EXTRANODAL ORAL NON-HODGKIN'S LYMPHOMAS. A RETROSPECTIVE STUDY OF 40 CASES IN ARGENTINA

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ABSTRACT

A retrospective study was conducted of extranodal oral Non-Hodgkin's Lymphomas diagnosed at the Surgical Pathology Laboratory of the School of Dentistry at Buenos Aires University, Argentina, between 1985 and 2004. The 40 cases found represent 0.2% of the oral biopsies diagnosed during that time and 4.6% of malignant neoplasias. Overall mean age of patients was 49.4 years, and frequency was greater in males. 80% affected soft tissues. Prevalent location was gingival, followed by palate. Intraosseous cases were more frequent in mandible (75%) than in upper maxilla. 100% of the cases were phenotype B, with a higher frequency of high-grade aggressiveness. The most common histological type was Diffuse Large Cell Lymphoma. 60% of the Plasmablastic Lymphomas in the series came from HIV+ patients. Evolution time prior to consultation was 1 to 3 months in 57.7% of the cases.

Key words: *Non-Hodgkin's lymphomas, oral cancer, extranodal lymphomas.*

LINFOMAS NO HODGKIN EXTRAGANGLIONARES BUCALES. ESTUDIO RETROSPECTIVO DE 40 CASOS EN ARGENTINA

RESUMEN

Se realizó un estudio retrospectivo de Linfomas No Hodgkin Extraganglionares bucales diagnosticados en el Laboratorio de Patología Quirúrgica de la Facultad de Odontología de la Universidad de Buenos Aires, Argentina, en el periodo 1985-2004. Los 40 casos hallados representan el 0.2% del total de biopsias bucales diagnosticadas en ese periodo y el 4.6% de las neoplasias malignas. La edad media general de los pacientes fue de 49.4 años con mayor frecuencia en el sexo masculino. El 80% afectaron tejidos blandos. La localización prevalente fue la gingival, seguida por el paladar. Los casos intraóseos fueron mas frecuentes en la mandíbula (75%) que en el maxilar superior. El 100% de los casos fueron fenotipo B, con mayor frecuencia de alto grado de agresividad. Dentro de ellos el tipo histológico más común fue el Linfoma Difuso de Células Grandes. El 60% de los Linfomas Plasmoblásticos de la serie correspondieron a pacientes HIV+. El tiempo de evolución previo a la consulta fue de entre 1 y 3 meses en el 57.5% de los casos.

Palabras clave: *Linfomas No Hogdkin, cáncer bucal, linfomas extraganglionares.*

INTRODUCTION

Non-Hodgkin's Lymphomas (NHL) are a heterogeneous group of malignant neoplasias formed by the clonal proliferation of B or T lymphocytes in any of their stages of differentiation. Since Rappaport[1] divided them histologically according to their follicular and diffuse pattern and cytological subtypes, several classifications have been proposed[2-6]. In 1994 the International Lymphoma Study Group developed a consensus classification known as R.E.A.L.[7], whose principles were used in the classification subsequently proposed by the WHO, which is currently in use internationally[8].

NHL usually develops on lymph nodes, but 24% to 30% of the cases are extranodal[9,10]. Its incidence has increased noticeably over recent decades. Epidemiological studies show that between 1973 and 1989 its incidence increased by about 60% in the USA[11]. It is one of the cancers that has most increased, estimated at 3% to 4% per year[11-13], and extranodal cases are the ones that have increased most rapidly[14]. This may be partly attributed to AIDS[15-17] although its frequency has also increased in the unaffected population[14]. Immunodeficiency, whether congenital or acquired, is the greatest risk factor, and the Epstein Barr virus seems to be an

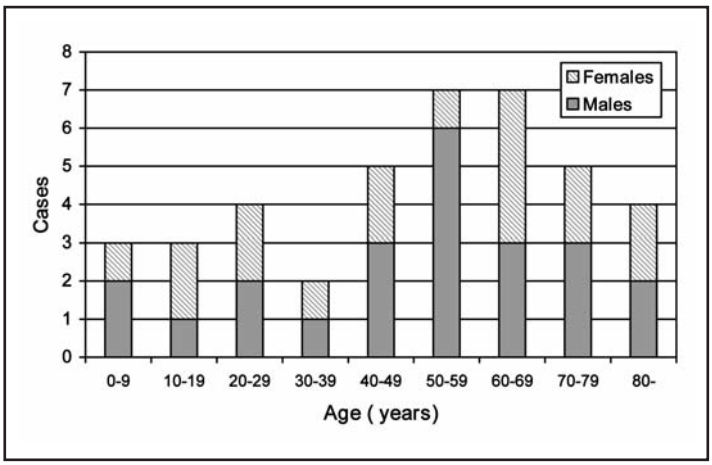

Fig. 1: Primary Oral Extranodal NHL by Sex And Age.

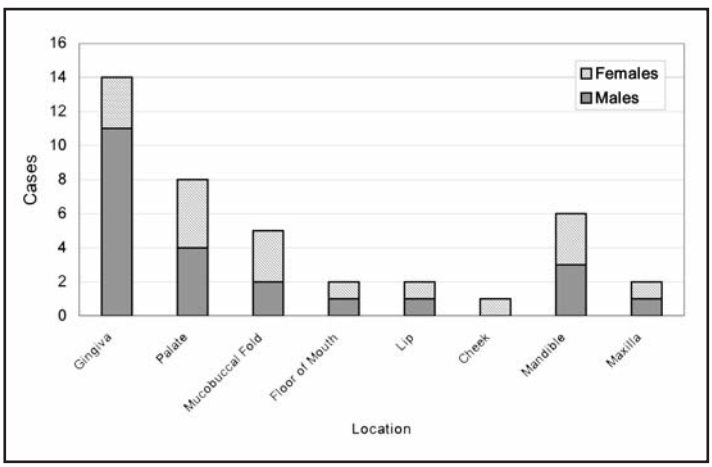

Fig. 2: Location of Primary Oral Extranodal NHL.

important co-factor in some cases[13,18]. Defects in immunological surveillance, cytokinin release and deregulation, and chronic antigenic stimulation also contribute[11,13,19]. Extranodal oral non-Hodgkin's lymphomas (ENHL) are rare in the head and neck. In this region the most frequent location is Waldeyer's ring, followed by oral cavity[20]. According to Freeman et al.[9] and Aozas et al.[23] respectively, 3% and 5% of ENHL are located in the mouth.

According to Epstein et al.[21] they represent 3.5% of oral malignant neoplasias, and are the most frequent of the non-epithelial ones, while Slootweg et al. [22] report that they make up 0.2% of the total number of cases that have been diagnosed at their oral pathology service over 30 years. They can affect soft tissues and/or bone[22,24,25]. The most frequent oral locations include palate[14,26,28], gingiva[18,27] and tongue[21]. They affect patients of a wide range of ages, including children, although most of them occur during the 6th and 7th decades of life[18,21,27].

The aim of this study was to conduct a retrospective study of oral ENHL collected at a Service specialized in oral histopathological diagnosis in Argentina, in order to analyze clinical aspects, determine the phenotype and histological type according to current criteria, and estimate its frequency in that population.

MATERIALS AND METHODS

All cases diagnosed as primary extranodal non-Hodgkin's lymphomas, plasmacytoma and malignant tumors suggestive of lymphoma, located in soft oral tissues and jawbones, were selected from the specimen archives of the Surgical Pathology Laboratory at the School of Dentistry of Buenos Aires University for the period between 1985 and 2004. New sections were prepared from the archive tissue block specimens fixed in 10% formalin and embedded in paraffin, which were stained with H.E. and Giemsa for morphological evaluation. The immunophenotypic study was done at the Institute of Hematological Investigation of the National Academy of Medicine (Instituto de Investigaciones Hematológicas de la Academia Nacional de Medicina), Buenos Aires, Argentina, using monoclonal antibodies, avidine-biotine-peroxidase detection system and amino- benzidine as a chromogen. A basic immunohistochemical panel was applied made up of Leukocyte Common Antigen, CD20 and CD3 in all cases. In addition, a second line panel that included CD79a, CD138, CD10, tdt, Bcl2, Bcl6, Kappa, Lambda and Ki67 was used to define the different entities. The cases were identified morphologically and phenotypically according to the R.E.A.L./WHO classification. Clinical data were obtained from the corresponding biopsy protocols in order to calculate mean age, distribution according to sex, most frequent location and evolution prior to diagnosis.

RESULTS

The 40 cases of diagnosed ENHL represent 0.2% of total oral biopsies (n: 19.907) corresponding to

TABLE 1. Diagnosis of 40 Extranodal Oral NHL and Distribution By Sex

GRADE OF MALIGNANCY	DIAGNOSIS	CASES		SEX			
		N	%	MALES	%	FEMALES	%
LOW	Small Lymphocytic B	5	12.5	2	40	3	60
	Follicular Grade I-II	4	10.0	2	50	2	50
	Plasmocytoma	9	22.5	6	66	3	33
HIGH	Follicular Grade III	1	2.5	1	100	-	-
	Diffuse Large B Cell	9	22.5	6	66	3	33
	Burkitt lymphoma	1	2.5	-	-	1	100
	Lymphoblastic B	5	12.5	3	60	2	40
	Plasmablastic	5	12.5	3	60	2	40
	High Grade B	1	2.5	-	-	1	100
TOTAL		40	100	23		17	

said period and 4.6% of malignant neoplasias (n: 859). In this series, there were 23 males and 17 females, with a male: female ratio of 1.35:1. Overall mean age at the time of diagnosis was 49.4 years. The youngest patients were 2 children, 1 boy and 1 girl, both aged 3 years; who were diagnosed with Lymphoblastic B Lymphoma and Burkitt's Lymphoma, respectively. Mean age broken down according to sex was 48.3 years (range 3-83) for females and 50.3 years (range 3-90) for males. Peak frequency was observed during the sixth and seventh decades of life (Fig. 1).

Thirty-two cases (80%) were located in oral mucosa and 8 (20%) were intraosseous. In soft tissues the prevalent location was gingiva-alveolar ridge (14 cases) with predominance in males, followed by palate (8 cases) with equal distribution according to sex, and mucobuccal fold (5 cases), which was more frequent in females. Other locations were floor of the mouth (2 cases), lip (two cases) and cheek (1 case). Intraosseous lesions involved mandible in 6 cases and upper maxilla in 2, with equal distribution according to sex (Fig. 2).

The most frequent initial symptoms were pain and rapidly increasing volume. In 57.5% of the cases evolution time prior to consultation was 1 to 3 months, in 22.5% it was 4 to 7 months and in the rest of the cases there was no recorded information.

Presumptive clinical diagnoses prior to the biopsies were malignant lesion in half the cases, distributed as 30% Squamous Cell Carcinoma and 20% Lymphoma. The remaining 50% included inflammatory, pseudotumoral or benign tumoral lesions for the cases located in soft tissues, and cystic or odontogenic tumor pathologies in the intraosseous cases.

All cases were phenotype B. According to the morphological and immunohistochemical study, 18 cases (45%) had low-grade aggressiveness and 22 cases (55%) had high-grade aggressiveness. The first group included 5 Small Lymphocytic Lymphomas (12.5%), 4 Follicular Lymphomas Grade I-II (10%) and 9 Plasmacytomas (22.5%). In the second group there was a prevalence of Diffuse Large Cell Lymphoma, with 9 cases (22.5%), followed in equal numbers by 5 cases (12.5%) each of Lymphoblastic and Plasmablastic Lymphomas. The remaining cases were 1 case of Follicular Lymphoma Grade III, 1 Burkitt's lymphoma and 1 High Grade B Lymphoma, (2.5% each). Table 1 shows the distribution of the different histological types by sex. According to their location, 78.5% of the lymphomas located on the gingiva were high-grade and the most frequent histological type was the Diffuse Large Cell Lymphoma. On the palate, 62.5% were low-grade, and on the mucobuccal fold, 60% were high-grade. Lymphomas located on lip and cheek were all low-grade. The 62.5% of the primi-

TABLE 2. Grade of Aggresiveness by Location

LOCATION	AGGRESSIVENESS			
	LOW GRADE		HIGH GRADE	
	N	%	N	%
Gingiva	3	21.4	11	78.5
Palate	5	62.5	3	37.5
Mucobuccal Fold	2	40.0	3	60.0
Floor of the Mouth	2	100	-	-
Lip	2	100	-	-
Cheek	1	100	-	-
Jaws	3	37.5	5	62.5
TOTAL	**18**		**22**	

tive intraosseous cases were high-grade Lymphoblastic, Plasmablastic and Burkitt type (Table 2).

DISCUSSION

Although NHL appear more frequently on lymph nodes, a significant percentage is extranodal in different locations. In the maxillofacial area it is the second most common malignant neoplasia after the Squamous Cell Carcinoma[21] and occurs mainly in Waldeyer's ring[21,29], while oral location would take second place[20]. An increase in the incidence of lymphomas has been found over recent decades, particularly those with high-grade aggressiveness and related to patients with AIDS or as a first clinical manifestation of HIV infection[24]. According to Colmenero et al.[30], intraoral lymphomas may appear as the first sign of infection in 50% of the cases. In addition, an entity with unique immunohistological characteristics and preference for the oral cavity, called Plasmablastic Lymphoma was defined in HIV+ patients[31]. Many papers refer to extranodal lymphomas in oral locations. It is difficult to compare data regarding frequency and histological types due to the different anatomical regions considered and/or the criteria and classifications used for their histological diagnosis. Some papers refer to oral lymphomas within the head and neck area[10,20,29], others within the maxillofacial region[14,21,32,34], and others consider the oral ones exclusively[18,22,28,33]. In the latter case some authors only report lymphomas affecting the soft oral tissues, while others also report cases in the jawbones[18,22,27] or include those developing on salivary glands[14,28].

At our Service, the frequency of ENHL over the total cases diagnosed during the period considered was 0.2%, matching the percentage reported by Slootweg et al.[22]. Our results match those in literature regarding the fact that ENHL takes second place in frequency of oral cancers, but our 4.6% is higher than the 2.3% and 3.5% reported by van der Waal et al.[33] and Epstein et al.[21] respectively. There are also differences in the most frequent locations. In our series, gingival location prevailed, in agreement with Fukuda et al.[27] and Yin et al.[34], while Kolotronics et al.[14] report palate as the most frequent location, Epstein et al.[21] report tongue, and Solomides et al.[18] report oral vestibule and upper maxilla. There is also discrepancy in the data on primitive bone lymphomas. While some authors report that it prevails in the upper maxilla[22,37], others find it is more frequent in mandible[38], as in this series. With the exception of Solomides et al.[18], who found that they are twice as frequent in females than in males, most papers and our data agree that frequency is higher in males[21,33,34]. The overall mean age of patients included in this study, 49.4 years, is about 10 years lower than in other papers, although peak frequency was also found during the sixth and seventh decades of life[18,21,27].

All the lymphomas in this series were phenotype B, in agreement with most western papers, which report it as highly predominant[21,29,33,35], and in contrast to what has been reported for oriental patients, in whom 25% or 28% were phenotype T[27,28]. According to several authors, Diffuse Large Cell Lymphoma (DLCL) is the predominant histological type[21,22,27,33] and in this study its frequency was 22.5%. In second place were Small Lymphocytic Lymphoma (SLL), Lymphoblastic Lymphoma (LL) and Plasmablastic Lymphoma (PL), each with a frequency of 12.5%. It should be noted that three of the five PL patients (60%) in this series were HIV+, while the rest were negative. This confirms previously reported information that although there is a strong association between this type of lymphoma and human immunodeficiency virus, it can also develop in HIV-patients[36]. On relating location to aggressiveness grade, it was found that high-grade ENHL were significantly more frequent on gingiva. They also prevailed on mucobuccal fold and maxilla, although the differences between them and low-grade ENHL were less marked. All the cases located on the floor of the mouth, lip and cheek were low-grade and also had higher frequency on the palate.

Plasmacytomas represented 22.5% of the cases included in this series, a much higher percentage than reported by Epstein et al.[21] and van der Waal et al.[33] who found 7% and 16% respectively, but in agreement with them regarding the greater incidence in males than females, and a similar distribution in soft tissues and jawbones.

Clinically, gingival lesions may appear to be of hyperplasia type with or without ulceration, while lesions on the palate may be mistaken for neoplasia of the minor salivary glands[39]. On maxilla, they often present non-specific signs and symptoms such as pain or enlargement, and a heterogeneous pattern in radiographs. Early lesions might be attributed to inflammatory or periodontal odontogenic pathologies[38,40] leading to unnecessary local odontological treatments and delaying a biopsy for proper diagnosis and treatment[25,41]. ENHL are the second most frequent malignant neoplasia in the oral cavity. According to the data reported here, there is prevalence of those with high-grade aggressiveness and marked incidence on the gingiva, where they may be clinically mistaken at first for other types of non-tumoral lesions. Early diagnosis is relevant. It is essential to take a biopsy and apply diagnostic techniques for proper histological typing, to enable the most adequate therapy to be applied, thus improving prognosis.

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