Primary Extranodal Non-Hodgkin Lymphoma of the Head and Neck in Patients with Acquired Immunodeficiency Syndrome: A Clinicopathologic Study of 24 Patients in a Single Hospital of Infectious Diseases in Argentina

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Abstract

Introduction Extranodal non-Hodgkin lymphomas (NHLs) are commonly described in patients with acquired immunodeficiency syndrome (AIDS) and are related with an atypical morphology and aggressive clinical course. AIDS-associated lymphomas are characterized by their rapid progression, frequent extranodal manifestations, and poor outcome.

Objective The aim of this article is to remake the clinical features of head and neck (HN) NHL in patients with AIDS to facilitate early diagnosis and treatment.

Methods We evaluated the epidemiologic, clinical, immunologic, virologic, and histopathologic characteristics of 24 patients with human immunodeficiency virus (HIV)/AIDS with primary HN NHL treated at a single institution between 2002 and 2012. Histopathologic diagnosis was made according to the criteria of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues. Additional immunohistochemical stains were applied in all cases.

Results Eighteen patients (75%) were men and the median of age was 39 years. The gingiva and the hard palate were the most common sites of the lesions (15 patients, 62.5%). Lactate dehydrogenase levels were elevated in 16 cases (84%). Bone marrow infiltration was detected only in 4 cases (16.6%). The median CD4 T-cell count was 100 cells/μL. According to the histopathologic evaluation, the most common subtype was diffuse large B-cell lymphoma (12 cases, 50%), followed by plasmablastic lymphoma (9 cases, 37.5%) and Burkitt lymphoma (3 cases, 12.5%).

Conclusion HN NHL is a severe complication of advanced HIV/AIDS disease. Early diagnosis followed by chemotherapy plus highly active antiretroviral treatment is necessary to improve the prognosis and the survival of these patients.

Keywords
- non-Hodgkin lymphoma
- head and neck
- AIDS
- HIV

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Introduction

Non-Hodgkin lymphoma (NHL) is an acquired immunodeficiency syndrome (AIDS)-defining neoplasm that is mostly a high-grade B-cell lymphoma. In patients with AIDS, NHL represents the second most common malignancy after Kaposi sarcoma. Patients with human immunodeficiency virus (HIV) infection are at increased risk to develop NHL.[1,2] HIV infection increases the risk to develop NHL 100 to 200 times higher than in the general population.[2] These lymphomas are characterized by their rapid progression, frequent extranodal initial manifestations, and poor outcome.[2] This characteristic of extranodal involvement as the clinical presentation of the disease is common to all subtypes of AIDS-related lymphomas, including diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and plasmablastic lymphoma (PBL).[3] Extranodal head and neck (HN) NHL comprises a group of various tumors with different histology, treatment, and prognosis.

Although the widespread use of highly active antiretroviral treatment has been associated with a significant decrease of some opportunistic infections and Kaposi sarcoma, this is not as clear in the case of NHL and Hodgkin lymphoma in HIV-seropositive patients.

The present study is a retrospective evaluation of patients with primary extranodal HN NHL treated at a reference Infectious Diseases Hospital in Buenos Aires, Argentina.

Methods

A retrospective study was performed of 24 patients with AIDS and extranodal HN NHL assisted at a single hospital in Argentina between 2002 and 2012. We revised retrospectively the epidemiologic, clinical, histopathologic, immunologic, and virologic findings and the outcome. The patients were clinically staged according to the Ann Arbor system and the American Joint Committee on Cancer (AJCC).[4] All diagnoses were confirmed by the histopathologic examination of biopsy smears obtained from the lesions. We examined all patients and obtained complete blood cell counts, serum biochemistry including lactate dehydrogenase (LDH) levels, and hepatitis B and C (HCV) serology for all patients. To define the neoplasm extension, we performed bone marrow aspirate, trephine biopsy, and chest X-ray and complete tomography scan of the head and neck region, brain, thorax, abdomen, and pelvis. Histopathologic diagnosis was made according to the criteria of the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues.[5] Additional immunohistochemical stains were applied in all cases. Immunohistochemistry examination included analysis of K_i 67 (proliferative) 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, Copenhagen, Denmark.

Epstein-Barr virus (EBV)-associated latent membrane protein-1 detected by immunohistochemical and EBV-encoded mRNAs (EBERs) by in situ hybridization were analyzed in biopsy smears. Based on the correct histopathologic setting, a cutoff of 10% was adopted to consider EBER as positive. Detection of human herpesvirus-8 (HHV-8) RNA was performed by reverse transcriptase polymerase chain reaction only in those patients with oral cavity involvement.

All available data were analyzed with Microsoft Office Excel 2003 (Microsoft Corp., Redmond, WA). Continuous variables were compared using Student test and the association levels were analyzed with chi-square or Fisher exact tests. A p value < 0.05 was considered to be statistically significant.

Results

During the 10-year period, 106 HIV-infected patients were diagnosed with lymphomas; 73 (69%) of them were NHL and 33 (31%) were Hodgkin disease. Twenty-four of the NHLs (32.8%) were diagnosed as HN NHL and were included in this study; 18 (75%) occurred in men and 11 (45.8%) in intravenous drug abusers (IVDAs). At the time of the neoplasm diagnosis, the median of age was 39 years. No difference between mean age, sexual practice, or IVDA of the whole cohort of patients with lymphoma and HIV/AIDS and the type of HN NHL was noted.

Considering the AJCC and using the Ann Arbor Classification System, 8 patients were stage Ie, 9 patients were stage IIe, and the last 7 were stage IV (►**Table 1**).

B symptoms, including fever, weight loss, and night sweats, were present in the majority of patients. No evidence of concomitant opportunistic infection was found in the microbiologic laboratory analysis.

LDH levels were available for 19 patients and were elevated in 16 (84%). The median LDH level was 1,225 U/L (313 to 5,800 U/L). As our laboratory established 450 U/L as the upper normal reference value, we stratified the HN NHL cohort into quartiles. All patients with normal LDH levels were included in the first quartile (range: 0 to 478.5 U/L). LDH level within the first quartile was associated with absence of bone marrow infiltration. After excluding an outlier patient with initial LDH level higher than 5,000 U/L, the range of the first quartile was set between 0 and 473.25 U/L. Again, normal LDH levels were correlated with absence of bone marrow infiltration. No correlation could be identified among LDH concentration and infiltration of skin or bone tissue, HCV serologic status, or survival rates.

Bone marrow infiltration was detected only in 4 patients (16.6%, 3 cases of DLBCL and 1 case of PBL) and only 4 patients (16.6%) presented regional nodal involvement, 2 with DLBCL and 2 with PBL. The 4 patients (16.6%) with nodal compromise were HCV-negative, and the bone marrow biopsy was negative to atypical cells in all of them. Demographic findings are summarized in ►**Table 1**.

The gingiva and the hard palate were the most common site of the lesions (15 patients, 62.5%), followed by the bone including the upper and lower maxilla (6 cases, 26%), the skin and soft tissue (5 cases, 21%) that involved the gingiva and the palate, the parotid gland (3 cases, 13%), and the tonsils (2 cases, 8%). Some patients presented more than one tumor tissue infiltration. Localizations are described in ►**Table 2**.

Table 1 Demographic and clinical findings in head and neck non-Hodgkin lymphomas in patients with HIV ($n = 24$)

Patient no.	Gender	Age (y)	Risk factor	Neoplasm stage	Bone marrow infiltration	LDH level
1	M	52	UHC	Ie	Negative	1,422
2	M	31	Hemophilic	Ie	Negative	N/D
3	M	44	IVDA	IVe	N/D	N/D
4	M	26	IVDA	IIe	N/D	843
5	M	32	IVDA	IIe	N/D	950
6	M	38	IVDA	IIe	Negative	1,375
7	M	43	IVDA	IVe	Positive	N/D
8	M	51	NPHC	IIe	Negative	N/D
9	M	37	UHC	IVes	Positive	1,265
10	M	51	IVDA	Ie	Negative	1,433
11	F	25	UHC	IIe	Negative	1,186
12	F	24	UHC	IIe	Negative	489
13	M	35	UHC	Ie	Negative	313
14	M	38	IVDA	IVe	N/D	1,404
15	M	47	NPHC	IVe	Positive	2,721
16	M	39	IVDA	IVe	Positive	1,365
17	M	43	UHC	Ie	N/D	460
18	F	35	UHC	Ie	N/D	5,800
19	M	29	NPHC	IIe	N/D	468
20	M	37	UHC	IIe	N/D	926
21	F	60	UHC	IIe	N/D	N/D
22	F	42	IVDA	IVe	N/D	2,988
23	M	39	IVDA	Ie	Negative	341
24	F	55	UHC	Ie	Negative	419

Abbreviations: HIV, human deficiency virus; IVDA, intravenous drug abuser; LDH, lactate dehydrogenase; N/D, not determined; NPHC, nonprotected homosexual contact; UHC, unprotected heterosexual contact.

The median CD4 T-cell count for the whole population at the time of neoplasm diagnosis was 100 cells/μL with minor differences between the histopathologic subtypes; for patients with DLBCL, the median was 64 cells/μL, 116 cells/μL in BL, and 128 cells/μL for those with PBL.

All diagnoses were confirmed by the histopathologic examination of excisional or punch biopsies. According to the histopathologic evaluation, the most common subtype was DLBCL (12 cases, 50%), followed by PBL (9 cases, 37.5%) and BL (3 cases, 12.5%).

HCV serologic status was available in 18 patients (75%); 7 of them (38.9%) were positive and were classified as coinfection (HIV/HCV). All patients with HCV infection were IVDA and one was hemophilic. The small size of this cohort represents a limitation to demonstrate any relation between coinfection with HCV and the risk to develop HN NHL.

In 9 patients, EBER determination was available; 7 cases were positive. In more than half (57.1%) of EBER-positive patients, a diagnosis of DLBCL was confirmed. In addition, detection of HHV-8 RNA was performed in 10 patients with oral cavity involvement; 3 of them were positive. These results are summarized in ►**Table 3**.

Discussion

In the general population, extranodal NHL comprises 24 to 48% of all NHLs; approximately 10% of NHLs involve the HN region.[6,7] Hodgkin lymphomas and NHLs can be seen in the HN region. Hodgkin lymphoma is most commonly located in the lymph nodes of the neck and mediastinum, and extranodal disease, with or without lymph node involvement, is more common among NHL.[5] The majority of series including patients with AIDS-related lymphomas report a predominance of these neoplasms among men (75% in our study) and in IVDAs (45.8% of our patients).[8,9]

The HN is the second most common site for extranodal lymphoma and can involve different areas such as Waldeyer ring (i.e., the tonsils, pharynx, and hypopharynx), salivary glands, orbit, paranasal sinuses, and thyroid glands.[10] In the general population, Waldeyer ring has been reported as a common site of primary extranodal NHL of the HN with the tonsils as the most prevalent localization.[11,12] Overall, 60 to 70% of head and neck NHLs occur in the Waldeyer ring and 10 to 20% of these arise from the nasopharynx,[6,9,13,14]

Table 2 Head and neck non-Hodgkin lymphoma localization ($n = 24$)

Patient no.	Skin and ST	Parotid gland	Cavum	Palate	Gingiva	Bone	Tonsils
1		Positive					
2			Positive				
3	Positive			Positive			
4					Positive	Positive	
5	Positive			Positive	Positive		
6				Positive	Positive	Positive	
7				Positive	Positive		
8		Positive					
9						Positive	
10			Positive				
11	Positive				Positive		
12					Positive		
13							Positive
14					Positive		
15		Positive					
16					Positive		
17					Positive		Positive
18					Positive		
19	Positive			Positive	Positive		
20	Positive						
21					Positive	Positive	
22						Positive	
23				Positive	Positive	Positive	
24				Positive	Positive		

Abbreviation: ST, soft tissues.

NHL of the head and neck in patients with AIDS presents frequently as large local masses, with destruction of the maxilla, mandible, and bones around the paranasal sinus.[15] When extending into the oral cavity, these large masses involving generally the gingiva and the hard palate frequently present as ulcerative lesions.[3] In our series, which included only patients with AIDS, the oral cavity was the most frequent tissue involvement. Also, in the general population, NHLs rarely involve the salivary glands, which constitute 4% of these lymphomas.[3,16] These tumors generally involve the parotid glands, as we could see in three patients of our series.[16–22] The majority of the patients in our series had B symptoms as clinical presentation (fever, night sweats, and weight loss) similar to various opportunistic infections in this population; 17 patients (70.8%) were diagnosed in the early stage (I or II) of the neoplasm disease and 7 patients (29.1%) had advanced stages (IV).

Even though all subtypes of NHL may be detected from the HN area, immunohistochemistry demonstrated that B-cell phenotype is predominant.[23,24] Consistent with other studies, in our series, DLBCL was the most common histopathologic subtype and represented 50% of the patients, followed by the PBL with the 37.5% of subjects and BL with 12.5%. WHO classifies PBL as an NHL of B-phenotype, predominantly occurring in HIV-seropositive patients. PBL was the second most common histopathologic subtype of HN NHL in our series. Also, PBL is an aggressive neoplasm, especially in immunosuppressed patients with HIV.[3,16]

As in the general population, LDH levels should be described as a prognostic factor in AIDS-associated NHL; 80% of the patients in this series had elevated levels of LDH. In our cohort, normal levels of LDH in the presentation were associated with no infiltration of bone marrow. These results may have therapeutic implications for future research, with the possibility of avoiding invasive procedures and reducing medical costs. However, the small size of the study group and the retrospective nature of the analysis are important limitations for a definitive conclusion. Future investigations in larger prospective cohorts may be useful to confirm these results.

In patients with AIDS, viral infections, especially EBV infection, have been associated with the pathogenesis of NHL. This association occurs with different frequencies depending on the clinical variant and the localization. HHV-8 is

Table 3 Immunologic and histopathologic subtypes and virologic findings in 24 patients with head and neck non-Hodgkin lymphomas

Patient no.	CD4 (cells/μL)	Type	EBV	HCV	HHV-8
1	50	DLBCL	Negative	Negative	N/D
2	177	DLBCL	N/D	Positive	N/D
3	78	BL	Positive	N/D	Negative
4	47	DLBCL	Positive	N/D	N/D
5	30	DLBCL	Positive	Negative	Negative
6	189	DLBCL	Positive	N/D	Negative
7	58	DLBCL	Positive	Positive	Negative
8	305	DLBCL	N/D	Negative	N/D
9	174	DLBCL	N/D	Negative	N/D
10	19	DLBCL	N/D	Positive	N/D
11	270	PBL	N/D	Negative	Negative
12	235	BL	N/D	Negative	Negative
13	173	DLBCL	N/D	Negative	Positive
14	116	BL	N/D	Positive	N/D
15	64	DLBCL	N/D	Negative	N/D
16	85	PBL	Negative	Positive	Negative
17	49	DLBCL	N/D	N/D	N/D
18	308	PBL	Positive	Negative	N/D
19	N/D	PBL	N/D	N/D	N/D
20	56	PBL	N/D	Negative	N/D
21	N/D	PBL	Positive	N/D	N/D
22	174	PBL	N/D	Positive	N/D
23	57	PBL	N/D	Positive	Positive
24	215	PBL	N/D	Negative	Positive

Abbreviations: BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HHV-8, human herpesvirus-8; N/D, not determined; PBL, plasmablastic lymphoma.

other oncogenic virus that has also been reported in association with lymphomas in patients with AIDS and HIV, especially in PBL.[3,25,26] Also, HCV should have a role in the pathogenesis of lymphomas in patients coinfected with HIV. Duberg et al describe that patients infected with HCV have a high risk to develop NHL in comparison with general population.[27] In our series, 7 of 18 patients (38.9%) were infected by HCV probably related with the source of HIV infection.

There are obvious limitations to this study, including its retrospective nature and the absence of follow-up in the included cases. The small size of the cohort and the characteristics of a single center of infectious diseases should be included as another limitation to study the outcome after the diagnosis.

Conclusion

In this case series that includes only patients with HIV-AIDS disease, primary HN NHL was a frequent complication, arising more than 30% of all NHL. The majority of patients presented with early stage of this neoplasm disease, but with clinical manifestations (especially B symptoms) similar to some opportunistic infections that can affect this kind of patient. In contrast with the general population, in patients with AIDS, large intraoral cavity lesions, especially with the involvement of the hard palate and the gingival, were the most common clinical presentation. Early diagnosis (based on a high clinical suspicion) followed by combination therapy including highly active antiretroviral therapy plus chemotherapy can improve the poor prognosis of these patients.

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