RESEARCH ARTICLE

Oral Extranodal Non Hodgkin's Lymphoma: Series of Forty Two Cases in Malaysia

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Abstract

Background: Lymphoma is a malignant neoplasm of lymphoid tissue classified into Hodgkin's and non-Hodgkin's types. It mostly affects lymph nodes although a considerable proportion of Non-Hodgkin's cases occur in extranodal sites. Materials and Methods: Selected cases diagnosed as non-Hodgkin's lymphoma (NHL) during the period of 1980 to 2012 were retrieved from the archives of the Oral Pathology Diagnostic Laboratory, Faculty of Dentistry, University of Malaya. The sections from the formalin-fixed paraffin embedded tissue blocks were stained with H&E as well as with LCA, CD20, and CD3. Results: The mean age was 41.6 years with a male: female ratio of 1.3:1. Out of the forty two cases, nineteen were Malays, eighteen were Chinese, followed by Indians (3) and Indonesians (2). The most common site of involvement was the mandible (22.2%), followed by the maxilla and palate (19.4% each). Most of the lesions presented as a painless progressive swelling. Only thirty six cases were further subdivided into B or T cell types. The majority were B-cell type (26 cases), of these 6 cases were Burkitt's lymphomas. Only ten cases were T-cell lymphoma, with three cases of NK/T-cell lymphoma. Conclusions: In this series of 42 patients diagnosed as extranodal non-Hodgkin's lymphoma, the lesions appeared as painless swellings, mostly in men with the mandible as the most frequent site of involvement. Majority were B-cell lymphomas with Malays and Chinese being equally affected whereas lymphomas were rare in the Indian ethnicity. T-cell lymphomas were found to be common in the Chinese ethnic group.

Keywords: Non-Hodgkin's lymphoma - extranodal oral - B-cell lymphoma T-cell lymphoma - ethnicity

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Introduction

Lymphoma is a malignant neoplasm of the lymphoid tissue; it is broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) depending on the presence or absence of the Reed-Sternberg cells. Non-Hodgkin lymphoma is further sub classified into B or T-cell types. Generally NHL is more common than HL representing about 92.1%, of these; the B-cell type accounts for 75% (Sukpanichnant, 2004). In the oral cavity NHL represent only 3.5% of all oral malignancies (Epstein et al., 2001). In this study we report a series of 36 cases of oral extranodal NHL and sub classify them into the B-cell and T-cell type.

Lymphomas usually involve lymph nodes; however 24% of the NHL occur in extranodal sites, quarter of these occur in the head and neck region (Piatelli et al., 1997). In a study of 1467 cases of NHL; 28% were found in head and neck (Freeman et al., 1972). Extranodal NHL is uncommon in the oral cavity with a percentage range from 2% (Freeman et al., 1972) to 8% (Shah et al., 2011), and often involves the central nervous system (Padhi et al., 2012).

This paper describes and compare NHL B-cell and T-cell types in relation to its clinical, histological and immunological characeristics of a series from the Oral Pathology Diagnostic Laboratory, Faculty of Dentistry, University of Malaya.

Materials and Methods

Selected cases (42 cases) diagnosed as Non-Hodgkin's lymphoma (NHL) during the period of 1980 to 2012 were retrieved from the archives of the Oral Pathology Diagnostic Laboratory, Faculty of Dentistry, University of Malaya. Only cases with complete demographic and site data were selected. Clinical data of these patients were obtained from the clinical files. New sections were made and stained with Hematoxylin and Eosin (H and E) and first examined by one of the author (RBZ). They were subsequently reconfirmed as lymphoma by immunopositivity to leukocyte common antigen (LCA) and the proliferation index was measured by Ki-67. Thirty six cases had sufficient material for further immunophenotyping into T- or B-cell categories. The T-cell phenotype was determined by tumor cell expression

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of CD3 or CD45O and the absence of B-cell antigens CD20 (L26), or CD79a, and B-cell phenotype determined vice versa.

Results

This series consisted of forty two patients with the diagnosis of extranodal NHL of the oral cavity. The clinical and pathological data of all cases are shown in Table 1. The majorities were males (24 cases) and the rests were females (18 cases), with a male: female ratio of 1.3:1 Their ages ranged from 2 to 90 years old with a mean age of 41.6 years and median age of 47 (IQR 14-63)

Table 1. Clinical and Pathological Data of Forty Two Patients Diagnosed as NHL

No.	Age	Gend	er Ethnicity	Site	Typ of Lymphoma	
1	15	M	Malay	Mandible	Lymphoma	
2	9	M	Chinese	Mandible	B-cell lymphoma	
					(Burkitt's)	
3	44	F	Chinese	Mandible	B-cell lymphoma	
4	70	M	Malay	Lip	B-cell lymphoma	
5	56	M	Malay	Palate	B-cell lymphoma	
6	59	M	Malay	Tongue	Lymphoma	
7	58	M	Indian	Gingiva	B-cell lymphoma	
8	11	F	Indian	Mandible	B-cell lymphoma	
					(Burkitt's)	
9	30	M	Malay	Cheek	B-cell lymphoma	
10	57	F	Malay	Mandible	Lymphoma	
11	11	M	Chinese	Maxilla	T-cell lymphoma	
12	39	M	Chinese	Maxilla	B-cell lymphoma	
					(Diffuse large)	
13	71	M	Chinese	Mandible	B-cell lymphoma	
14	7	F	Indian	Cheek	Lymphoma	
15	48	M	Chinese	Palate	T-cell lymphoma	
16	50	F	Chinese	Maxilla	T-cell lymphoma	
17	65	M	Chinese	Palate	NK/T-cell lymphoma	
18	70	F	Chinese	Palate	B-cell lymphoma	
19	11	F	Malay	Mandible	B-cell lymphoma	
20	31	F	Malay	Cheek	T-cell lymphoma	
21	90	M	Malay	Soft palate	B-cell lymphoma	
22	66	M	Malay	Palate	B-cell lymphoma	
23	68	F	Chinese	Palate	B-cell lymphoma	
24	59	F	Malay	Parotid and	B-cell lymphoma	
24	37	1	ivialay	submandibular	B-cen tymphoma	
25	48	M	Chinese	Cheek	T-cell lymphoma	
26	65	F	Malay	Submandibular	B-cell lymphoma	
20	05	1	withing	Submandibulai	(Burkitt's)	
27	63	M	Malay	Cheek	B-cell lymphoma	
21	05	171	ivialay	CHECK	(Burkitt's)	
28	29	M	Indonesian	Palate	NK/T-cell lymphoma	
29	11	F	Chinese	Mandible	B-cell lymphoma	
30	12	M	Chinese	Gingiva	B-cell lymphoma	
50	12	101	Cillicse	Giligiva	(Burkitt's)	
31	33	F	Chinese	Cheek	B-cell lymphoma	
31	33	1	Cimicse	CHECK	(Diffuse large)	
32	73	M	Molov	Maxilla	T-cell lymphoma	
33	73	M	Malay	Maxilla	B-cell lymphoma	
34	18	F	Malay Chinese	Maxilla	• •	
35	2	M		Maxilla	Lymphoma	
36	49	F	Malay		Lymphoma	
37	32	г М	Malay	Submandibular	B-cell lymphoma	
	32 49			Floor of the mouth	T-cell lymphoma	
38		F		ubmandibular region		
39	4	M	Malay	Mandible	B-cell lymphoma (Burkitt's)	
40	44	M	Chinese	Cheek	B-cell lymphoma	
					(Diffuse large)	
41	2	M	Malay	Cheek	NK/T-cell lymphoma	
42	48	F	Indonesian	Soft palate	B-cell lymphoma	
				-ore parate		

*Female: F; Male: M

years. The cases were almost equally distributed between Malay (19) and Chinese (18), and the rest were made of Indian (3 cases) and 2 Indonesians.

The mandible (9 cases) was the most commonly involved site with NHL, followed by the cheek (8 cases) then the palate and maxilla (7 cases each). Four cases were in the salivary glands, and one of them involves both the parotid and submandibular glands. Three of the salivary gland tumors were in Malay. Soft palate and gingiva constitute ywo cases each. And one case for tongue, lip, and foor of the mouth.

Most patients reported with painless progressive swelling. One of the patients (case no. 18) had a recurrent NHL which had been treated with chemotherapy; and another patient (case no. 1) had a metastatic tumor in the mandible with the primary tumor in the thymus and thoracic vertebrae. Immunohistochemical examination was performed in 36 of the 42 cases, and more than two third (26 case) were diagnosed as B-cell lymphoma of these 6 cases (23.07%) were Burkitt's lymphomas and only ten cases were diagnosed as T-cell lymphoma, with three cases of NK/T-cell lymphoma.

There was equal distribution of the B-cell lymphomas between males and females (13 case each), however 8 out of the ten cases of T-cell lymphomas were in males (Table 2). About 60% of the T-cell lymphomas were in Chinese, while the B-cell lymphomas was frequently encountered in Malay (46%) and the two Indian cases were B-cell lymphomas. The mean age of the B-cell lymphomas (46.2±24) is higher than the T-cell lymphomas (38.9±22). Four cases with Burkitt's lymphomas were below 15 years old and two patients over 60 years old.

About 66.6% of the lesions were in the soft tissue, of these 70.8% were of the B-cell phenotype. All the seven mandibular, and the two gingival tumors were of the B-cell type. Nine out of the ten T-cell lymphomas were equally distributed between the palate, the maxilla, and the cheek (3 cases each). There were only three NK/T-cell lymphomas in this series; two of wich occurred in the hard palate. There was one rare case of lymphoma of the tongue however, the exact phenotype of this patient was not determined due to insufficient tissue.

B-cell lymphoma: The cases of the B-cell phenotype show a diffuse infiltration of malignant cells with scanty cytoplasm; these cells are small round with dark nuclei and occasional mitosis in few cases (case no. 10, 18, and 19), the remainder of the cases demonstrates a medium to large size cells with round to oval nuclei and vesicular nuclei,

Table 2. Distribution of The Type of Lymphoma According to Gender Ethnicity and Site

		B-ce	ll lymphoma	T-ce	ll lymphoma	Total
Gender	Male	13	(61.9%)	8	(38.1%)	21
	Female	13	(86.7%)	2	(13.3%)	15
Ethnicity	Malay	12	(80.0%)	3	(20.0%)	15
	Chinese	11	(64.7%)	6	(35.3%)	17
	Indian	2	(100%)	0	(00.0%)	2
	Indonesian	1	(50.0%)	1	(50.0%)	2
Site	Soft tissue	17	(70.8%)	7	(29.2%)	24
	Bone	9	(75.0%)	3	(25.0%)	12

Ki-67 labeling index were also observed.

prominent nucleoli, and frequent mitosis. Four cases (case no. 12, 29, 31, and 40) of the large cell type were Bcl-2 positive, CD10 and cyclin D1 negative, this allow further classification as diffuse large B-cell lymphoma.

The histopathology of the Burkitt's lymphoma cases (case no. 2, 8, 26, 27, 30, and 39) shows diffuse infiltrating sheets of uniform small neoplastic cells, with a thin rim of cytoplasm. The nuclei of these tumor cells were noncleaved, round with several prominent nucleoli. Mitoses were abundant together with interspersed histiocytes imparting the classical starry sky appearance (Figure 1). Diffuse LCA and CD20 immunoreactivity, and very high

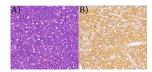


Figure 1. A) Photomicrograph of Burkitt's Lymphoma Showing Small Round Cells with Scanty Cytoplasm and Multiple Small Nuclei Interspersed by Macrophages (H and E Stain, Magnification 10X); B) Photomicrograph Showing Ki-67 Labeling Index was 100% (Magnification 10X)

T-cell lymphoma

The seven cases of T-cell type show a diffuse infiltration by small round cells with minimal cytoplasm and dark staining nuclei. However the NK/T-cell cases (case no. 17, 28, and 41) demonstrates large pleomorphic cells with hyperchromatic nuclei and angiocentric features.

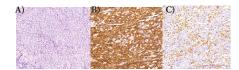


Figure 2. A) Photomicrograph Showing B-Cell Lymphoma. Tumor Cells Contain Large Non-Cleaved Nuclei With Coarse Chromatin Distribution, Prominent Nucleoli, and Frequent Mitotic Figures. (H&E Stain, Magnification 20X); B) Photomicrograph Demonstrating Diffusely Positive for Anti-CD20 Antibody (Magnification 10X); (C) Photomicrograph Demonstrating Patchy Immune-Stain of Anti-CD3 Antibody (Magnification 10X)

Table 3. Case Series of Oral Extranodal Non Hodgkin's Lymphoma (Case Series Having 6 or More Cases are Included in This Table)

Author (year)	No. of cases	Age years	Gender (M/F)	Site		B- or T-cell lymphoma
Hashimoto and Kurihara (1982)	9	3-87	7/2			B-cell lymphoma-8 (89%) Unclassified-1
Eisenbud et al. (1983; 1984)	31	3-89	14/17	Maxilla-9 Palate-10 Tongue-1 Floor of the mouth-1 Retro molar trigon-1	Mandible-5 Cheek-1	Large B-cell lymphoma-9 (29%)
Stoolweg et al. (1985)	20					
Takahashi et al. (1987)	11	19-78	6/5	Palate-3 Cheek-4	Gingiva-4	Diffuse Large B-cell lymphoma-8 Diffuse mixed type lymphoma-2 Burkitt's lymphoma-1
Handlers et al. (1986)			16/18	Vestibule, gingiva, mandible, soft palate and maxilla are commonsites.		B-cell lymphoma-31 (91%)
Howell et al. (1987)	34					
Fukada et al. (1987)	20	11-80 51 (Median)	12/8	Gingiva-11 Mandible-3 Floor of the mouth-3	Cheek-2 Lip-1	Diffuse large B-cell lymphoma-15 (75%) T-cell lymphoma-2 (10%) Histiocytosis-3 (15%)
Wolvius et al. (1994)	34					
Nocini et al. (2000)	10	51	3/2			Large B-cell lymphoma-10 (100%)
Epstine et al. (2001)	57		28/29	Tongue-30 Gingiva-7	Palate-17 Lip-3	Large cell and small cell lymphomas B-cell lymphoma-92% T-cell lymphoma-8%
Solomides et al. (2002)	71		1-2			B-cell lymphoma-92% T-cell lymphoma-8%
Van der Waal (2005)	40	3-88 59 (Mean)	24/16	Upper jaw-20 Cheek-6	Lower jaw-7 Tongue-6	B-cell lymphoma-100% Large B-cell-20 (50%)
Djavanmardi et al. (2008)	15			Law		
Kemp et al. (2008)	40	71 years (Mean)	47/53			B-cell lymphoma-98%
Shah et al. (2011)	15	42.6 years (Median)	3:2 ratio	Gingivobuccal comple Labial mucosa-1 Cheek-1	ex-12 Tongue-1	



Figure 3. A) Photomicrograph Showing T-Cell Lymphoma, with Tumor Cells Having Medium-Size Nuclei (H and E Stain, Magnification 20X); B) Photomicrograph Demonstrating Tumour Negative Immune-Stain of Anti-CD20 Antibody (Magnification 20X); C) Photomicrograph Demonstrating Positivity for The T-Cell Marker (Anti-CD3 Antibody) (Magnification 20X)

Discussion

The first case series of extranodal NHL of oral cavity (30 cases) was published in 1972 by Freeman et al. (1972). Hashimoto and Kurihara (1982) and the largest case series of extranodal NHL of oral cavity (71 cases) was by Solomides et al. (2002) (Table 3). In this study 42 cases of extranodal NHL of oral cavity is reported. Van der Waal et al. (2005) published a series (40 cases) of primary extranodal NHL of the oral cavity in which males were most commonly affected. This male predominance was noted in other series (Table 3), however Kemp et al. (2008) found 53% of these tumors in females and is also observed in other series (Table 3). In this study the majority of cases were in males with a male: female ratio of 1.3:1. This ratio is smaller than the 2.4:1 ratio reported by a previous study of lymphoma carried out at the Department of Pathology, University of Malaya, however that study described lymphomas from all over the body (Peh, 2001). The median age is 47 years, with previous case series of oral NHL reporting a mean of 59 (van der Waal et al., 2005) and 42.6 years (Shah et al., 2011).

In Malaysia, the NHL occurs more commonly in Chinese (22.51-79%) followed by those of Malay (5-16.37%) and lastly Indians (2.5-16%) (Peh, 2001; Peh et al., 2004). However, in this study, there was equal distribution between Malay and Chinese (43.9%). The occurance of NHL in Indians has been reported to be rare (Shah et al., 2011) which was also reflected in this study (2 cases).

The most common site involved in oral cavity is palate and gingiva (Takahashi et al., 1987; Shah et al., 2011) in this series the palate and gingiva represent about 17.7 and 4.8% of the lesions respectively. It was reported that 15-45% of intra-oral NHL occurs in the jaws, with the mandible being the less frequent site. Larson et al. (1984) studied 100 patients with extra nodal lymphoma of the head and neck and non involved the mandible. Eisnbound et al. (1983; 1984) in their study of 31 case of oral NHL found 14 patients with bone involvement, only 5 of them were in the mandible. However, Pazoki et al. (2003) reported 3 mandibular and 1 maxillary intrabony NHLs, and Etemad-Moghadam et al. (2010) found that the mandibular lesion exceed the maxillary. In this study 38.1% of the tumors were intra-bony however the mandible was more affected than the maxilla and other oral cavity sites.

Lymphomas of the salivary glands accounts for

approximately 2-5% of salivary gland neoplasms and Triantafillidon et al. (2012) reported 41% (24 cases) involving the salivary glands. Parotid gland was the most frequently affected among the salivary glands (Weber et al., 2003). In this study, three cases were in the submandibular gland with one case involving both the submandibular and parotid gland. Previous report stated that the buccal mucosa were rarely involved by NHL (Handlers et al., 1986; Howell et al., 1987; Zanakis et al., 1992) however in this series 19.1% of the cases were in the cheek.

The majority of the oral cavity lymphomas are of B-cell type, Kemp et al. (2008) reported a 98% in their study as B-cell lymphomas while, van der Waal et al.(2005) found all his patients to be of the B-cell type however, in the present study, we report 72.2% to be of B-cell origin.

An EBV-associated lymphomas that occurs commonly in Chinese is Burkitt's lymphoma which in a previous study from University Malaya accounted for 100% occurrence in this group (Peh, 2001), nevertheless in this study; 3 of the cases occur in Malay and two cases were in Chinese and one case in Indian ethnicity. Burkitt's lymphoma is a high-grade, aggressive type of NHL, it accounts for 3-5% of all lymphomas (Solomides et al., 2002). Three subtypes of Burkitt's lymphoma have been recognized: (1) African (endemic) Burkitt's lymphoma; (2) American (sporadic) Burkitt's lymphoma; and (3) HIV-associated Burkitt's lymphoma. In endemic regions; Burkitt's lymphoma accounts for nearly half of all childhood malignancies (Solomides et al., 2002). In this study 6 cases were diagnosed as Burkitt's lymphoma, four of them (66.6%) occured in patients ≤15 years of age and accounts for 36.4% of all children in this study, this comes in line with an earlier Malaysian study of childhood malignancies which stated that Burkitt's lymphoma is the second most common lymphoma in children (Peh et al., 2004).

Only 8% of oral extranodal lymphomas were of the T-cell type (Epstein et al., 2001; Solomides et al., 2002), however the percentage of T-cell lymphomas in this series is quite high (27.8%), of these 60% were in Chinese. The reason for this high percentage is unknown but may be due to that 43.9% of the cases in this series were Chinese and it is reported that there is a higher prevalence of EBV-associated lymphomas namely NK/T-cell lymphoma in the Chinese when compared to other ethnic group (Howell et al., 1987).

The mainstream treatment of diffuse large B-cell lymphoma is chemotherapy. The CHOP regimen is most widely used which consists of cyclophosphomide, hydrodaunorubicin, vincristin and prednisolone. It is given in either 2, 3 or 4 weekly cycles for 6 to 8 courses. The R-CHOP regimen includes anti-CD20 (rituxianab) which improves the cure rate. Combined radiotherapy along with chemotherapy may be optimal therapy for localized disease. Ifosfamide, epirubicin and etoposide (IVE) are used in cases of relapse and which are chemosensitive. Another regimen that is used in cases of relapse and chemosensitive cases is etoposide, cytosine, arabinoside, methylprednisolone and cisplatin (ESHAP). In cases of

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- cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, **105**, 194-201.
- poor and there are various drug trial being carried out.

 emtuzumab may be used in both B-and T-cell NHL.

 e prognosis of Burkitt's lymphoma was poor until

 e introduction of chemotherapy regimens such as high
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- primary refractory or chemoresistant disease the prognosis is poor and there are various drug trial being carried out. Alemtuzumab may be used in both B-and T-cell NHL. The prognosis of Burkitt's lymphoma was poor until the introduction of chemotherapy regimens such as high dose of methotrexate and cyclophosphamide (Hoffbrand et al., 2006).
- In conclusion, we herein described a series of forty two patients diagnosed as extranodal Non-Hodgkin's lymphoma of the oral cavity. These lesions generally appear as a painless swelling and they mostly occur in men. The mandible is the most frequent site of involvement. The majority of cases were lymphomas of B-cell with Malays and Chinese being equally affected whereas lymphomas were rare in Indian ethincity.

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