Head and Neck Lymphoma: Clinico-demographic Profile and Pattern of Presentations in a South-Western Nigerian Tertiary Institution

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ABSTRACT

Objectives:
Lymphoma is the second commonest malignancy of the head and neck region, broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), and affecting nodal and extra-nodal sites. The clinical presentation is largely determined by the anatomical distribution of the disease, the clinical stage of the disease, the age of the patient, and the presence of underlying diseases. This study analyzed the presentation of head and neck lymphomas over a fifteen-year period at the Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife. The objectives were to determine the prevalence and demographic indices (age and sex) of the head and neck regions, document the histopathologic types, and determine the association between the anatomical sites and histopathologic subtypes of lymphomas.

Materials and Methods:
This was a retrospective study among patients seen and diagnosed histologically with head and neck lymphomas between 2005 and 2019 at the departments of Oral Medicine and Pathology and Morbid Anatomy and Forensic Medicine, OAUTHC. Relevant records were retrieved from patients' records and the histological register from the hospital registry. Patients with incomplete data were excluded. The study was conducted in accordance with the Declaration of Helsinki and approved by our institution's Ethics Committee Board.

Results:
A total of 54 cases of head and neck lymphoma were analyzed, with a prevalence of 30.9%. Out of the 54 cases, 46 were NHL and 8 cases were HL, with a ratio of 5.8:1, respectively. A male preponderance was observed (M: F; 2.4:1). The lesion commonly affected patients in their 3rd and 4th decades of life. All the histologic variants seen affected males more than females, except the unclassified variant of HL, which affected both sexes equally. Low-grade and intermediate-grade NHL affected the older patients more, while high-grade and miscellaneous subtypes affected the younger males. The cervical lymph nodes were the most common nodal sites, while the jaw was the most common extra-nodal site. Eighteen (39.1%) of the NHL cases were diagnosed histologically as miscellaneous,

while there were seven (15.2%) cases a piece of the high and low grade varieties.

Conclusion:
Head and neck lymphomas remain relatively rare. One of every six lymphomas seen in our center was a HL, with a male preponderance. High-grade lymphoma was commoner among younger patients. Also, lymphoma predominantly affected the cervical lymph nodes, while the jaw was the most common extra-nodal site. However, while obesity may be a predisposing factor in our environment, it requires future study to confirm.

INTRODUCTION

Lymphomas are the most common neoplastic cause of lymphadenopathy, affecting lymph nodes and extra-nodal structures such as tonsils, major salivary glands, the sino-nasal system, and the hypopharynx in the head and neck regions.[1,2] Approximately 287,000 new cases of lymphoma are reported globally each year,[3] with 100,000 new cases reported annually in the United States.[4] Local studies[5-7] also show that lymphomas are the second-commonest malignancy of the head and neck, with an incidence ranging between 17.5% and 21.5%. Also, lymphoma generally affects more males than females, with incidence increasing with age and predilection for the third, fourth, and fifth decades. [8]Lymphoma is broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma is commoner in younger patients and more aggressive when compared with Hodgkin lymphoma. [2]Hodgkin lymphoma primarily affects the lymphoid tissue, and it is characterized by Reed-sternberg cells. HL is rarely seen in the oral cavity.[9] NHL, on the other hand, is usually found in lymph nodes or extra-nodal organs, especially the gastrointestinal tract and the head and neck regions. [10]Non-Hodgkin lymphoma is relatively rare among Africans, but the high incidence of Burkitt's lymphoma (BL) in children in north and sub-Saharan Africa makes the overall lymphoma prevalence higher than the world average. [3, 11]Burkitt's lymphoma (BL) is also endemic in Nigeria, accounting for 39% of all childhood malignancies, with a male predilection.[12]

The clinical presentation is largely determined by the anatomical distribution of the disease, the clinical stage of the disease, the age of the patients, and the presence of underlying diseases.[9] Two-thirds of NHL and virtually all HL present as enlarged, non-tender lymph nodes, usually greater than 2cm.[8] The remaining one-third of NHLs show heterogeneous extra-nodal manifestations such as in the major salivary glands, paranasal sinuses, mandible, maxilla, skin, brain, and Waldeyer's ring, which is greatly dependent and often characteristic of the specific NHL subtype. [4,9,13] Staging of lymphomas helps define the location and extent of the disease, forecast prognosis, and provide a baseline for evaluation of disease progression or otherwise and comparison between different studies.[14] The Ann Arbor classification is a widely accepted clinical staging system and includes four stages with sub-classification based on the absence (A) or presence (B) of the following symptoms: unexplained fever (greater than 101degree F), drenching night sweats, and/or unexplained weight loss of greater than 10% of normal body weight.[4]

Hodgkin lymphoma is characterized by the appearance of Reed-Sternberg (RS) cells, a specific type of lymphoid precursor cell identified on lymph node biopsies of patients with a peculiar morphological appearance, bi- or multinucleated, with large round to oval nuclei.[10] Histologically, it is classified into nodular lymphocyte predominant and classical HL, which includes lymphocyte predominant, nodular sclerosing, mixed cellularity, and lymphocyte depleted based on the ratio of RS cells to the lymphocytic population. In addition, NHLs are characterized by diffuse or nodular sheets of lymphocytes or lymphoblasts without Reed-Sternberg cells.[8] The proliferating lymphocytic-appearing cells show varying degrees of differentiation: low-grade, intermediate-

grade, and high-grade lesions. The management of head and neck lymphomas depends on a detailed history and examination, the clinical stage, and the histological grade of the lesion. Chemotherapy alone will often suffice for patients with stages I and II of Hodgkin lymphoma. However, stage III or IV disease requires chemotherapy with adjuvant radiation therapy if significant mediastinal involvement or residual disease is detected. The prognosis is therefore better for patients with stage I and II disease.

Lymphomas of the head and neck are rare. Studies [12, 15]in Nigeria have focused more on NHL because Burkitt lymphoma is endemic in Africa. However, only a few studies have been done on lymphoma with a focus on the head and neck in low- and middle-income countries. Furthermore, there is a dearth of information on the pattern of presentation of lymphomas in the head and neck. [1]Meanwhile, findings about patterns of presentation are important in order to draw the attention of the clinician, raise awareness of the common sites of occurrence and the common age groups affected, raise early suspicion, and ensure early diagnosis and a good prognosis. This study therefore aimed to analyze the presentation of head and neck lymphomas spanning over fifteen years at the Obafemi Awolowo University Teaching Hospital Complex (OAUTHC) with respect to demographics, anatomical sites, and histopathologic parameters to determine the prevalence of disease and possibly add to the existing body of knowledge. The objectives include: to determine the prevalence and demographic indices (age and sex) of head and neck lymphoma cases seen over the study period; to document the histopathologic subtypes; and to determine the association between the anatomical sites and histopathologic subtypes of lymphomas.

MATERIALS AND METHODS

This was a retrospective study of fifty-four (54) consecutive patients with histologically diagnosed lymphomas seen between 2005 and 2019 at the departments of oral medicine, oral pathology, and morbid anatomy and forensic medicine at the Obafemi Awolowo University Teaching Hospital Complex, Nigeria. The study was conducted in accordance with the Declaration of Helsinki and approved by our institution's Ethics Committee Board with protocol number IPH/OAU/12/1638. Histologically diagnosed lymphoma of the head and neck within the study period (2005–2019) was retrieved from hospital records in September 2021. Data collected include: patients' age, sex, anatomical site of the lesion, histologic diagnosis, and the year of diagnosis. The findings were carefully recorded on a spread sheet. Patients' records with incomplete data were excluded from the study. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 21. Descriptive analysis was done for age, sex, anatomic sites, and histologic diagnosis using frequency tables and line graphs. The analysis of continuous variables—ages of the patients—was done using mean, median, mode, and standard deviation. The association between the site of presentation and histologic diagnosis was tested using the Fisher's exact test, with a p-value of 0.05 (5% level of significance) as the acceptable level of significance.

Results: The clinico-demographic profile of patients with head and neck lymphoma

The total number of lymphomas diagnosed between 2005 and 2019 was **175**. Head and neck lymphoma accounted for 54 of the cases; thus, the prevalence of head and neck lymphoma was **30.9%**. Non-Hodgkin lymphoma (46) was more common than Hodgkin lymphoma (8), with a ratio of 5.8:1, respectively. The occurrence of head and neck lymphoma showed sex predilection, with a twice-occurrence in males for every female (M: F, 2.4:1), with lesions mostly reported in the third to fourth decade of life (35.2%). More than half of the lesion

occurred in the cervical lymph node (51.8%), with over three-quarters of the lesion diagnosed as non-Hodgkin lymphomas (85.2%), as shown in Table 1. In addition, the cervical lymph node was most involved with both types of lymphoma (HL and NHL), while the supraclavicular lymph node and jaw were commonly involved with NHL. (Table 1)

Table 1: Clinico-demographic profile of patients with head and neck lymphoma

Variable		Frequency	Percentage (%)
Agegroup	0-19	10	18.5
	20-39	19	35.2
	40-59	14	25.9
	60-79	11	20.4
	Total	54	100.0
Sex	Male	38	70.4
	Female	16	29.6
	Total	54	100.0
Anatomic Site	Cervical lymph node	28	51.8
	Submandibular lymph node	1	1.9
	Supraclavicular lymph node	8	14.8
	Submandibular gland	1	1.9
	Scalp	1	1.9
	Sinonasal	1	1.9
	Oropharynx	2	3.8
	Neck	3	5.6
	Jaws	6	11.1
	Frontal skull	1	1.9
	Infraclavicular lymph node	1	1.9
	Tonsils	1	1.9
	Total	54	100.0
Diagnosis	HL	8	14.8
	NHL	46	85.2
	Total	54	100.0

Figure 1, shows the change in patterns of presentation over time. The number of cases nose-dived from 2008 to 2009 and rose steadily with a peak in 2012. Two-thirds of the cases of NHL were seen between 2012 and 2019.

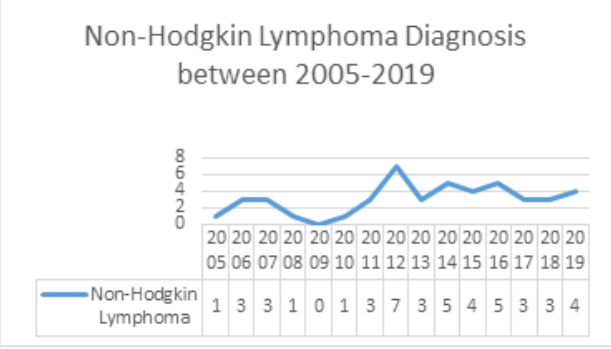

Figure 1: Pattern of patient presentation diagnosed with NHL over the study period

Eight cases of HL were seen within the study period. The line graphs showed the change in the pattern of presentation over time, with most cases seen between 2010 and 2012.

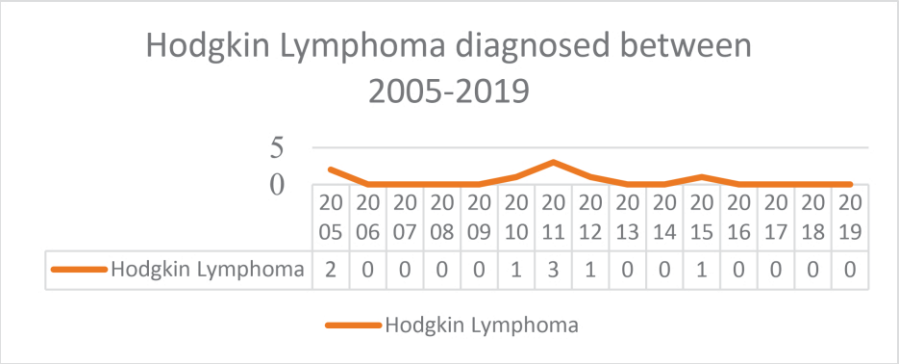

Figure 2:Pattern of patient presentation diagnosed with HL over the study period.

Age and Sex Structure of Patients Diagnosed with Non-Hodgkin Lymphoma and Hodgkin Lymphoma

All the histologic variants of lymphoma were seen to affect males than females except for the unclassified variant of HL which affected males and females equally. Low grade and intermediate grade NHL affected older individuals (mean age 52.9 years, 46.0years respectively) while High grade and Miscellaneous subtypes affected younger individuals (39.3 years, 38.7 years respectively). HL generally affected younger individuals. (Table 2)

Table 2: Age and Sex Structure of Patients Diagnosed with Non-Hodgkin Lymphoma and Hodgkin Lymphoma

	NHL			
	Low grade	Intermediategrad	High grade	Miscellaneous
No of patients	7	14	7	18
Females	2	4	3	5
Males	5	10	4	13
Ages	No. of cases	No. of cases	No. of cases	No. of cases
7-19	1	1	1	3
20-29	0	3	2	1
30-39	0	1	1	7
40-49	2	1	0	3
50-59	0	5	1	2
60-69	3	2	2	1
70-79	1	1	0	1
Mean age	52.9	46.0	39.2	38.7
Mean age F	45.5± 0.7	45.5± 4.7	60.0±6.5	37.6±24.0
Mean age M	55.8±22.5	46.0±14.0	23.5±7.0	39.0±15.7
	HL			
	Lymphocyte depleted	Lymphocyte Rich	Nodular sclerosis	Unclassified
No of patients	1	2	1	4
Sex (F:M)	0:1	0:2	0:1	1:1
Age range	24	9-24	9	6-30
Mean age	24	16.5	9	17.8
Mean age F	-	-	-	18±16.9
Mean age M	24	16.5±10.6	9	17.5±13.4

Table 3 reveals the relationship between histologic behaviour and involved anatomic sites of patient diagnosed of NHL. The cervical lymph node (23; 50.0%) was the most common nodal site. The most common extra-nodal site was the jaw (5; 10.9%). Eighteen (39.1%) cases of NHL were diagnosed histological as miscellaneous while high and low grade had seven (15.2%) cases each. The relationship between the histologic behaviour and anatomic site was statistically significant (p<0,001). (Table 3)

Table 3: Relationship between the histologic behaviour and anatomic sites of NHL

Variable	Biologic behaviour (NHL)						
		Miscellaneous	Intermediate grade	High grade	Low grade	Total	P value
Anatomic sites	Cervical lymph node	10	9	1	3	23	0.001
	Frontal skull	0	0	0	1	1	
	Infraclavicular Lymph node	1	0	0	0	5	
	Jaw	1	1	3	0	5	
	Neck	1	1	0	1	2	
	Oropharynx	1	0	1	0	1	
	scalp	1	0	0	0	1	
	Sinonasal	1	0	0	0	1	
	Submandibular gland	0	1	0	0	1	
	Tonsil	0	0	1	0	1	
	Supraclavicul ar Lymph node	2	2	1	2	7	
		18 (39.1%)	14 (30.4%)	7 (15.2%)	7 (15.2%)	46	

p-value: <0.001*** Fisher's Exact Test = 73.466 ***Significant at 1% level

Table 4 depicts the relationship between histologic behaviour and involved anatomic sites of the patients with Hodgkin Lymphoma. The cervical lymph node (62,5%) is the mostly affected, with the jaw (12.5%) being the only extra-nodal site involved. The unclassified HL was most common histological diagnosis (3; 37.5%), while lymphocyte depleted was seen in only one patient (12.5%).(Table 4)

Table 4: Relationship between the histologic behaviour and anatomic sites of HL

Variable		Biologic behaviour HL					
		Lymphocyte depleted	Lymphocyte Rich	Nodular sclerosis	Unclassified	Total	P value
Anatomic site	Cervical lymph node	1	0	1	3	5 (62.5%)	0.001
	Jaw	0	1	0	0	1 (12.5%)	
	Submandibular Lymph node	0	0	0	1	1 (12.5%)	
	Supraclavicular	0	1	0	0	1 (12.5%)	
		1 (12.5%)	2 (25.0%)	2 (25.0%)	3 (37.5%)	8	

Fisher's Exact Test = 69.946. ***Significant at 1% level

DISCUSSION

We reported a higher prevalence of lymphoma (30.9%), which contrasted with other studies.[6, 16] However, this is lower than the prevalence (40.2%) reported by Amusa et al.[17] While their study focused on head and neck malignancy, irrespective of any specific cancer, we considered the incidence of lymphoma sited in the head and neck among all the lymphoma cases seen within the study period. This may account for the dissimilarity. Most studies[1,3,18] found a male predilection for head and neck lymphoma, though the sex incidence varies between studies. However, our findings revealed that most patients presented within the third to fourth decade. While we found a peak incidence in the third decade, in contrast, a similar local study[3] found a peak incidence of head and neck lymphoma in the second decade. This discrepancy could be explained by the different methodology adopted. Their study was not specific to head and neck lymphoma. It also considered environmental exposures and working conditions that are often linked to uncontrolled lymphoproliferation, which tends to occur in male-driven careers such as industrial or engineering work.[19] This may be responsible for the bias toward males. However, the occupation of the patients was not assessed in this study.

Non-Hodgkin lymphoma was commoner than Hodgkin lymphoma in this study. This is consistent with previous studies.[2,3,20] Lymphoma progresses as a slow lesion of the lymph node, with non-Hodgkin lymphoma having more extra-nodal spread compared to Hodgkin lymphoma, which may be responsible for this finding. Besides, Hodgkin lymphoma is almost always limited to the lymph node, with more systemic dissemination. The cervical lymph node was the most common site of presentation of lymphoma in the head and neck,[1,2] while the jaw bone was the most common extra-nodal site of presentation. Other similar studies[12, 15, 21] have reported this finding, which is also consistent by our findings. A study[18] in north-eastern Nigeria, however, found the maxilla as the commonest site of presentation of lymphoma. Other studies[2, 22] showed palatine tonsils as the commonest extra-nodal site. There are several risk factors identified as being associated with the risk of lymphoma. HIV is highly associated with the risk of both HL and NHL.[23] A report of the Joint United Nations Programme on HIV/AIDS (UNAIDS) predicted that new HIV infections would increase by 31% from 2001 to 2013.[23] However, Nigeria has experienced a steady decline in the prevalence of HIV since 2005 (4.4%) to 2013 (3.4%), attributed to effective reporting and an interventional system.

The spike noticed in both types of lymphoma in this study could not be attributed to HIV/AIDS, as none of the patients included in the current study were HIV positive at the time of routine screening. This finding is comparable to an earlier study[15] conducted in Nigeria. However, Epstein-Barr virus and Helicobacter pylori remain two well-known risk factors for lymphoma. These pathogens were not assessed in this study. Larrson et al,[24] also found an increase in body mass to be positively associated with the risk of NHL and HL, as well as with NHL mortality. However, a more recent study[25] found no association between obesity and lymphoma-specific survival in patients with diffuse large B-cell lymphoma and small lymphocytic lymphoma. Obesity has been on the increase in Nigeria, with more prevalence in the southern region. [26]But while this may be responsible for the increase in the number of cases seen, it will require future studies to confirm this observation. Non-Hodgkin lymphoma is more prevalent than Hodgkin lymphoma in both sexes.[6,7] In contrast to our findings, Abdel Sater et al[20], in a comparative study of Hodgkin and non-Hodgkin lymphoma in Lebanon, reported non-Hodgkin lymphoma to be more prevalent in both sexes but showed a significant male predilection in Hodgkin lymphoma. Interestingly, in the Hodgkin lymphoma group, all the subtypes of HL were seen in males except the mixed

cellularity. This should be interpreted with caution due to the limited number of HL seen within the study period.

Although the majority of NHL arises in the lymph node, primary extra-nodal lymphomas of the head and neck are relatively rare[17], with the involvement of the oral cavity being particularly rare, accounting for 0.1–5%. [13, 15]When lymphoma occurs in the oral cavity, it could either involve the soft tissue or arise centrally within bone. Gusenbauer et al[27], reported a case of NHL of the mandible. We also found more jaw involvement (33.3%; 5 of 15) of all extra-nodal NHL seen within the study period. One of the five cases of jaw involvement involved both the maxilla and mandible. Involvement of only the mandible was seen in one case, supporting the rarity of NHL in the mandible[27]. The other three cases involved the maxilla only.Burkitt lymphoma is endemic in Africa and accounts for the high prevalence of NHL seen in low- and middle-income countries. Three of the five cases of NHL affecting the jaw are high-grade NHL, and all were histologically diagnosed as Burkitt lymphoma. BL is a small-cell non-cleave malignant lymphoma classified as high-grade NHL. NHL is also commonly seen in adults, although the more aggressive high-grade NHL is mostly reported in children.[28] Burkitt lymphoma is the most common malignant jaw tumor among Nigerian children. [21,29]

A group of American pathologists devised the Working Formulation (1982) for grading NHL. NHL was broadly classified into low, intermediate, high, and miscellaneous-grade lymphomas. Although the working formulation was simple to use and generally acceptable, many recently described lesions were not considered in this classification. The Revised European American Lymphoma (REAL) classification was proposed in the early 1990s. This system of classification employed a combination of histopathologic features, immunologic cell surface markers, and gene rearrangement studies to categorize lymphoma. The World Health Organization (WHO) also recently revised its lymphoma classification based on the REAL system of classification, with the modified REAL classification. These classifications appear to be more precise than the working formulation. However, we adopted the Working Formulation due to the unavailability of molecular studies in our center. Thus, HL in this study was classified into nodular sclerosis, lymphocyte-rich, lymphocyte-depleted, and unclassified based on the ratio of RS cells to the lymphocytic population. Most of the non-Hodgkin lymphoma cases fell into the miscellaneous category. This is due to the fact that many of the NHL diagnoses were unclassified, which could be related to the limited diagnostic resources in the facility. Intermediate-grade NHL was the second-commonest class, of which diffuse large B-cell lymphoma accounted for the majority of the cases. This is in agreement with what is found in the literature.[18]

Advancements in diagnostic technique (light morphologic, phenotypic, and genotypic) as well as distinct clinical findings have led to the recent classification of HL. Nodular lymphocyte-predominant Hodgkin's lymphoma is regarded as a separate entity from classic Hodgkin's lymphoma (CHL).[13] CHL comprises the following subtypes: nodular sclerosing, mixed cellularity, lymphocyte-depleted, and the diffused form of lymphocyte-rich. However, this classification was not used due to the retrospective nature of this study, as the diagnosis was made using the old classification. So, patients with nodular sclerosis or lymphocyte predominance types of HL have stage I-II disease and are usually free of systemic manifestations. However, patients with disseminated disease (stages III–IV) or the mixed cellularity or lymphocyte depletion subtypes are more likely to have constitutional symptoms such as fever, night sweats, and weight loss.[4]

High-grade and miscellaneous NHL were associated with poor prognosis. In the NHL

group, the mean age declined (4th decade) as the grade of the disease increased or became more severe. This is in agreement with an earlier local study. [12,18] A similar study [2] conducted in Germany also reported a similar result. Ironically, there is a marked decline in the incidence of high-grade non-Hodgkin lymphoma compared to what was earlier reported in Ile-Ife, Nigeria.[12] Such a decline was also observed in a similar study[3] conducted in Ibadan and was attributed to improved living conditions and greater control of malaria, which is a predisposing factor for developing the disease.[3] HL disease has a bimodal age distribution, with a first peak between 15 and 35 years and a second peak at 65 years and a slight male preponderance. [30,31] but we could not confirm this assertion due to the limited number of cases. Poor health financing and insurance remain a major hindrance to access to quality health care. This may be responsible for poor utilization of advanced diagnostic techniques, as patients are required to pay out of pocket. A future study on the prognosis and survival trends of patients with head and neck lymphoma in low- or middle-income country settings is therefore desirable.

Conclusion

Non-Hodgkin lymphoma was more common than Hodgkin lymphoma in the head and neck regions in this study. Cervical lymphoma nodes were the commonest sites in both HL and NHL, while the commonest extra-nodal site of involvement remains the jaw bone, with the maxilla being mostly involved. In addition, high-grade lymphomas were mostly seen in younger patients.

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