

Prevalence and Morphological Pattern of Haematopoietic Malignancy Involving Oral Cavity at a Tertiary Care Hospital, Chengalpattu District, Tamil Nadu, India

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ABSTRACT

Introduction: Lymphomas, a cancer of lymphoid tissue (either B or T-lymphocytes) are the second most common malignant tumour in the head and neck after squamous cell carcinoma. Extranodal Non-Hodgkin's Lymphoma (NHL) in the oral cavity is thought to be rather uncommon.

Aim: To study the prevalence and morphology of oral cavity-related haematopoietic malignancies.

Materials and Methods: A descriptive cross-sectional study on 1089 cases of oral lesions at a Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Chengalpattu, Tamil Nadu, India, was undertaken in the Pathology Department from July 2012 to July 2022. Demographic information including age, sex, clinical information, histopathological diagnosis, and investigational details were recorded. Morphology of oral

cavity lesion was considered as primary outcome variable and the data was represented in frequency and percentage and the descriptive analysis was done using Statistical Package for Social Sciences (SPSS) version 22.0.

Results: A total of 1089 patients, age distribution range from 10-70 years were analysed in this study. Majority were noted among 41-50 years 423 (38.8%), followed by 51-60 years 257 (23.5%). Buccal mucosa was the commonest site for lymphomas constituting 510 (46.8%), gingiva occupied 132 (12.2%). All NHL (N=3) cases were reported as B cell lymphoma constituting 03 (100%).

Conclusion: Non-Hodgkins Lymphoma in oral cavity is very rare in occurrence and amongst them B-cell form of oral NHL was more frequent. It should always be considered in the differential diagnosis of intraoral malignant diseases.

Keywords: B cell lymphoma, Buccal mucosa, Non-Hodgkin's lymphoma

INTRODUCTION

About 2% of all extranodal lymphomas originate in the oral cavity, which includes the lips, tongue, buccal mucosa, gingiva, palate and floor of the mouth [1]. The body's lymphoid tissues stand out due to their intricate anatomical configuration and capacity to host an immune response. The malignant lymphomas are lymphocyte cell line tumours. Generally speaking, they are categorised as either Hodgkin's or NHL. NHL is a diverse category of lymphoid tumours that can range in behaviour from being somewhat indolent to being extremely aggressive and potentially lethal [2]. Only the extranodal appearance of Hodgkin's disease is uncommon; extranodal presentations of NHL lymphomas are very prevalent. The stomach, bowel, lung, orbital tissue, sinuses, thyroid, tonsil, salivary glands, breast, testis, and kidney are typical sites for extranodal NHLs. Waldeyer's ring has a lower incidence of extranodal NHL than the gastrointestinal tract but primary lymphomas of the oral cavity are rare [3].

The classification of more than 40 cancers affecting the system demonstrates the variability of this cell line [4,5]. The oral symptoms of lymphomas are frequently due to a more extensive involvement. They represent 2.2% of all head and neck cancer cases, 5% of salivary gland tumours, 3.5% of intraoral cancer cases and 2.5% of all instances of lymphomas, making it the second most common oropharyngeal malignancy [6].

The NHL, mature T and Natural Killer (NK) neoplasms, Hodgkin's Lymphoma (HL) and Post-transplant Lymphoproliferative Disorders (PTLD) are the most common types of lymphomas [7,8]. Additionally, cases of large B-cell lymphoma have been documented to appear as palatal and gingival masses. The vestibular region of the maxilla was similarly affected by the palatal mass, which was also linked

to ulcerated tissue, bone degeneration and exposed dental roots. Exophytic/hyperplastic tongue or buccal mucosa masses were a PTLD symptom. Neurologic manifestations: NHL, HL plasma cell myeloma and histiocytic sarcoma have all been associated with numbness and paresthesia [9,10].

Dentists must have training in the signs and symptoms of the disease due to the ambiguous presentation of head and neck lymphomas in order to prevent misdiagnosis. When there is an unexplained toothache, sensitivity or mobility as well as an increase in volume, an ulceration and a mass in the extraction alveolus or an unclear lytic bone alteration in conjunction with enlarged lymph nodes, lymphoma must be taken into consideration as a differential diagnosis [11].

This study was conducted to fill in the lacunae regarding the prevalence of NHL in the study area-Chengalpattu. This is first of its kind study done in a single hospital with large sample size. This study was aimed to find the prevalence and morphology of oral cavity-related haematopoietic malignancies in the study population.

MATERIALS AND METHODS

A descriptive cross-sectional 10-year study on 1089 patients of oral lesions at Department of Pathology in Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Chengalpattu, Tamil Nadu, India, using both retrospective and prospective data collection (ambispective). The Institutional Ethical Clearance was obtained. (IEC/ECR/1425/INST/TN/2020).

Inclusion criteria: Records of patients aged between 10-70 years with lesions in oral cavity (non neoplastic, premalignant and malignant) and with histologically confirmed diagnosis were included in the study.

Exclusion criteria: Patients with other lesions, non specific diagnosis and without histological diagnosis were excluded. Incomplete data and missing data in the records were also excluded from the study.

Over the course of ten years, 1089 cases in the Pathology Department were studied both retrospectively (from July 2012 to July 2020) and prospectively (from August 2020 to July 2022).

Study Procedure

Demographic information, including age, sex, clinical information, histopathological diagnosis, and investigational details were recorded with the Medical Records section's approval. The duration of the oral mass, its location in the oral cavity, symptoms (such as B-symptoms which comprises of fever higher than 38°C, intense night sweats, unintentional weight loss of atleast 10% of their body weight over six months or less) and signs were among the clinical aspects (i.e., tooth mobility and mucosal bleeding). Prior to 2008, Revised European American Lymphoma (REAL) categorisation for histologic specimens was used; after which World Health Organisation (WHO) classification was used [12]. Additionally, all patients had contrast Computed Tomography (CT) scans of their chest, abdomen, pelvis, head and neck, and other body parts. The most pertinent radiological evaluation data were gathered. Investigations comprised standard checks as well as Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV).

STATISTICAL ANALYSIS

The collected data was entered in Microsoft excel 2007. Descriptive analysis of continuous variables was done using mean and standard deviation and for categorical variables frequency and percentage were used. The data has been summarised in tables and figures. The descriptive analysis was done using Statistical Package for Social Sciences (SPSS) version 22.0.

RESULTS

For final analysis, 1089 patients were included. Out of the 1089 patients, three had NHL. Hence, the prevalence of haematopoietic malignancy in this current study was 0.27%. Age distribution in the current study spans from 10-70 years. Majority were in the 41-50 year group (423/38.8%), followed by 51-60 year group (257/23.5%). The lowest percentages were seen in the age groups of 10-20 and 61-70 (43/3.9 and 98/8.9%, respectively) [Table/Fig-1]. Males 677 patients (62.2%) were more affected than female 412 cases (37.8%), in the current study. Patients with ulcers made up of the majority (54.6%, or 595/1089), followed by swelling (24.24%, or 264/1089), and discomfort (21.13%, or 230/1089). A total of 55.75% of participants had symptoms that had lasted longer than two years (607/1089), 2.38% had symptoms that had lasted between one month and one year (26/1089), and 3.1% had symptoms that had lasted less than a month (34/1089) [Table/Fig-1].

In this analysis, gingiva accounted for 132 cases (12.2%) of all lymphomas, with buccal mucosa accounting for 510 cases (46.8%) of all cases. Cheek occupied 67 cases (6.2%), whereas the tongue and palate each took up 190 cases (17.4%) [Table/Fig-2]. The majority (1041/1089) were unilateral lesions, accounting for 95.5% of the total, and 48 (1089) were bilateral lesions. Most of the lesions, 544 (49.96%) were hyperechoic in radiological investigation [Table/Fig-2].

Histopathological analysis revealed that NHL was diagnosed in 3 (0.27%) cases out of total. Non neoplastic lesions were diagnosed in 344 (31.5%) cases, SCC in 486 (44.6%) cases and BCC in 2 (0.18%) cases. Premalignant lesions were seen in 254 cases out of 1089 which accounted for 23.3% [Table/Fig-3]. All NHL cases were reported as B cell lymphoma constituting 100%.

Three B cell lymphoma cases were found, two of which were diffuse large cell lymphomas and one of which was Burkitt's lymphoma. Diffuse large B cell lymphoma in a 59-year-old female patient was reported once with oral lesion in the buccal cavity. A 69-year-old

Baseline characteristics	Number of cases	%
Age distribution		
10-20 years	43	3.9
21-30 years	125	11.4
31-40 years	143	13.1
41-50 years	423	38.8
51-60 years	257	23.5
61-70 years	98	8.9
Sex distribution		
Male	677	62.2
Female	412	37.8
Signs and symptoms		
Ulceration	595	54.63
Swelling	264	24.24
Discomfort	230	21.13
Duration of illness		
<1 month	34	3.12
1 month-<1 year	26	2.38
1-2 years	422	38.75
>2 years	607	55.75

[Table/Fig-1]: Baseline distribution of the study participants (N=1089).

Clinical details	Number of cases	%
Site of lesion		
Cheek	67	6.2
Palate	190	17.4
Tongue	190	17.4
Buccal mucosa	510	46.8
Gingiva	132	12.2
Radiological features		
Hypoechoic lesion	492	45.17
Hyperechoic lesion	544	49.96
Isodense lesion	53	4.87

[Table/Fig-2]: Site of lesion and radiological features (N=1089).

Histopathological examination	No. of cases	%
Hodgkin's Lymphoma (HL)	-	-
Non-Hodgkin's Lymphoma (NHL)	03	0.2
Squamous Cell Carcinoma (SCC)	486	44.6
Basal Cell Carcinoma (BCC)	02	0.18
Non neoplastic lesions	344	31.5
Premalignant lesions	254	23.3
Total	1089	99.9%

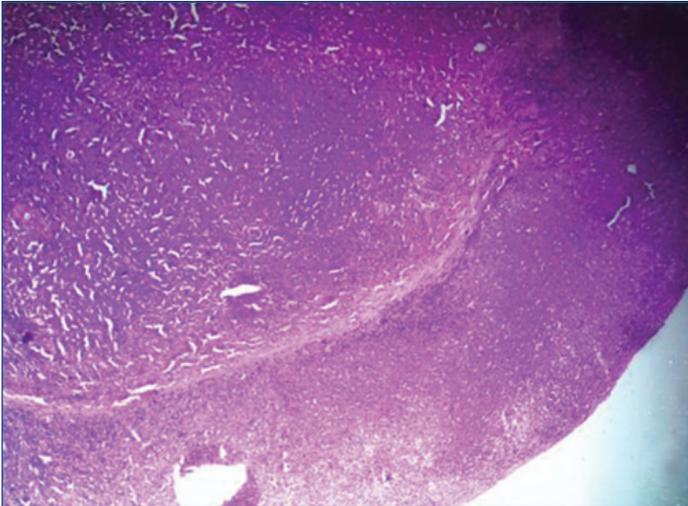
[Table/Fig-3]: Distribution of cases on HPE.

male patient was diagnosed with the second instance of Diffuse Large B Cell Lymphoma (DLBCL). One male patient, 55-year-old was diagnosed with Burkitt's lymphoma.

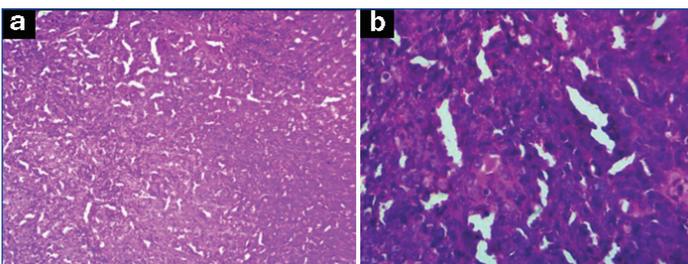
[Table/Fig-4a-c] depicts the clinical images of the patients, the gingival overgrowth as examined by the clinicians whether its firm as depicted in case 1, well-defined white swelling as in case 2 or an ill-defined mass in buccal mucosa with foci of ulceration as in case 3. In one case, the mucosa is infiltrated by sheets of large atypical lymphoid cells [Table/Fig-5]. Large atypical lymphoid cells with interspersed apoptotic bodies and macrophages are seen. Atypical lymphoid cells are medium to large with large round or oval centrally located nuclei, multiple small prominent nucleoli and moderate amount of cytoplasm. Numerous mitoses noted [Table/Fig-6(a,b)]. CD45 and CD20 depicts diffuse strong membrane positivity [Table/Fig-7,8]. [Table/Fig-9] presents the summary of the three cases.



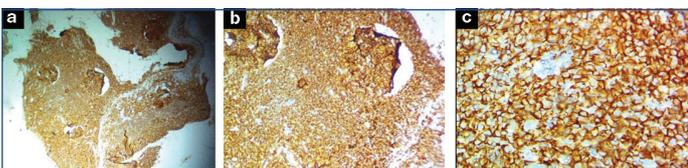
[Table/Fig-4]: (a) Case 1: A firm gingival over growth. (b) Case 2: A well-defined grey white swelling in the gingiva. (c) Case 3: An ill-defined mass in the buccal mucosa with foci of ulceration.



[Table/Fig-5]: Case 2: 4x, Haematoxylin and Eosin stain. The mucosa is infiltrated by sheets of large atypical lymphoid cells.



[Table/Fig-6]: (a) Case 3: 10x, Haematoxylin and Eosin stain. Large atypical lymphoid cells in sheets. (b) Case 3: 40x, Haematoxylin and Eosin stain. Large atypical lymphoid cells in sheets with interspersed apoptotic bodies and macrophages. Atypical lymphoid cells are medium to large with large round or oval centrally located nuclei, multiple small prominent nucleoli and moderate amount of cytoplasm. Numerous mitoses noted.



[Table/Fig-7]: (a) Case 2: 4x, Immunohistochemistry (IHC)-CD 20, Diffuse strong membranous positivity. (b) Case 3: 10x, IHC-CD 20, Diffuse strong membranous positivity. (c) Case 3: 40x, IHC-CD 20, Diffuse strong membranous positivity.



[Table/Fig-8]: (a) Case 2: 4x, IHC-CD 45, Diffuse strong membranous positivity. (b) Case 3: 10x, IHC-CD 45, Diffuse strong membranous positivity. (c) Case 3: 40x, IHC-CD 45, Diffuse strong membranous positivity.

S. No.	Age (years)/ Gender	Clinical features	Histopathological features	IHC findings	Follow-up details
Case 1	55/M	Gingival growth and discomfort for 1 year	Sheets of monotonous intermediate sized cells having squared off borders with starry sky appearance.	CD 20 (+), PAX5 (+), BCL 2 (-)	Uneventful
Case 2	69/M	Gingival swelling and discomfort for 6 months	Large atypical lymphoid cells in sheets with interspersed apoptotic bodies and macrophages. Atypical lymphoid cells are medium to large with large round or oval centrally located nuclei, multiple small prominent nucleoli and moderate amount of cytoplasm. Numerous mitoses noted.	CD 20 (+) CD 45 (+)	Uneventful
Case 3	59/F	Buccal mucosal swelling with surface ulceration for 2 years	The mucosa is infiltrated by sheets of large atypical lymphoid cells.	CD 20 (+) CD 45 (+)	Uneventful

[Table/Fig-9]: Case details.
IHC: Immunohistochemistry; CD: Cluster differentiation; PAX5: Paired box 5; BCL: B-cell lymphoma

and 100 percent of HL cases both involved cervical lymph nodes. A 50% of patients with head and neck NHL may have abdominal adenopathies. Most articles state that instances of head and neck NHL are uncommonly associated with other B symptoms. However, in his series of 31 cases, Enrique A et al., found B symptoms in 27% of patients with head and neck NHL [14].

This incidence, according to Velez I and Hogge M, accounts for 5% of all lymphomas [7]. This is an extremely uncommon illness that is sometimes confused with an infection, cyst, or odontogenic tumour. Additionally, it can imitate an endodontic lesion, periodontal disease, odontogenic cyst, or tumour on radiographs, leading to a number of needless extractions and/or root canal procedures. In 50% of cases, oral symptoms of intraoral lymphomas are the first and only indicators of the condition, according to Colmenero C et al., [10]. Additionally, the author analysed trials in which patients either underwent scale or extraction, which delayed prognosis and worsened disease prognosis.

In non immunocompromised individuals, Diffuse Large B-Cell Lymphoma (DLBCL) in the head and neck region was the most frequently observed type, according to Hicks MJ and Flaitz CM although other types such as mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt's lymphoma, peripheral T-cell lymphoma and anaplastic large cell lymphoma can also occur [15]; while plasmablastic variant is the most typical histotype seen in immunocompromised patients, according to Teruya-Feldstein J et al., [16].

On examination of the pathological features of oral NHL in 1982 [17], Hashimoto N and Kurihara K, came to the conclusion that B-cell lymphoma is the most prevalent histotype based on his analysis of nine cases and the literature. However, Pazoki A et al., observed that the most prevalent histotype in jaw bones was diffuse histiocytic lymphoma (an older term for DLBCL) [18].

Comparative studies related to age and sex distribution: Age distribution in the current study spans 10-70 years. A 41-50 year group made up the majority (38.8%), followed by 51-60 year

DISCUSSION

Primary NHL in the oral mucosa occurs seldom and when oral soft tissue lesions first manifest, they typically take the form of a firm to non tender swelling of the region, frequently accompanied by overlaying ulcerations [13], which can frequently result in misdiagnosis. Enrique A et al., found that 86.6 percent of NHL cases

group (23.5%). In the Kemp S et al., study, 50% of the participants were female and the mean age was 71 [19]. Males 62.2 percent (677/1089) were more severely affected than females 37.8 percent (412/1089). There were 546 men and 432 women in the Bernardes ST et al., study [20]. NHL was discovered in the youngest patient, who was only two-year-old and the oldest patient, who was 96. The average patient age at the time of biopsy in the Kolokotronis A et al., research was 64 years [21]. Males were affected more frequently than females in Bhagat R et al., study with a Male:female ratio of 4:1 [22]. In the study by Shah GH et al., the male to female ratio was 3:2, and the median age at presentation was 42.6 years [23].

Comparative studies related to site of lesion: In this analysis, gingiva accounted for 12.2% (132/1089), with buccal mucosa making up 46.8% of the total sites. Palate and tongue each took up 17.4% (190/1089), whereas cheeks accounted for 16.15%. In Bernardes ST et al., the maxilla was the most impacted bone region with 90 cases reported, while the tonsils were the most afflicted in head and neck region appearing in 119 cases. Salivary glands were next, with 109 occurrences in their study [20]. NHL manifestations, in Barone S et al., study stated clinical localisation revealed that both hard and soft tissues were affected by extranodal NHL [24]. The majority of disease (80.7 percent) affected soft tissues with 10 cases occurring in the buccal mucosa (38.4 percent) 3 in the gingiva (11.5%), 3 on the cheek (11.5%), and 5 in the tongue (19.2%). The upper jaw (maxilla or palatal bone), mandible, palatal soft tissue, vestibule, and gingivae (maxillary or mandibular soft tissue involvement exclusively) were, accordingly, the most frequent locations in Kemp S et al., investigation [19]. In the study by Kolokotronis A et al., a painless local mass that could be bilateral or unilateral was the typical clinical presentation [21]. The tumour mass frequently has a surface ulceration. The most common location for NHL affecting eight patients was tonsils followed by the oral cavity, the salivary glands, and the jaw. According to Bhagat R et al., the tongue and buccal mucosa were the two most typical sites involved (28 percent) [22]. Out of 103 cases, 26 cases (25.2%) were benign and 77 cases (74.7%) were malignant. Of all the lesions examined, squamous cell carcinoma is the most prevalent accounting for 67.9% of all cases. The gingivobuccal complex was the most frequently affected site (12/15) in the Shah GH et al., study, with 7 individuals having lower gingivobuccal complex involvement [23]. One patient's buccal mucosa, one patient's anterior tongue, and one patient's labial mucosa were all affected.

Comparative studies related to clinical manifestations: In this study, ulcers made up the majority (54.6 percent or 595/1089), followed by swelling (24.6 percent or 264/1089) and discomfort (21.1 percent or 230/1089). The most frequent clinical manifestations in Barone S et al., study were swelling or masses that gradually grew in size (21 patients, 80.7 percent) [24]. Thirteen patients had ulcerations (50 percent). Six patients (23%) reported experiencing discomfort, with a mean Visual Analog Scale (VAS) pain score (on a scale of 0-10) of 5. Other indications or symptoms included paraesthesia, swallowing issues, tooth movement and mucosal haemorrhage. The most common symptoms in the Kemp S et al., [19] investigation were oedema, ulceration and radiographic bone loss. In the study, by Shah GH et al., the majority of patients experienced painless increasing swelling and no patient had any B symptoms (systemic) [23].

Comparative studies related to histopathological findings and diagnosis: According to the histopathological analysis of current study, NHL made up 0.27% (03/1089). SCC was present in 44.6 percent (486/1089), BCC was present in 0.18 percent (02/1089), non neoplastic lesions were present in 31.5 percent (344/1089) and premalignant lesions were present in 23.3 percent (254/1089). According to reports, B cell lymphoma accounts for 100% of all NHL cases. Three B cell lymphoma cases were found, two of which were DLBCL and one of which was Burkitt's

lymphoma. In contrast, in a study by Barone S et al., the most prevalent histologic subtype was DLBCL (11 patients, 42.3%) which was followed by plasmablastic lymphoma (7 patients, 26.9%), extranodal marginal zone lymphoma of Mucosa Associated Lymphoid Tissue (MALT) (2 patients, 7.6%), peripheral T-cell lymphoma (2 patients, 7.6%) and Burkitt (1 patient, 3.8 percent) [24]. The bulk of the lymphomas in the Kemp S et al., [19] study were B cell lymphomas (98%) with a high percentage of these B cell lymphomas being histologically subtyped as Diffuse Large B cell Lymphoma, which is thought to have an aggressive clinical course.

According to Freeman C et al., 28% of cases were discovered in the oral cavity and 28% affected the head and neck region [25]. The findings from Takahashi H et al., obtained the results demonstrating that 8% of extra nodal NHL was in the oral cavity [26]. This could be considered a low incidence of NHL oral manifestation, even more so if focused only on its intra-osseous occurrence. Current literature described about 100 cases of mandible NHL [27]. Various publications about single NHL occurrences are also available [28,29]. In the same publication, several writers reported two cases of NHL [30,31]. No mandible localisation was observed by Larson DL et al., in their analysis of 100 patients with extra nodal lymphoma of head and neck [32]. However, Conley SF et al., reported one case with oral manifestation in their study [33].

Kobler P et al., reported lymphoma in a 63-year-old man in oral region and diagnosed as high-grade NHL of B-cell origin [34]. A biopsy taken showed DLBCL replaces the normal architecture of the underlying extra nodal tissue in a diffuse pattern. The lymphoma cells are large, with relatively abundant cytoplasm and irregular nuclei. Deng D et al., studied NHL in oral cavity in a 70-year-old man at the right angulus oris. Microscopically, there were neoplastic cells angio-centrally distributed in a typical flower-ring-like pattern among subcutaneous fat lobules [35]. Varun BR et al., reported NHL in a 65-year-old male patient reported to the dental hospital with the complaint of a growth in the left lower back tooth region since five days [36]. NHL most commonly affects older adults. Van der Waal RI et al., reviewed 40 cases of primary extranodal NHL of the oral cavity and reported the mean age of occurrence as 59 years [37].

The prevalence of haematopoietic malignancy in this current study was 0.27%. A similar study in Iranian population had a prevalence of 1% of oral lymphomas among head and neck malignancies [38]. This study showed that the NHL occurrence is high in elderly population and B-cell type of oral NHL has to be considered as differential diagnosis in every case.

Limitation(s)

The limitation of the present study is its lack of long term follow-up data. A long-term follow-up studies will throw light on the disease progression and complications also. Since the study was conducted in single centre, the representativeness of the population is questionable.

CONCLUSION(S)

The NHL in the oral cavity is extremely uncommon and it should be considered as differential diagnosis of intraoral malignant lesions. Appropriate clinical evaluation along with imaging, histopathological diagnosis and immunohistochemical correlation will lead to early intervention, treatment and better prognosis. In future, multicentric studies involving large population is recommended with long term follow-up time period.

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