

SYSTEMATIC REVIEW OF LYMPHOMA IN ORAL CAVITY AND MAXILLOFACIAL REGION

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ABSTRACT

The aim of this paper is to determine, compare and summarize presentation characteristics of patients with lymphoma of the oral cavity and maxillofacial region using the results of different primary studies. Articles from the PubMed database published between 1990 and 2010 were reviewed. The key words "Lymphoma" and "Oral" were used to search for titles, identifying 215 articles, of which 178 were excluded and 37 were used for this review. After evaluation, the researchers agreed to include 15 of the papers in the study. This paper describes the author, year published, number of cases, sex, age, location, signs and symptoms, classification, diagnosis, staging and treatment reported in each of the 15 studies. A total 714 patients are described. In 11

of 13 studies, there were more cases in males than females. Ages ranged from 3 to 96 years. Presentation was most frequently the gingiva and the main sign was swelling. Staging was described for only 177 cases and treatment was described for only 110 cases. It is concluded that the presentation of most of the lymphomas of the oral cavity and maxillofacial region is extranodal, non-Hodgkin's. The most common locations are gingiva in the oral cavity and Waldeyer's ring in the maxillofacial region. Although these lymphomas are rare pathological entities, it is important to describe the complete manifestation of their natural history in order to provide knowledge of their development.

Key words: lymphoma, mouth, review.

REVISIÓN SISTEMÁTICA DE LINFOMA EN LA CAVIDAD ORAL Y LA REGIÓN MAXILOFACIAL

RESUMEN

El objetivo del presente trabajo fue determinar, las características de presentación de pacientes con linfoma en la cavidad oral y la región maxilofacial para comparar estas presentaciones y permitir sintetizar los resultados provenientes de diversos estudios primarios. Fueron incluidos artículos de la base de datos PubMed desde el año 1990 hasta el año 2010. Se incluyeron como palabras claves en el título de los artículos: "Lymphoma" y "Oral". Se identificaron 215 artículos de los que fueron excluidos 178 estudios quedando para este estudio 37 artículos. Los investigadores evaluaron estos artículos alcanzando un acuerdo para la inclusión de 15 artículos para este estudio. Se describe de los 15 estudios autor, año de publicación del estudio, número de casos, sexo, edad, localización, signos y síntomas, clasificación, diagnóstico, estadiaje y tratamiento.

Un total de 714 pacientes se describen siendo en 11 de 13 estudios el mayor número de casos en hombres que mujeres; la edad estuvo en un rango de 3 a 96 años. La localización de mayor presentación fue la gingiva y el aumento de volumen fue el principal signo. Solo de 177 casos fueron descritos su estadiaje y solo de 110 casos su tratamiento. Se concluye que los linfomas de la cavidad oral y la región maxilofacial son de mayor presentación del tipo no Hodgkin, a nivel extranodal. La gingiva en la cavidad oral y el anillo de Waldeyer en la región maxilofacial son las localizaciones más comunes. Son entidades patológicas raras, pero la descripción de la historia natural de esta patología en su completa manifestación es importante para el conocimiento del desarrollo de esta enfermedad.

Palabras claves: linfoma, oral, revisión.

INTRODUCTION

Simply defined, lymphomas are malignant neoplasms of lymphocytes and their cell precursors¹. They are classified mainly as Hodgkin's or non-Hodgkin's lymphoma² according to differences in their histology and behavioral patterns.

Hodgkin's lymphoma often appears as a nodal disease with a preference for cervical and mediastinal nodes, while over 40% of non-Hodgkin's are extranodal³. Lymphoma is the second most common malignant neoplasm in head and neck, after epithelial malignant tumors in the oral cavity and maxillofacial

region⁴. Lymphoma represents 2.2% of all malignant neoplasms of head and neck, 3.5% of malignant intraoral neoplasms, 5% of tumors of salivary glands and 2.5% of all lymphomas on head and neck⁵. 85% of the lesions affect tonsils and palate⁶.

Waldeyer's ring takes second place for the incidence of extranodal non-Hodgkin lymphoma⁷. In the oral cavity it includes palate, gingiva, tongue, cheek, floor of the mouth and lips as primary sites in approximately 2% of extranodal lymphomas⁸.

Patients have signs of localized or diffuse swelling, ulceration of mucosa, paresthesia, anesthesia and tooth loss⁹.

Diagnosis includes a combination of physical examination, blood tests, diagnostic imaging and selective biopsies¹⁰.

The most widely used system for classifying lymphoma stages is the Ann Arbor staging classification, which was initially introduced for Hodgkin's lymphoma^{11,12} and later adopted for classifying non-Hodgkin lymphoma¹³.

Lymphoma malignancy prognosis is revealed by the following factors: age, performance status, number of extranodal sites involved, Ann Arbor stage and serum level of lactate dehydrogenase (LDH), all of which make up the International Prognostic Index¹⁴. Treatment of non-Hodgkin's lymphoma in the head and neck region is complex due to the many variables involved¹⁵. Local lesions respond to both radiotherapy and chemotherapy, but cure rates have been low¹⁶.

The main aim of this systematic review was to determine, from a series of cases, the presentation

characteristics of patients with lymphoma in the oral cavity and maxillofacial region. The systematic review was proposed in order to compare these presentations and summarize results from various primary studies using strategies to minimize bias and random error.

MATERIALS AND METHODS

Search strategy for studies

Articles from the PubMed database published between 1990 and 2010 were included. The search was performed 72 days after the deadline for article inclusion. The key words "Lymphoma" and "Oral" in article titles were entered in the field "advanced search" field.

Selection of studies

215 studies were identified. After reading the abstracts, 178 were excluded for the reasons shown in Table 1. The 37 remaining full papers were read independently by 3 researchers.

Study assessment criteria

It was decided that at least two researchers should agree to include each article in this study, according to the abovementioned criteria. The most frequent reason for exclusion was insufficient data for evaluation. The Kappa values for agreement among researchers were as expected ($K \geq 0.67$). In the end, 15 papers were selected^{1,4,5,15,17-27} which had different designs, but all contained information on the clinical characteristics of the lymphoma in the oral cavity and maxillofacial region: age, sex, location, signs and symptoms, classification, diagnosis, staging and treatment; even if not all the data were reported in every article.

Data extraction

The data on the characteristics found and all the documented results are summarized in a general table.

RESULTS

Table 2 summarizes the information from the articles that were included. For the 15 studies it provides author, year published, number of cases, gender, age, location, signs and symptoms, classification, diagnosis, staging and treatment (certain data were not included in some of the articles).

The studies presented 7 to 361 cases each and were published between 1990 and 2010. Altogether they described 714 patients, and in 11 out of 13 studies there were more males than females. Ages ranged from 3 to

Table 1: Reasons for excluding studies.

Reason for exclusion	Number of studies
Reports of systemic treatment of the lymphoma	102
Reports of cases with fewer than 5 patients	28
About HIV positive patients	30
In a language other than English	01
Oral diseases as a result of treatment of lymphoma	03
About lymphoma in animals	02
Presentation in children only	05
Oral lesion together with lymphoma at a site not in the maxillofacial region	02
Does not present cases	05
Total	178

Table 2: Characteristics of the selected studies.

Study	Nº	Gender	Age	Location	Signs and Symptoms	Classification	Diagnosis	Staging	Treatment
<i>Wolvius 1994</i>	34	20 M 14 F	59 (03-88)	10 Soft tissue of palate 07 Gingiva 05 Tongue 05 Maxilla 02 Palate 05 Mandible	24 Swelling 08 Pain 03 Numbness 10 Ulceration	Kiel	12 Centroblastic lymphoma 01 Immunoblastic lymphoma 01 Burkitt's lymphoma 02 Large cell anaplastic 02 Lymphoblastic 08 Centroblastic-centrocytic lymphoma 06 Centrocytic lymphoma	20 Stage I 01 Stage III 11 Stage IV	05 Cht + Rt 01 Stage II Of 33 cases
<i>Shindoh 1997</i>	31	23 M 08 F	52.83 (05-86)	29 Gingiva 02 Buccal mucosa	44 Swelling 09 Pain 06 Paresthesia 03 Disturbed healing of an extraction wound	WF	05 Lymphoma, large cell, immunoblastic 05 Lymphoma, small non-cleaved cell 01 Lymphoma, lymphoblastic 15 Diffuse lymphoma, large cell type 01 Diffuse lymphoma, mixed small and large cell 02 Diffuse lymphoma, small cleaved cell 02 Unclassified	14 Stage I 03 Stage II 02 Stage III 10 Stage IV Of 29 cases	
<i>Mishima 1998</i>	18			03 Gingiva 01 Mandible 03 Soft palate 01 Submandibular gland 01 Parotid gland 03 Tongue 03 Nasal cavity 03 Maxillary sinus		REAL	9 DLBCL 1 FCL 2 PTCL 2 MALT 4 Indefinite		
<i>Ardekian 1999</i>	13	08 M 05 F	15.3 (05-70)	03 Mandible 03 Maxilla and mandible 02 Palate 05 Maxilla	5 Swelling 7 Pain 2 Paresthesia		Burkitt's lymphoma	06 Stage I 07 Stage II	10 Cht 03 Cht + Rt
<i>Sunaba 2000</i>	37	27 M 10 F	65 (29-86)	12 Palate 09 Gingiva superior 09 Gingiva inferior 03 Buccal mucosa 02 Tongue 01 Floor of mouth 01 Lip		WF	31 Intermediate grade lymphoma 06 High grade lymphoma	24 Stage IE 13 Stage IIE	23 Rt 14 Cht + Rt
<i>Yin 2001</i>	27	18 M 09 F	61 (18-86)	15 Gingiva 06 Buccal mucosa 05 Palate 01 Lip		REAL	25 DLBCL 01 Lymphoplasmacytoid 01 Small lymphocytic	08 Stage I 09 Stage II 09 Stage IV Of 26 cases	
<i>Leong 2001</i>	58	32 M 16 F Of 48 cases	56.96 (19-89)	14 Palate 13 Gingiva 11 Maxilla 05 Mandible 06 Tongue 03 Floor of mouth 02 Buccal mucosa 01 Lower lip 04 Other	25 Swelling 02 Loosening of the teeth 03 Extensive bone destruction 01 Paresthesia	REAL	26 DLBCL 1 SLL 1 LPL 2 MCL 8 FCL 3 MALT 4 Myeloma 11 PTCL 2 ALCL		
<i>Epstein 2001</i>	361	200 M 161 F	62.5 (02-96)	118 Tonsil 58 Parotid gland 40 Nasopharynx 34 Maxillary sinus 32 Nasal cavity 30 Tongue 17 Palate 07 Submandibular lymph nodes 07 Gingiva 18 Other			137 Large cell lymphoma 99 Small cell lymphoma 23 Plasmacytoma 11 Immunoblastic lymphoma 06 Burkitt's lymphoma 82 Lymphoma NOS 03 Hodgkin's disease		

Table 2: Cont.

Study	Nº	Gender	Age	Location	Signs and Symptoms	Classification	Diagnosis	Staging	Treatment
<i>Kolokotronis 2005</i>	18	08 M 10 F	64 (27-84)	8 Tonsil 5 Palate 4 Parotid gland 1 Mandible	2 B symptoms	WHO 2001	05 MALT 01 Follicular 01 MCL 01 Diffuse follicular 10 DLBCL	11 Stage IE 02 Stage IIE 02 Stage IIIE 01 Stage IVE 02 Stage IV	06 Cht 03 Sg 08 Cht + Sg 01 Cht + Rt
<i>Kojima 2007</i>	7	03 M 04 F	64 (23-83)	3 Soft palate 3 Buccal mucosa 1 Gingiva		MALT			03 Rt 02 Cht + Rt 02 Sg
<i>Kemp 2008</i>	40	19 M 21 F	71 (35-89)	11 Maxilla 08 Mandible 08 Palate 07 Gingiva 04 Buccal mucosa 01 Floor of mouth 01 Lower lip	Swelling Ulceration Radiographic destruction of bone Paresthesia	WHO 2001	23 DLBCL 06 Follicular lymphoma 05 ENMZL 03 Plasmacytoma 02 SLL/CLL		
<i>Sato 2009</i>	21	11 M 10 F	68 (53-86)	11Gingiva 06 Hard palate 02 Soft palate 01 Tongue 01 Buccal mucosa	Swelling Painless		07 Low intermediate risk IPI 14 Low risk IPI	17 Stage IE 04 Stage IIE	10 Cht + Rt 05 Cht 01 Rt 01 Cht + Sg
<i>Kane 2009</i>	40						10 DLBCL 25 Plasmablastic lymphoma 01 Plasmacytoma WD 02 Plasmacytoma PD 01 Burkitt's lymphoma 01 Marginal zone lymphoma		
<i>Guggisberg 2010</i>	9	05 M 04 F	70.3 (62-87)	4 Palate 1 Floor of mouth 2 Tongue 2 Base of tongue	6 Swelling 1 Dysphagia		Mantle cell lymphoma		04 Cht 02 Cht + Rt 02 NIA 01 Declined
<i>Bhattacharyya 2010</i>	13	07 M 06 F	66.4 (38-91)			WHO 2008	05 DLBCL Germinal center 08 DLBCL Non-germinal center		03 Cht 04 Cht + Rt 02 Declined 04 NIA

M: Male. F: Female. WD: Well-differentiated. PD: Poorly differentiated. DLBCL: Diffuse large B-cell lymphoma. FCL: Follicle center lymphoma. PTCL: Peripheral T-cell lymphoma. MALT: Extranodal marginal zone B cell lymphoma of the mucosa associated lymphoid tissue. SLL: Small lymphocytic lymphoma. LPL: Lymphoplasmacytoid lymphoma/immunocytoma. MCL: Mantle cell lymphoma. ALCL: Anaplastic large cell lymphoma. ENMZL: Extranodal marginal zone lymphoma. CLL: Chronic lymphocytic leukemia. IPI: International Prognostic Index. Cht: Chemotherapy. Rt: Radiotherapy. Sg: Surgical. NIA: No information available. NOS: Not otherwise specified. WF: International Working Formulation for Clinical Usage. REAL: Revised European-American of Lymphoma. WHO: World Health Organization.

96 years, and in 7 out of 13 studies patients were in their seventies, on average. The most frequent intra-oral location was gingiva, with 111 cases, followed by palate with 64 cases, while the most frequent location for the maxillofacial region was tonsil, with 126 cases, followed by parotid gland, with 63 of the cases described. In all the studies describing local signs and symptoms, the main feature is swelling. Diagnoses varied, but they were all non-Hodgkin lymphoma, mostly of B cells. Of the 177 cases for which staging is described, 100 were at stage IE, 39 were at stage IIE, 5 were at stage IIIE and 33 were at stage IV. The treatments of the cases pre-

sented in 8 of the 15 studies shown are: chemotherapy plus radiotherapy for 41 cases, chemotherapy for 28 cases, radiotherapy for 27 cases, chemotherapy plus surgery for 9 cases and surgery for 5 cases.

DISCUSSION

Few researchers have conducted studies on lymphoma in the oral cavity and maxillofacial region. The highest number of cases was reported in the study by Epstein et al.⁵ in 2001, which reports 361 cases in oral cavity and paraoral region. Van der Waal et al.²⁸ in 2004 and Kemp et al.²³ in 2008 reported 40 cases of non-Hodg-

kin lymphoma in the oral cavity in each study. This systematic review gathers 714 cases from 15 studies.

Regarding gender in the studies of oral cavity lymphoma, Kemp et al.²³ find 53% female, although they say that the difference between sexes is not statistically significant, like Urquhart et al.²⁹ in a review of 235 non-Hodgkin lymphomas of the head and neck in 2001, although Mawardi et al.¹⁰ say that gender is a risk factor because men are more often affected than women. In the review of 15 studies, there were 381 men and 278 women out of a total 659 cases for which gender was specified.

Regarding the age of patients with lymphoma of the oral cavity and maxillofacial region, the range in the studies reviewed was 3 to 96 years, and in most studies the average patient was in his/her seventies, in agreement with studies such as Urquhart et al.²⁹ which reports that non-Hodgkin lymphoma is more frequently diagnosed for ages 70 to 80 years.

The most frequent location for lymphomas of the maxillofacial region is Waldeyer's ring³⁰, which is similar to what was found in this review, even though some studies only refer to cases in the oral cavity while others specifically exclude Waldeyer's ring^{4,24,25}. Within the oral cavity, gingiva was the most frequent location according to the 15 studies described. Highest frequency for gingival location found in the set of 13 out of 15 studies matches individual studies such as the one by Solomides et al.³¹.

Swelling of the area involved and absence of pain were the two signs and symptoms most often described in the evaluated studies. Systemic signs and symptoms (fever of unknown origin (>38°C), inexplicable weight loss and night sweating) are usually more often described in patients with Hodgkin's

lymphoma than with non-Hodgkin lymphoma³⁰, and in the oral cavity there may be swelling only⁹.

This review describes studies published between 1990 and 2010, so they use different versions of lymphoma classification, including the International Working Formulation for Clinical Usage³² of 1982, Kiel classification³³ of 1988, the Revised European-American Lymphoma (REAL) classification³⁴ of 1994, the World Health Organization (WHO) classification³⁵ of 2001 and the latest update of the World Health Organization (WHO)³⁶ of 2008.

Out of the 177 cases for which staging was described, most were in stages I and II. Early diagnosis can allow the disease to be treated in its early stages, providing better patient prognosis⁵.

Chemotherapy with radiotherapy was the treatment of choice in 41 cases from the 15 studies describing treatment. Non-Hodgkin lymphomas located on head and neck were treated with radiotherapy alone or combined with chemotherapy³⁷. Based on a review of 53 patients, it was suggested that radiotherapy was the adequate treatment for localized lymphoma and that chemotherapy was preferable for patients with systemic complication³⁷. A retrospective study of 92 patients with intermediate- and high-grade lymphoma showed a good response to combined chemotherapy and radiotherapy³⁸.

To conclude, the presentation of lymphomas of the oral cavity and maxillofacial region is more often the extranodal, non-Hodgkin type. The most common locations are gingiva in the oral cavity and Waldeyer's ring in the maxillofacial region. Although lymphomas of the oral cavity and maxillofacial region are rare pathological entities, it is important to describe the complete manifestation of their natural history in order to provide knowledge of their development.

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