



Original Article

Clinical manifestations of oral lymphomas — Retrospective study of 15 cases in a Taiwanese population and a review of 592 cases from the literature



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Received 5 February 2020; received in revised form 5 May 2020; accepted 17 May 2020

KEYWORDS

Clinical
manifestation;
Lymphoma;
Oral;
Review;
Taiwan

Background/Purpose: Due to the rarity of oral lymphoma (OL), we aimed to evaluate the clinical features of OL and discuss these findings in light of the literature.

Methods: English language literature (1980–2019) related to OL was searched in two electronic databases. Patients (2000–2019) diagnosed with OL were also selected from the database of the Oral Pathology Department in our institution. The clinical features, radiographic appearance, and histopathological diagnosis in these selected cases from publications and our institution were then analyzed.

Results: 607 cases of OL (15 in our institution and 592 from literature) in patients aged between 0 and 92 years (average, 51.8 years) with a male to female ratio of 1.6:1 were included. The most common diagnosis was diffuse large B-cell lymphoma ($n = 205$), followed by Burkitt lymphoma ($n = 72$) and T-cell lymphoma ($n = 37$). The most frequent site was the gingiva, followed by palate, maxilla, mandible, tongue and buccal mucosa. The most frequent symptoms were swelling, ulceration, paresthesia, mobile tooth and pain. Radiographic findings included ill-defined osteolytic lesion, thickening of the periodontal ligament, loss of lamina dura and tooth displacement.

Conclusion: Despite the rarity of extranodal lymphomas in oral cavity, their occurrence may be part of disseminated disease. Detailed history-taking, clinical and imaging examination and awareness of the patient's signs and symptoms are important for early diagnosis and an

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improved prognosis. The current data form a useful basis for clinical investigation and teaching regarding lymphoma occurring in the oral cavity.

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Introduction

Lymphomas are a heterogeneous group of malignant diseases characterized by proliferation of malignant lymphoid cells or their precursors. Lymphomas are the ninth most common cancer and constitute 3.2% of malignant tumors, which also account for 2.7% of cancer deaths worldwide.¹

Lymphomas are generally classified into two main categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), approximately 90% of cases being NHL. NHL and HL have been estimated to represent 4.3% and 0.5%, respectively, of all new cancer cases in the US in 2018.² In Taiwan, NHL is the ninth most common cancer in male patients and the eleventh in female patients³; NHL and HL accounted for 2.4% and 0.2% of new cancer cases, respectively, in 2015.³ According to the 2016 WHO classification of lymphoid neoplasms, these neoplasms are subclassified into mature B-cell neoplasms, mature T and natural-killer (NK) neoplasms, HL, post-transplant lymphoproliferative disorder and histiocytic and dendritic cell neoplasms.⁴ Lymphomas may arise in the lymph nodes or any organ, with 2% of extranodal lymphomas occurring in the oral cavity.⁵ However, lymphomas are the most common nonepithelial malignant neoplasm in the oral cavity and maxillofacial region, and represent the third most frequent group of malignant lesions in the oral cavity, followed by squamous cell carcinoma and salivary gland tumors.⁶

The oral manifestations of lymphomas are not specific, and are similar to many other diseases, such as advanced periodontal disease, osteomyelitis or other malignancies encountered in the oral cavity. In most cases, the involvement of lymphomas in the oral cavity represents part of a disseminated disease,⁷ and early detection and diagnosis could promote adequate treatment and a better prognosis. The current study aimed to review the oral manifestations of lymphomas in 592 previously-published cases and 15 cases in our institution in order to obtain updated information so as to assist oral care practitioners in daily practice.

Materials and methods

An extensive search of the English language literature published from 1 January 1980 to 31 December 2019 was performed using the key words oral (manifestation), lymphoma and human in PubMed and Embase including the cases diagnosed with lymphoma before and then occurred in oral cavity later or vice versa as well as the cases occurred only in the oral cavity. The selected literature included retrospective studies, literature reviews and case reports. Moreover, the articles without documentation of

the results of immunohistochemical analyses for their cases were excluded. Consequently, a total of 89 publications were finally selected.

Furthermore, according to the definition of anatomic structure in the American Joint Committee on Cancer (AJCC) cancer staging manual, 8th edition, the oral cavity only includes the following structures: the mucosal lip, buccal mucosa, alveolar mucosa, retromolar, floor of the mouth, hard palate and anterior two-thirds of the tongue. Hence, the cases recorded within the 89 selected articles that did not occur in the sites of the oral cavity as designated by the 8th edition of AJCC staging manual were excluded. Additionally, the cases that had been included in previous case series were also excluded from the current study.

With the same aforementioned inclusion and exclusion criteria, cases that were histopathologically diagnosed as lymphoma of the region of the oral cavity and jawbones were selected from the archives of the Department of Oral Pathology in our institution between January 2000 and the end of December 2019. Informed consent was waived by the ethical committee because this was a retrospective analysis. The histopathological diagnoses were rendered by board-certified oral and maxillofacial pathologists. Taken together, a total of 607 cases of lymphoma with oral manifestations (15 cases in our institution and 592 cases retrieved from the literature) were included in the present review. The clinical features, radiographic appearance, and histopathological diagnosis of these selected cases from publications and our institution were analyzed.

Data analyses were performed with the SPSS software for windows (version 22.0; SPSS, Chicago, IL). Intergroup comparison values were calculated by using χ^2 or Fisher exact test. Statistical significance was defined as $P < .05$.

Results

A total of 15 cases from our institution and 592 cases from the 89 previously-published articles in the English language literature were recruited to the current study. The detailed data of these cases are listed in [Table 1](#) and [Supplementary Table S1](#). We found that oral lymphomas affected patients aged 0–92 years (average, 51.8 years) ([Fig. 1](#)), occurring approximately 1.6 times as often in males than in females (male: 358; female: 226). The most common site of involvement was the gingiva, followed by the palate, maxilla, mandible, tongue and buccal mucosa ([Fig. 2](#)). The most frequent symptoms were swelling, ulceration, paresthesia, pain and palpable lymph node ([Fig. 3](#)). Tooth displacement and hypermobility were also frequently seen when the alveolar bone was involved. The distribution of locations and symptoms according to different age ranges

Table 1 Clinical features of the 15 cases of oral lymphoma in our institution.

Case no.	Year of diagnosis	Gender	Age (years)	Site of involvement	Symptom(s)	Radiographic findings	Result of IHC	Diagnosis	Other extranodal involvement	Treatment/Follow-up
1	2004	M	28	Lower right alveolar mucosa	Swelling	No alteration	Positive: CD45, CD20, Kappa Negative: CD3, Lambda, BCL-2, BCL-6, CD30	DLBCL	N/A	N/A
2	2006	M	43	Left maxilla	Swelling	N/A	Positive: CD45, CD20, Lambda Negative: CD3, CD1a, S100	BCL	No other involvement	Chemotherapy, free of disease 13 years
3	2006	M	77	Upper left edentulous ridge, maxilla	Swelling	Bony destruction	Positive: CD20, BCL2 Negative: CD3, Kappa, Lambda, BCL-6	BCL	No other involvement	Chemotherapy, free of disease 13 years
4	2006	M	51	Hard palate, lower left gingiva, mandible	Swelling; ulcerative lesion	Bony destruction	Positive: CD45, CD3, CD20	SCL	No other involvement	Chemotherapy, free of disease 11 years
5	2007	F	74	Left maxilla (hard palate)	Swelling	Bony destruction	Positive: CD45, CD20, Kappa Negative: CD3, Lambda	SLL	No other involvement	N/A
6	2007	M	28	Upper left gingiva, maxilla	Ulcerative lesion	Bony destruction	Positive: CD3, CD56 Negative: CD5, CD10, CD20, CD30, CD79a	NK/T	Present before oral diagnosis (skin of thigh)	N/A
7	2008	F	49	Left buccal mucosa	Swelling	N/A	Positive: CD45, CD20, Kappa, BCL-2	SLL	No other involvement	Chemotherapy + radiotherapy, free of disease 6 years
8	2010	F	72	Retromolar, right	Swelling	N/A	Positive: CD20, CD5, CD79a	SLL	Present after oral diagnosis (mediastinum)	N/A
9	2011	F	43	Lower right gingiva, mandible	Swelling	Bony destruction	Positive: CD20, BCL-2 Negative: CD3, BCL-6	DLBCL	N/A	N/A
10	2013	F	73	Left buccal mucosa	Swelling	No alteration	Positive: CD45, CD20, CD79a Negative: CD3, CD30, CK	DLBCL	Present after oral diagnosis (mediastinum, sacroiliac joint)	Chemotherapy + radiotherapy, expired 1 year later

(continued on next page)

Table 1 (continued)

Case no.	Year of diagnosis	Gender	Age (years)	Site of involvement	Symptom(s)	Radiographic findings	Result of IHC	Diagnosis	Other extranodal involvement	Treatment/Follow-up
11	2014	M	45	Lower left vestibule, mandible	Swelling	Bony destruction; loss of lamina dura	Positive: CD20 Negative: CD3, CK	DLBCL	area) Present before oral diagnosis (adrenal gland)	Chemotherapy, expired 2 months later
12	2015	M	54	Left hard palate	Swelling	N/A	Positive: CD20, CD79a	DLBCL	Present after oral diagnosis (spleen and right kidney)	Chemotherapy, expired 9 months later
13	2017	M	84	Lower right gingiva, mandible	Swelling	Bony destruction	Positive: CD20, CD10, BCL-6, c-myc Negative: CD3, BCL-2, CK	BL	Present after oral diagnosis (mediastinum)	Hospice care, expired 1 month later
14	2018	M	84	Lower right gingiva, mandible	Swelling; ulcerative lesion; mobile tooth	Bony destruction	Positive: CD45, CD3, CD56 Negative: CD20, CD30, CDK4, CK, CK5/6, S100	NK/T	No other involvement	Radiotherapy, expired 4 months later
15	2018	M	46	Right buccal mucosa	Swelling	N/A	Positive: CD20, BCL-2 Negative: CD3, BCL-6, cyclin D1	MALT	N/A	N/A

N/A: not available; M: male; F: female.

IHC, immunohistochemistry; BCL, B-cell lymphoma; BL, Burkitt's lymphoma; DLBCL, diffuse large B-cell lymphoma; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; NK/T, extranodal natural killer (NK)/T-cell lymphoma; SCL, small cell lymphoma; SLL, small lymphocytic lymphoma.

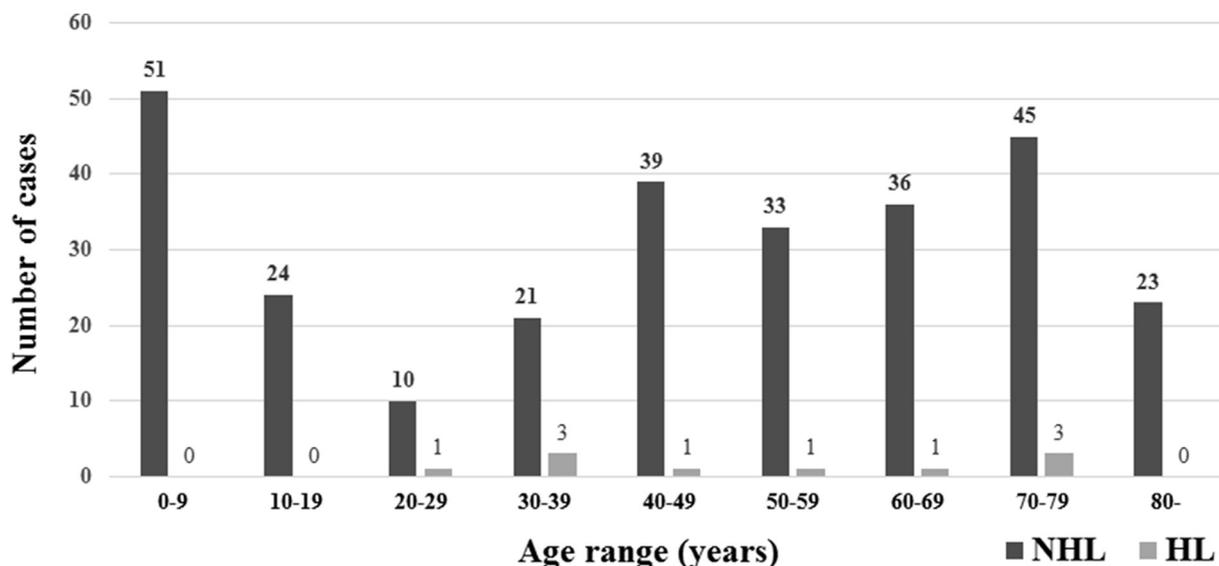


Figure 1 The number of cases of oral lymphoma with respect to age range in the current study. Values within the brackets represent the total number of cases.

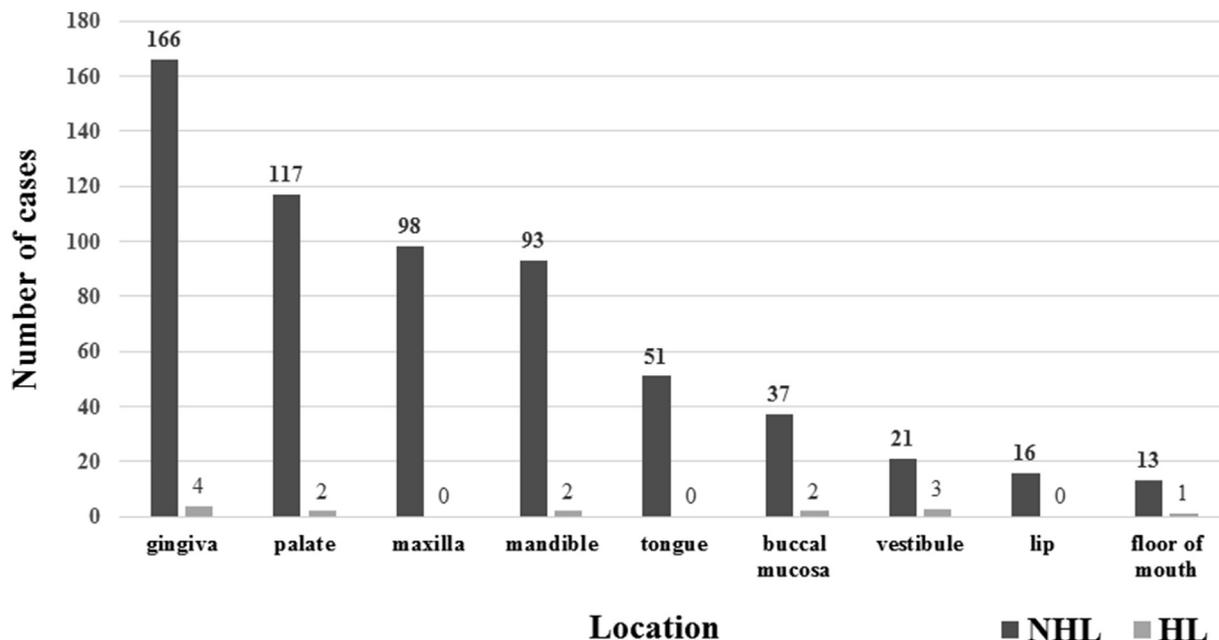


Figure 2 The number of cases of oral lymphoma with respect to location in the current study. The most commonly involved site in the cases of oral lymphoma was the gingiva, followed by the palate, maxilla, mandible, tongue, buccal mucosa, vestibule, lip, and floor of the mouth. Values within the brackets represent the total number of cases.

and gender were presented in [Supplementary Figs. 1–4](#). Correlations between the examined parameters including locations in different age ranges ([Supplementary Fig. 1](#)); locations between genders ([Supplementary Fig. 2](#)); symptoms in different age ranges ([Supplementary Fig. 3](#)); symptoms between genders ([Supplementary Fig. 4](#)) were evaluated. There was a statistical significance between age and location of oral lymphoma ($P < .001$) ([Supplementary Table S2](#)). By application of post hoc analysis with Bonferroni correction, oral lymphomas involved the maxilla were significantly in age range of 0–9 years ($P < .0001$), cases

involved the mandible were significantly in age range of 10–19 years ($P = .00019$) and the involvement of gingiva were significantly lesser in age range of 0–9 years ($P = .00029$) ([Supplementary Table S2](#)).

The radiographic findings were non-specific as osteolytic lesions. Thickening of the periodontal ligament, loss of lamina dura and tooth displacement were also documented in some cases with invasion of the jaw bones ([Fig. 4](#)). The most common histopathological diagnosis was diffuse large B-cell lymphoma (DLBCL), accounting for 40.0% of all cases with documents of diagnosis ($n = 513$), followed by 72

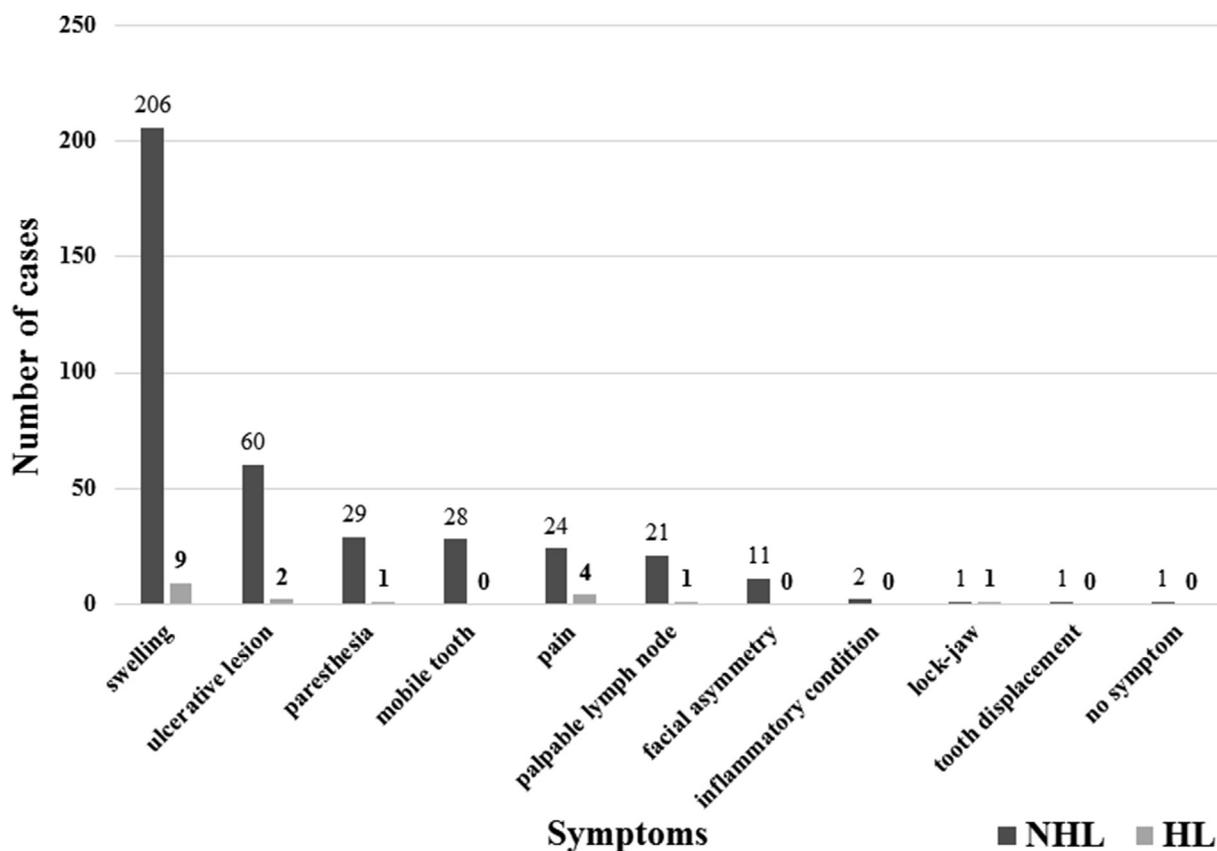


Figure 3 The number of cases of oral lymphoma with respect to symptoms in the current study. The most common symptoms of oral lymphoma included swelling, ulceration, paresthesia, pain and palpable lymph node. When the alveolar bone was involved, tooth displacement and hypermobile teeth may be noted. Values within the brackets represent the total number of cases.

cases (14.0%) of Burkitt lymphoma and 37 cases (7.2%) of T-cell lymphoma (Fig. 5).

In the NHL group, the data of further systemic survey before and/or after diagnosis of oral lymphomas were available in 90 cases. Forty-five cases (50.0%) showed other

extranodal lymphomas after the diagnosis of oral lymphoma, and 39 cases (43.3%) only present the oral involvement. The oral lymphomas in the remaining six cases (6.7%) were detected after the diagnosis of other extranodal lymphoma. For the eight cases of HL with data of

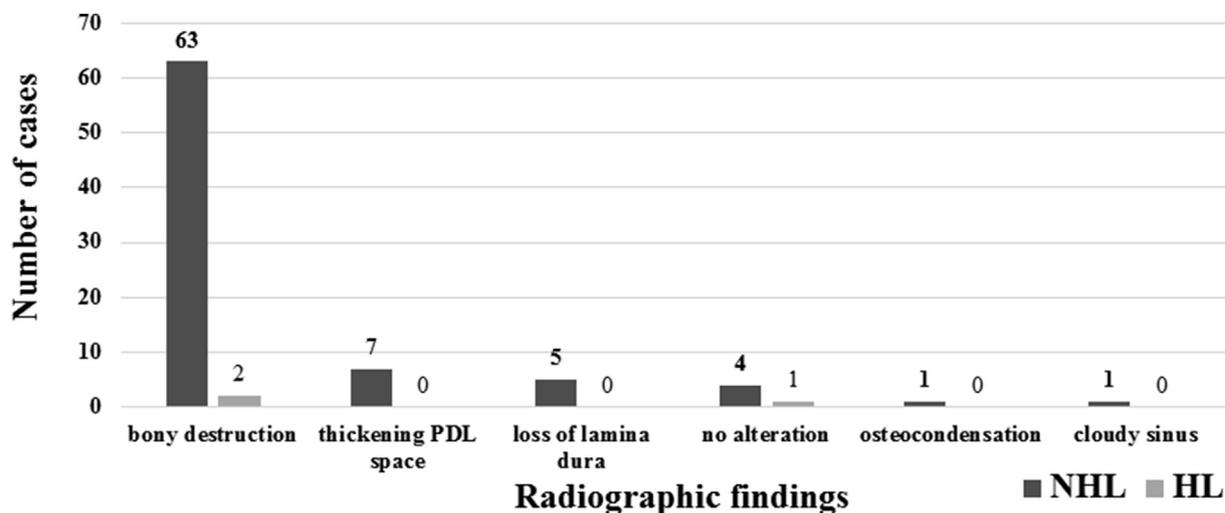


Figure 4 The number of cases of oral lymphoma with respect to radiographic findings in the current study. The most common radiographic finding was bony destruction. Loss of lamina dura and thickening of the periodontal ligament were also observed when the alveolar bone was involved. Values within the brackets represent the total number of cases.

systemic survey, five cases (62.5%) only occurred in the oral cavity. Other extranodal lesions were found after the presence of oral lymphomas in two cases, and one case was diagnosed with history of other extranodal HL.

For geographical and race distribution of NHL in the current study, there were 237 Americans (39.7%), 218 Asians (36.5%), 105 Caucasians (17.6%), and 37 (6.2) Africans; on the other hand, for HL, there were six Americans (60.0%), three Asians (30.0%), and one Caucasian (10.0%) but without African.

Fifteen patients with extranodal NHL of the oral cavity in our institution were enrolled in the study (Table 1, Supplementary Fig. 5) 10 males and 5 females. The patients ranged in age from 28 to 84 years, with a mean age of 56.7 years. The most prevalent site of involvement was the gingiva (7 cases), followed by the mandible (5 cases), maxilla (4 cases), buccal mucosa (3 cases), palate (3 cases) and vestibule (1 case). The initial symptoms included swelling (14/15, 93.3%), ulceration (3/15, 20.0%) and mobile tooth (1/15, 6.7%). Eight cases revealed bony destruction with an ill-defined border upon radiographic examination, and one case displayed loss of lamina dura. The histopathological types were as follows: DLBCL (5 cases); SLL (3 cases); BCL (2 cases); NK/T (2 cases); BL (1 case); MALT (1 case); and SCL (1 case).

For the 12 cases with records of previous and further examination in our institution, six cases (50%) only

presented in the oral cavity. Other extranodal lymphomas were identified later in four cases (33.3%). Two cases (16.7%) developed oral lymphoma after diagnosis of other extranodal lymphomas.

All cases were diagnosed in adjunct with a suitable panel of immunohistochemical markers. Nine cases had the treatment modalities using chemotherapy and/or radiotherapy in which four of them had been free of disease ranged from six to 13 years; however, five were expired soon after the treatment.

Discussion

The current study included 592 cases reported in 89 previously-published articles and 15 cases in our institution. The cases enrolled in this study strictly adhered to the definition of structures of the oral cavity in the AJCC 8th edition. The most frequently involved structure was the gingiva, followed by the palate, maxilla, mandible, tongue, buccal mucosa, vestibule, lip and floor of the mouth. Due to the adjacency between the gingiva, jaw bones and palate, these areas were often simultaneously involved in the tumors, which may be the reason for which the gingiva was the most frequently involved structure.

Among the 292 cases with definite records of the patient's age, the age distribution was wide-ranging (Fig. 1);

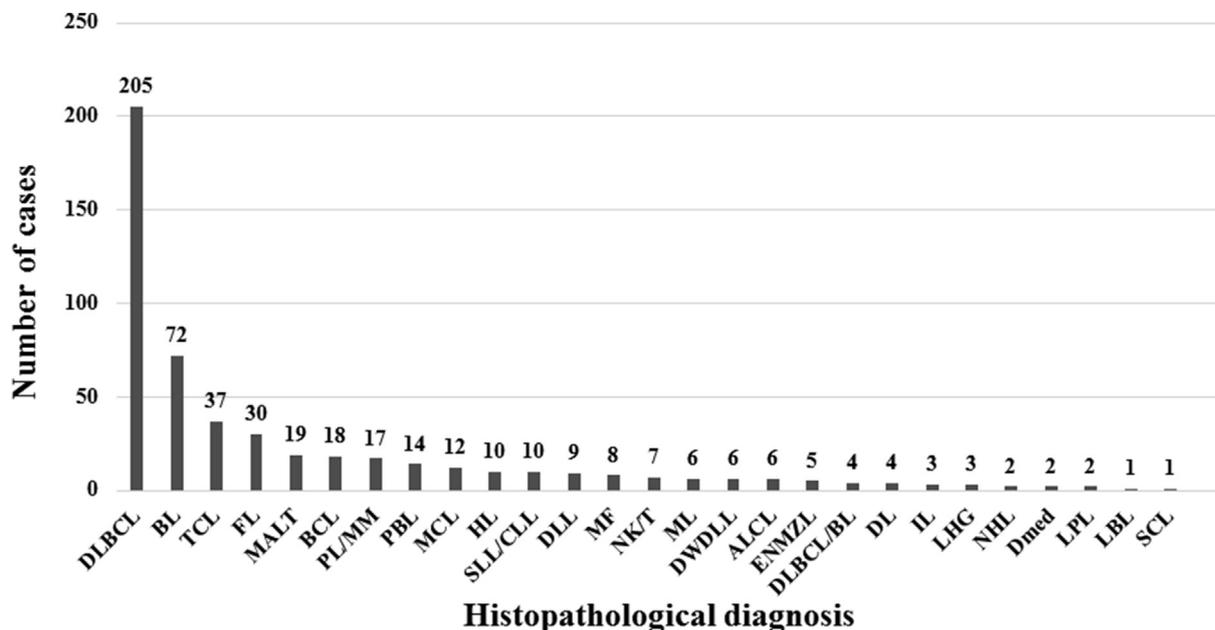


Figure 5 The number of cases of oral lymphoma with respect to histopathological diagnosis in the current study. The most common diagnosis was diffuse large B-cell lymphoma, which accounted for 40.0% of all cases with records of diagnosis. Values within the brackets represent the total number of cases. ALCL, anaplastic large-cell lymphoma; BCL, B-cell lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; DLBCL/BL, B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL; DL: diffuse lymphoma, large cell type; DLL, diffuse lymphoblastic lymphoma; DMed, diffuse lymphoma, medium-sized cell type; DWDL, diffuse well-differentiated lymphocytic lymphoma; ENMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; HL, Hodgkin's lymphoma; IL, immunoblastic lymphoma; LBL, lymphoblastic lymphoma; LHG, high-grade lymphoma B; LPL, lymphoplasmacytic lymphoma; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; MCL, mantle-cell lymphoma; MF, mycosis fungoides; ML, malignant lymphoma; NHL, non-Hodgkin lymphoma; NK/T, extranodal natural killer (NK)/T-cell lymphoma; PBL, plasmablastic lymphoma; PL/MM, plasmacytoma/multiple myeloma; SCL, small cell lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; TCL, T-cell lymphoma.

62.7% of patients were diagnosed in 5th to the 8th decade of life. The mean age of the patients in our institution was 56.7 years, which was slightly older than the mean age calculated from the 513 patients with reported age of occurrence in the literature (51.7 years), which may be due to the fact that quite a high proportion (27.1%) of patients below 18 years old were noted for the 277 patients with definite reported age of occurrence in the literature; however, a lack of specimens taken from patients below 18 years old were noted in our department.

Unlike patients with nodal HL and NHL or extranodal HL and NHL in other organs, who more frequently present with B symptoms (a fever greater than 38 °C; drenching night sweats; unintentional weight loss of at least 10% of their body weight over six months or fewer),⁸ patients with oral lymphoma (OL) seldom show B symptoms and mostly present with a swollen mass, followed by ulcerated lesions. Other clinical presentations include hypermobile tooth, paresthesia, pain, palpable lymph nodes, fascial asymmetry and inflammatory-like lesions. As is the case with the clinical appearance of oral lymphoma, the radiographic presentation of OL occurring in the jaw bones is unspecific. The most frequent appearance is an osteolytic lesion with an ill-defined border. These findings are similar to those of other diseases with bony involvement, such as osteomyelitis, a deep fungal infection, or malignant lesions such as squamous cell carcinoma or salivary gland neoplasm. Some cases in this study revealed widening of the periodontal ligament space^{9–14} and loss of the lamina dura^{10,13–15} as radiographic findings, which may mimic the presentation of advanced periodontal disease. Cases may also present with a periapical radiolucency resembling periapical lesions of endodontic origin on a periapical radiograph.^{9,16–18} Clinical oral practitioners should be alert to these radiographic changes and correlate the clinical findings with the radiographic findings. If the radiographic features do not conform to the clinical findings, a biopsy is required for proper diagnosis.

Extranodal HL primarily occur in the oral cavity are uncommon. Only 10 cases of HL involving the oral cavity were confirmed in the current study, indicating that the incidence of HL present in the oral cavity is extremely rare. Our finding concurs with a retrospective study of 3500 HL patients,¹⁹ in which only 34 cases originated in one or more sites of the head and neck area, most of these cases being located in Waldeyer's ring (which includes the nasopharynx, base of the tongue, faucial tonsils, oropharynx, and adenoids), and no cases were identified with tumors in the oral cavity. Furthermore, Iyengar et al.²⁰ reviewed 2006 cases of HL, and found that 269 cases had bone involvement, but only two involved jaw bones.

The most common diagnosis in the 513 cases with records of diagnoses was DLBCL (40.0%), similar to the results of previous case series. DLBCL is also the most frequently diagnosed type of NHL in the whole body, accounting for 30–40% of reported cases in different geographic regions. About 40% of patients present with extranodal disease, and the most common site of involvement is the

gastrointestinal tract.²¹ The clinical appearance of DLBCL is non-specific, most commonly presenting as a painless swollen mass. The prevalence of DLBCL is increased in elderly patients, being on average most common in the 7th decade of life. In the oral cavity, DLBCL affects both the osseous and soft tissue, including the jaw bones, gingiva, vestibule, palate and buccal mucosa. Currently, the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) is the standard therapy for patients with DLBCL, which has a 60–70% cure rate.²¹

Epidemiologic investigation revealed that human cancers such as HL, NHL, Kaposi's sarcoma, and cancer of the liver, stomach, cervix, vagina/vulva, penis, anus, oral cavity and pharynx, skin, lip, esophagus, larynx, trachea/bronchus/lung, eye and kidney occur more frequently in immunosuppressed individuals.²² The immunocompromised condition leads to breakage of immune surveillance against human oncogenic viruses. Among these known oncogenic viruses, the Epstein-Barr virus (EBV) was found to play a causative role in the development of nasopharyngeal cancer, endemic BL, immune suppression-related NHL, extranodal NK/T-cell lymphoma (nasal type) and a subset of HL.²³ NHL was found to be the most common malignant tumor related to the human immunodeficiency virus (HIV), followed by Kaposi's sarcoma.²⁴ Among the 607 reviewed cases in the present study, 25 cases were immunocompromised patients comprising one case of renal transplant recipient and 24 cases of AIDS patients. The data of specific diagnosis were available in 16 cases of the AIDS patients, including five cases of PBL,^{24–28} four cases of DLBCL,^{29,30} three cases of BL,^{10,31} two cases of IL,^{32,33} and one case each of HL³⁴ and non-classified NHL.³⁵ The mean age of diagnosis of these 16 AIDS patients was 37.0 years, which has been about 15 years younger than those immunocompetent patients (mean: 52.2 years).

Although the number of new HIV infections has decreased from 2010 to 2016 according to UNAIDS data, the number of patients living with HIV has still increased. Guevara-Canales et al.⁸ showed that the presence of previous HIV and EBV infections was related to a lower overall survival. The presence of OL can be an initial manifestation of HIV infection. Careful evaluation and knowledge of HIV-related malignancies could improve the possibility of early diagnosis and the patient outcome in terms of survival.

From the current 607 reviewed cases, 110 cases had records of previous history and further systemic survey. Other extranodal lymphomas were identified after oral diagnoses in 46.4% of these cases ($n = 51$), which reflects that the involvement of oral cavity represents part of a disseminated disease.

In conclusion, the current study collected the clinical features, radiographic appearance, and histopathological diagnosis in 607 cases of OL from published articles and our institution. Although extranodal lymphomas occurring in the oral cavity are uncommon, their presence may be a part of a disseminated disease. Detailed history-taking, clinical and imaging examination and awareness of the patient's signs and symptoms are crucial for early diagnosis and an improved prognosis.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

Acknowledgement

The authors thank the help from the Division of Medical Statistics and Bioinformatics, Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jfma.2020.05.025>.

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