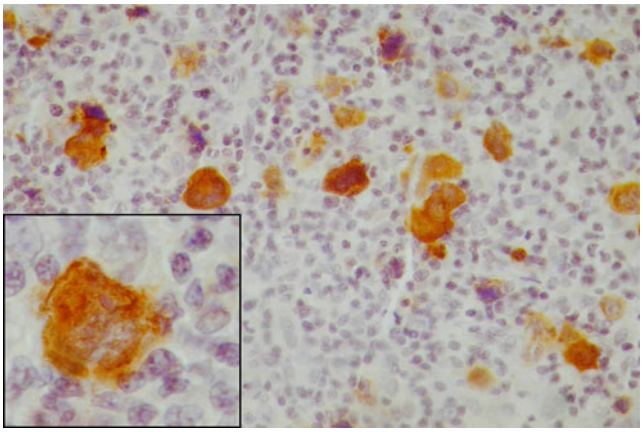

Fig. 5 IHQ expression of EBV latent membrane protein-1 in the atypical cells

cases of NHL in HIV-negative individuals and 123 cases diagnosed among HIV-seropositive subjects, oral cavity lymphomas (OCL) are more frequent in HIV-positive patients in comparison with immunocompetent population (7.3% vs. 1.6%) [3]. If well, the oral cavity involvement in HIV-positive patients appears to be more frequent in homosexual men; in our series, intravenous drug users were the most common source for HIV infection [6].

Clinical appearance of these neoplasms includes large masses or ulcers which involve the palate, tonsil, tongue, cavum, hypopharynx, maxilla, and the lower jaw as predominant clinical manifestations [3, 7]. In the general population, only 3% of NHL arises in the oral cavity; in AIDS patients, NHL with an oral lesion appears in 4% of cases [8, 9]. In our series, within the oral cavity, the most common site of involvement was the soft tissue of the gingiva in more than half of the patients. Eight of the 11 patients showed large lesions with gingiva, palate, and bone involvement. Clinical presentation of these neoplasms

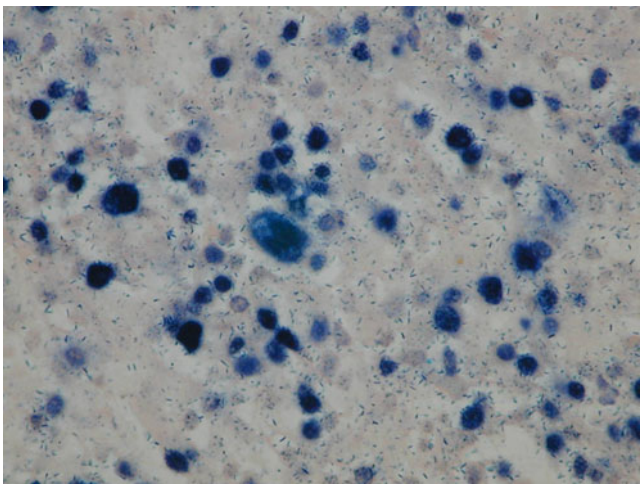

Fig. 6 ISH (EBERs of EBV), positive in the atypical cells

should be influenced by the immunodeficiency associated with the HIV infection.

In this context, gingival involvement is characteristic of HIV-positive patients whereas, tongue lesions were more frequent in the general population [3]. The hard palate infiltration appears to be typical of the plasmablastic variant of DLBCL. Two patients of our series presented as a primary lymphoma of the cavum [10] and one had tonsil involvement.

The plasmablastic subtype of these lymphomas is usually detected in HIV-seropositive population with a markedly predilection for the oral cavity, in particular with the involvement of the gingiva and the palate mucosa [11]. Oral plasmablastic lymphoma in AIDS patients was described in 1997 by Delecluse and colleagues as a variant of NHL which is associated with a poor prognosis with an average survival time of 6 months [12, 13]. This lymphoma was recognized as a distinct entity, a subtype of DLBCL in the WHO classification [5, 12]. In our series, only one patient had the plasmablastic form of the disease; three were a Burkitt's lymphoma; six were DLBCL; and in the other patient, the histopathological subtype was not available. The distinction between a DLBCL of the immunoblastic subtype and the plasmablastic differentiation is difficult in some cases; the abscense of CD20 and CD45 and the strong reactivity of the tumor cell population with the VS38c monoclonal antibody allow the difference between these two entities. The frequent expression of BCL-6 in DLBCL helps to distinguish from the majority of DLBCL, because the plasmablastic variant does not express these antigens or express them only in a low level. The histopathological subtype was available in ten of the 11 patients of our series; all were high-grade B-cell lymphomas, six were DLBCL, three were Burkitt's subtype, and the other one was a plasmablastic lymphoma [12].

HIV-related NHL is strongly associated with EBV infection. EBV expression by atypical cells is frequent in AIDS-associated lymphomas. This relation between EBV and NHL occurs in almost all cases of primary central nervous system lymphomas, in 60-80% of DLBCL, and in 50% of Burkitt histopathological subtype. In addition, EBV has been routinely detected in the majority of OCL associated with AIDS. However, in our series, the EBV genome was demonstrated in the tumor cells in four patients by ISH and IHC; two of them affected by a Burkitt's lymphoma, one with a DLBCL and the other one with the plasmablastic subtype [14].

Also, HCV should have a role in the pathogenesis of lymphomas in patients co-infected with HIV. Sofi Duberg et al. [15] describe that patients infected with HCV have a high risk to develop NHL in comparison with general population. In our series, all except three of the patients were infected by HCV probably related with the predominant source of HIV infection.

HHV-8 has been involved in the pathogenesis of two diseases usually associated with HIV infection: the primary effusion lymphoma and the multicentric Castleman's disease [16]. Cioc et al. [11] demonstrated the HHV-8 genome by the IHQ technique in five patients with AIDS-related OCL.

In our series, viral sequences of DNA were detected in only one patient of the eight tested by PCR amplification.

Conclusion

We conclude that primary OCL is an important cause of morbidity and mortality associated with AIDS. Plasmablastic lymphoma of the oral cavity is almost an HIV-related entity. The clinical course of this subtype of lymphoma was aggressive and rapidly fatal in the majority of cases. The poor prognosis of HIV-associated OCL is related to a high tendency of lymphoma relapse and the high mortality associated with the progressive disease. However, the combination of HAART plus aggressive chemotherapy may result in a better long-term survival [17].

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