Medical Molecular Morphology (2019) 52:123–134
https://doi.org/10.1007/s00795-018-0210-2

REVIEW

Oral lymphoid lesions: a 47-year clinicopathological study in a Brazilian population

Juliana Campos Pinheiro[1] · Caio César da Silva Barros[1] · Larissa Santos Amaral Rolim[1] · Leão Pereira Pinto[2] · Lélia Batista de Souza[2] · Pedro Paulo de Andrade Santos[3]

Received: 25 September 2018 / Accepted: 25 October 2018 / Published online: 31 October 2018
© The Japanese Society for Clinical Molecular Morphology 2018

Abstract

We performed an epidemiological, clinical and histopathological analysis of oral lymphoid lesions (OLLs) during a 47-year period. Data regarding patient age, sex, duration, location, symptomatology, type of growth, implantation, staining, presence of ulceration and bleeding of all cases were compiled from the clinical data. For the histopathological analyses, all slides stained by H/E were reassessed. During the analyzed period, 14,565 patients with oral and maxillofacial lesions were diagnosed, with 45 cases diagnosed as OLLs. The most prevalent location was the tongue. Females were more affected, and the mean age was 40.8 years. OLLs presented a heterogeneous frequency, with the prevalence of reactive lesions (42.3%) followed by developmental lesions (35.6%). Among the reactive lesions, foreign body granulomas were the most common. Regarding diagnosed neoplasms, malignant represented 13.2% of the cases. The average time of evolution of OLLs in general was of 22.2 months. Regarding the histopathological characteristics, the presence of primary lymphoid follicles was observed in 37.8% of the cases, while inflammatory infiltrates were diffuse in 66.7% and epimyoepithelial islands were observed in 13.3%. Our study concludes that OLLs involves a broad spectrum of lesions that share the presence of the lymphoid component, which can range from indolent to more aggressive behavior.

Keywords Lymphoid lesions · Lymphoid neoplasms · Lymphoid tissue · Lymphoma

Introduction

The oral cavity, in addition to the nasopharynx and ocular conjunctiva, are gateways for different types of antigens to enter the head and neck region. This region is rich in strategically positioned lymphoid tissue, composing a chain of multiple regional lymph nodes, in addition to mucosal associated lymphoid tissue (MALT), which plays a role in surveying and eliminating potentially dangerous antigens [1].

OLLs represent a broad spectrum of disorders, encompassing developmental, reactional, benign and malignant neoplasms. In most cases, lymphocytic infiltrates are the major components of the disease [2–5].

Many reactional conditions that affect lymphoid tissue may mimic neoplasms, and it is relatively difficult to distinguish between benign and malignant lymphoid neoplasms in the head and neck region [1]. Thus, a careful clinical examination is required to identify suspicious lesions, establishing an early diagnosis for better patient prognosis [4, 5].

The most frequent OLL appearance sites in the oral cavity are the jugal mucosa, palate, salivary glands, peritonsillar region and regional lymph nodes [4, 5]. Among the main OLLs, oral lymphoepithelial cysts, benign lymphoid hyperplasias, chronic sclerosing sialodenites, lymphomatous papillary cystadenomas and Hodgkin's and non-Hodgkin's lymphomas are noteworthy [2–5].

Considering the diagnostic difficulty and the scarce amount of investigations on OLLs, the aim of the present study was to verify the prevalence of OLLs diagnosed during 47 years in a pathological anatomy service, emphasizing

✉ Pedro Paulo de Andrade Santos
ppdasantos@gmail.com

[1] Oral Pathology Post-Graduation Program Student, Federal University of Rio Grande do Norte, Natal, RN, Brazil

[2] Oral Pathology Post-Graduation Program, Dentistry Department, Federal University of Rio Grande do Norte, Natal, RN, Brazil

[3] Oral Pathology Post-Graduation Program, Morphology Department, Federal University of Rio Grande do Norte, Natal, RN, Brazil

their epidemiological, clinical and histopathological characteristics.

Materials and methods

The study protocol was approved by the Ethics Committee of the Federal University of Rio Grande do Norte (UFRN) (Number 1.883.170). The inclusion criteria were all cases of oral lymphoid lesions diagnosed between January 1969 and December 2016, selected for this study among 14.000 oral lesions diagnosed in the Oral Pathology Service files at UFRN. This service is one of the referral centers in oral and maxillofacial pathology in Brazil and the main center in the state of Rio Grande do Norte. Data regarding patient age, sex, duration, location, symptomatology, type of growth, implantation, staining, presence of ulceration and bleeding of all cases were compiled from the clinical data sent together with the biopsy records.

For histopathologic analysis, all slides containing hematoxylin/eosin-stained 5-µm-thick sections were reassessed. Under light microscopy (Olympus CX31; Olympus Japan Co., Tokyo, JPN), oral lymphoid lesions were histologically reviewed by two previously trained examiners. Regarding histological findings, the presence or absence of primary and/or secondary lymphoid follicles, type of inflammatory infiltrate (diffuse or local) and the presence or absence of epi-myoepithelial islands were analyzed.

The data were tabulated and analyzed by descriptive statistics using the IBM SPSS Statistics (version 20.0; IBM Corp., Armonk, NY, USA).

Results

During the assessed period, 14,565 patients with oral and maxillofacial lesions were diagnosed. Of these, 45 cases were reassessed and characterized as OLL, with lymphocytic infiltrates as the main component.

The most prevalent anatomical location was the tongue, at 24.4%, followed by the lip (15.6%) and the mandible (11.1%). Twenty-four cases (53.3%) were asymptomatic and 20 (44.5%) presented as exophytic growth lesions, while 30 presented with sessile implantation (66.7%). Ten cases (22.2%) presented normochromic staining, while 77.8% of the lesions showed no ulceration at the time of the first consultation. Only one case showed evidence of bleeding (Table 1). Regarding gender, females were the most affected (64.4%), at an F:M ratio of 1.8:1 and a mean age of 40.8 (Table 2).

OLLs presented a heterogeneous frequency, with the prevalence of reactive lesions (42.3%), followed by developmental lesions (35.6%). Among the reactive lesions, foreign body type granuloma was the most common (17.9%), followed by benign lymphoid hyperplasia (8.9%), while oral lymphoepithelial cyst, the only developmental lesion, corresponded to 16 (35.6%) of the 45 cases (Table 2). Regarding non-neoplastic epithelial lesions, only one case was

Table 1 Distribution of clinical aspects in oral lymphoid lesions

Clinical aspects	*n*	%
Anatomical site		
Tongue	11	24.4
Lip	7	15.6
Mandible	5	11.1
Palate	4	8.9
Floor of mouth	3	6.7
Inferior vestibule	2	4.4
Others	7	17.8
NI	5	11.1
Symptomatology		
Asymptomatic	24	53.3
Symptomatic	6	13.4
NI	15	33.3
Type of growth		
Exophytic	20	44.5
Endophytic	8	17.8
Exo and endophytic	1	2.2
Others	6	13.3
NI	10	22.2
Implantation		
Sessile	30	66.7
Pedunculated	3	6.7
Intraosseous	1	2.2
NI	11	24.4
Staining		
Normochromic	10	22.2
Red	8	17.8
Yellowish	7	15.7
White	3	6.7
Brownish	2	4.4
Pink	2	4.4
Violaceous	2	4.4
Black	1	2.2
NI	10	22.2
Ulceration		
Presence	0	0
Absence	35	77.8
NI	10	22.2
Bleeding		
Presence	1	2.2
Absence	17	37.8
NI	27	60.0

NI not informed, *n* number of cases, % percentage

Table 2 Number of cases, age, duration and sex distribution

Lesion	*n* (%)	Mean age (years)	Mean duration (months)	Sex	
				Female *n* (%)	Male *n* (%)
Reactive/lymphoid-like lesion	19 (42.3)	40.4	26.1	11 (57.8)	8 (42.2)
Foreign body granuloma	8 (17.9)	45.5	30.5	5 (62.5)	3 (37.5)
Folicular lymphoid hyperplasia	4 (8.9)	43	10	4 (100)	0
Lymph node hyperplasia	3 (6.7)	24.6	25.6	2 (66.7)	1 (33.3)
Chronic sclerosing sialadenitis	2 (4.4)	56.5	NA	0	2 (100)
Angiolymphoid hyperplasia with eosinophilia	1 (2.2)	50	84	0	1 (100)
Eosinophilic granuloma	1 (2.2)	8	1	0	1 (100)
Developmental lesion	16 (35.6)	46	28	13 (81.2)	3 (18.8)
Oral lymphoepithelial cyst	16 (35.6)	46	28	13 (81.2)	3 (18.8)
Non-neoplastic lymphoepithelial lesion	1 (2.2)	54	3	1 (100)	0
Benign lymphoepithelial lesion	1 (2.2)	54	3	1 (100)	0
Benign neoplasm	3 (6.7)	51.3	16	2 (66.7)	1 (33.3)
Warthin tumor	3 (6.7)	51.3	16	2 (66.7)	1 (33.3)
Malignant neoplasm	6 (13.2)	18.6	4.5	2 (33.3)	4 (66.7)
Non-Hodgkin lymphoma	2 (4.4)	27	NA	1 (50)	1 (50)
Burkitt lymphoma	2 (4.4)	6.5	1.5	NA	2 (100)
Unclassified lymphoma	2 (4.4)	26.5	6.2	1 (50)	1 (50)
Total	45 (100)	40.8	22.2	29 (64.4)	16(36.6)

n number of cases, % percentage, *NA* not available

diagnosed as a benign lymphoepithelial lesion (2.2%). Malignant neoplasms represented 13.2% of the total cases, with Burkitt's lymphoma and Non-Hodgkin's lymphoma corresponding to 4.4% of the cases. Benign neoplasms accounted for 6.7% of the cases and all were diagnosed as papillary lymphomatous cystadenoma (Whartin's tumor). Regarding gender, females were more affected by reactive lesions, developmental lesions, non-neoplastic lymphoepithelial lesions and benign neoplasms, while malignant neoplasms were more prevalent in males (Table 2).

The mean time for OLL evolution was approximately 22.2 months: 4.5 months for malignant neoplasms and 16 months for benign neoplasms (Table 2).

Concerning histopathological characteristics, the presence of primary lymphoid follicles was observed in 15.6% of the cases, while secondary follicles with evidence of germinal centers were present in 37.8% of the lesions. Inflammatory infiltrates were diffuse in 30 cases (66.7%), while only 3% of the cases presented epimyoepithelial islands (Table 3).

Discussion

In the daily practice of pathology, it is common to microscopically analyze biopsies from the head and neck region to verify the presence of lymphoid tissue, which may be either a normal component of the region, a lymphoid hyperplasia or a malignant neoplasia. In some cases, molecular studies, immunophenotyping and hematopathological consultations may be required for the detection of possible lymphoproliferative disorders. Regarding benign processes, it is important to investigate possible relationships with viral infections, autoimmune diseases and exposure to drugs/toxins or unidentified etiologic agents [1].

Few studies have attempted to classify oral lymphoid lesions, so we can highlight the studies by Jaffe [6], Doyle et al [7], Seifert [8] and Ellis [2] involving lymphoid lesions of salivary glands and, according to the analysis of these previous studies, we can categorize OLLs into 5 groups: reactive lesions, developmental lesions, non-neoplastic lymphoepithelial lesions, benign and malignant neoplasms. In the present study, 45 OLLs cases were identified, with the prevalence of reactive lesions (42.3%), followed by developmental lesions (35.6%), both of which were more prevalent in women. Regarding neoplasias, benign lesions presented a frequency of 6.7% when compared to the other detected lymphoid lesions, again more prevalent in women (66.7%), with an average lesion duration of 16 months, whereas malignant neoplasias presented a frequency of 13.2%, but were more prevalent in men (66.7%) and of shorter duration, of about 4.5 months compared to the non-neoplastic epithelial lesion group. Only one case (2.2%) of a benign lymphoepithelial lesion was identified (Table 2).

Concerning reactive lesions, foreign body granulomas (FBG) are characterized by a local inflammatory response in tissues, induced both by trauma related to surgical

Table 3 Morphological features of oral lymphoid lesions

Lesion	Primary lymphoid follicle		Secondary lymphoid follicle		Diffuse inflammatory infiltrate		Local inflammatory infiltrate		Epi-myoepithelial islands	
	Presence *n*	Absence *n*	Presence *n*	Absence *n*	Presence *n*	Absence *n*	Presence *n*	Absence *n*	Presence *n*	Absence *n*
Reactive/ lymphoid-like lesion										
Foreign body granuloma	0	8	1	7	4	4	3	5	0	8
Foliculary lymphoid hyperplasia	2	2	1	3	2	2	2	2	0	3
Lymph node hyperplasia	0	3	3	0	2	1	1	2	0	2
Chronic sclerosing sialadenitis	1	1	0	2	1	1	1	1	0	1
Angiolymphoid hyperplasia with eosinophilia	0	1	1	0	1	0	0	1	0	1
Eosinophilic granuloma	0	1	0	1	1	0	0	1	0	1
Developmental lesion										
Oral lymphoepithelial cyst	2	14	10	6	11	5	4	12	0	16

Table 3 (continued)

Lesion	Primary lymphoid follicle		Secondary lymphoid follicle		Diffuse inflammatory infiltrate			Local inflammatory infiltrate		Epi-myoepithelial islands	
	Presence *n*	Absence *n*	Presence *n*	Absence *n*	Presence *n*	Absence *n*		Presence *n*	Absence *n*	Presence *n*	Absence *n*
Non-neoplastic lymphoepithelial lesion											
Benign lymphoepithelial lesion	0	1	1	0	1	0	0	1		1	0
Benign neoplasm											
Warthin tumor	0	3	0	3	1	2	2	1		0	0
Malignant neoplasm											
Non-Hodgkin lymphoma	1	1	0	2	2	0	0	2		0	2
Burkitt lymphoma	1	1	0	2	2	0	0	2		0	2
Unclassified lymphoma	0	2	0	2	2	0	0	2		0	2
Total *n* (%)	7 (15.6)	38 (84.4)	17 (37.8)	28 (62.2)	30 (66.7)	15 (33.3)	13 (28.9) 32 (71.1)			1 (3) 38 (97)	

n number of cases, % percentage

implantation and the presence of biomaterials [9]. According to Seifert [8], FBG does not present features typical of a purely lymphoid lesion, it can be categorized as a lymphoid-like lesion. In the present study, this was the most frequent lesion in women, at 62.5%, mainly related to the use of cosmetic filling materials such as hyaluronic acid gel, collagen gel, silicone oil, polyacrylamide gel, calcium hydroxylapatite (CHA) and poly-L-lactic acid (PLA), and was present on the lips in 50% of the cases, mean age of 45 years, asymptomatic in 55.5% cases and with clinical presentation of fibrotic nodular type in 66.6%. This is in accordance with Shahrabi-Farahani et al. [10] and Owosho et al. [11]. Histopathologically, the presence of macrophages that act on the phagocytosis of exogenously implanted material was observed. During this process, macrophages acquire a similar morphology to epithelial cells and are named epithelioid cells. Several multinucleated giant cells develop from the fusion of macrophages, presenting themselves dispersed in the mass of epithelioid cells. An infiltrate of chronic inflammatory cells, represented by lymphocytes, involves this epithelioid nodule and acts on the secretion of cytokines responsible for macrophage activation [12]. These histopathological findings were verified in the 8 FBG cases detected herein (Fig. 1a). One case also presented with a secondary lymphoid follicle, four cases with diffuse inflammatory infiltrate and three cases showed a local inflammatory process (Table 3).

Another condition, follicular lymphoid hyperplasia (FLH), also known as benign lymphoid hyperplasia, lymphoid reactive hyperplasia or pseudolymphoma, is a rare

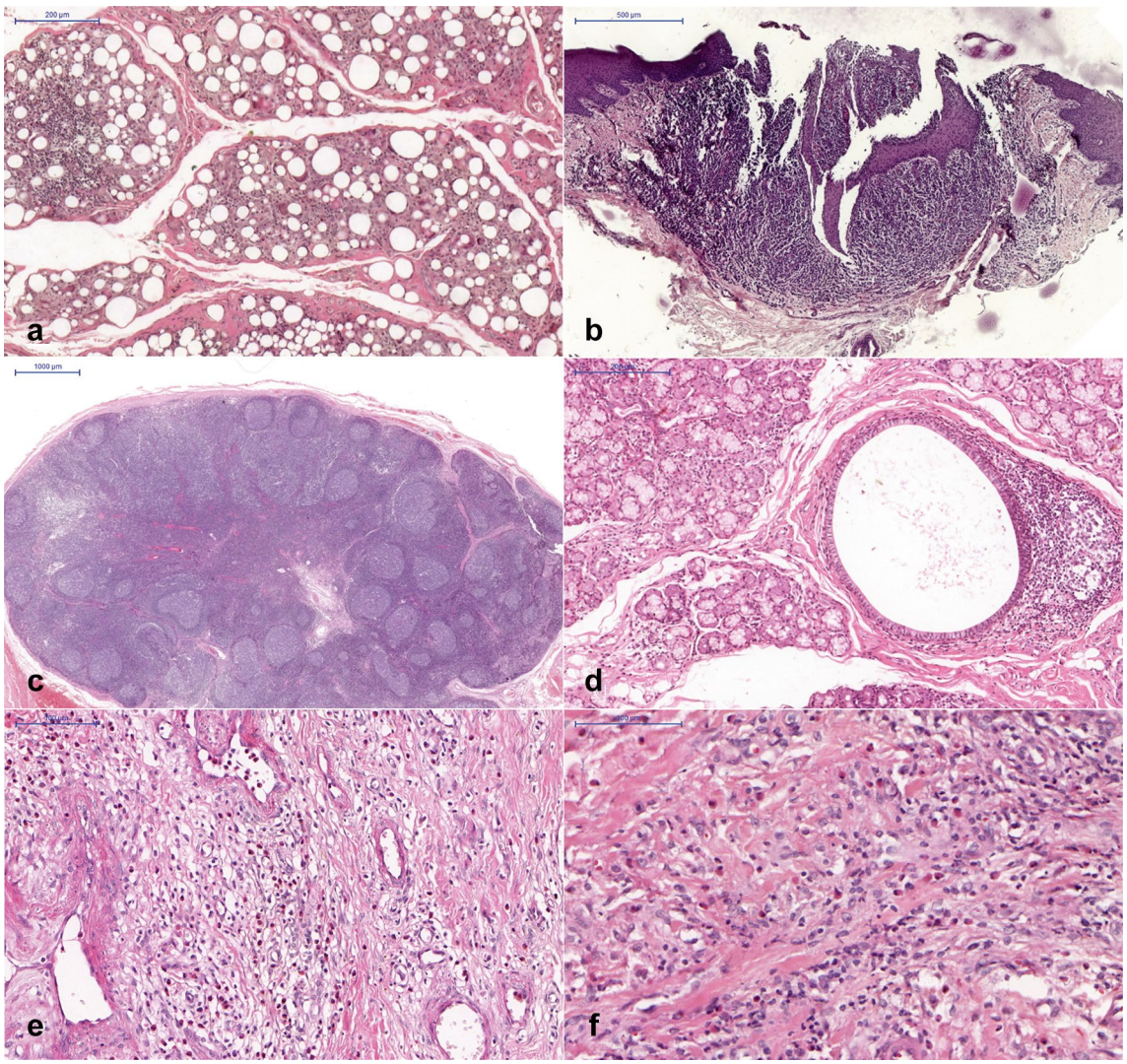

Fig. 1 Histopathologic analysis of foreign body granuloma (**a**), follicular lymphoid hyperplasia (**b**), lymph node hyperplasia (**c**), chronic sclerosing sialadenitis (d), angiolymphoid hyperplasia with eosinophilia (**e**) and eosinophilic granuloma (**f**) (hematoxylin–eosin stain; Pannoramic Viewer)

benign proliferative process that has been described as occurring in several regions of the body, such as the skin, gastrointestinal tract, lungs, nasopharynx, larynx, breasts, and only rarely involving the oral cavity [5]. In the oral cavity, lymphoid tissue proliferation occurs in response to antigenic agents with consequent development of FLHs that are clinically presented as firm, well-delimited, usually non-ulcerated, asymptomatic and slow-growing volume increases [13]. In the present study, all FLH cases (Fig. 1b) occurred in females (four cases) at around 43 years old, involving the palate in 50% of the cases, with a mean lesion evolution time of around 10 months (Table 2). The same prevalence for females was evidenced in a review by Taguchi et al. [14] that analyzed 51 liver FLH cases, and by Anjomshoaa et al. [13], which investigated 19 palate FLH cases. In both studies, the mean age of the affected patients was higher than that observed in the present study, of 58.9 years for liver FLH and 60.7 years for palate FLH. In another review involving only palate FLH cases, the mean duration of the lesion was 9.7 months [15], a mean close to that observed in the present study. With respect to the histopathological characteristics, we observed the presence of a primary lymphoid follicle in two cases (50%), followed in only one case of secondary lymphoid follicle (25%), regarding the distribution of the infiltrate to the contrary, we observed in two cases (50%). A diffuse inflammatory infiltrate and a local inflammatory infiltrate were also found in two cases (50%). The findings were in concordance with the findings of Jham et al. [5] and Kolokotronis et al. [15], who described that it is usually composed of multiple germinal centers, with a rim of well-differentiated B lymphocytes. A mixed, mainly mononuclear inflammatory infiltrate with many plasmacytoid lymphocytes may also be seen. Frequently, the microscopic pattern is classic and causes no difficulties in the diagnosis.

Lymph node hyperplasia (LH) is characterized by increased lymphoid follicle size, exhibiting well-developed germinal centers, and secondary organ enlargement due to follicular lymphoid hyperplasia. It may be difficult for the pathologist to distinguish between follicular hyperplasia and lymphoma, because of the wide variety of follicular hyperplasias in the lymph node [16]. Due to this diagnosis difficulty, Villa et al. [17] performed a cytogenetic analysis in two cases histopathologically diagnosed as reactional lymph node hyperplasia. In both cases, chromosomal clonal abnormalities were found in non-neoplastic cells, raising doubts about the meaning of these alterations. One of the lymph node hyperplasias was defined as a pre-lymphoma condition and the other identified as a residual patient lymphoma cell site, with patient monitoring necessary due to the risk of progression to lymphoma. In the present study, the three cases diagnosed as LH (Fig. 1c) presented secondary lymphoid follicles with well-developed germinative centers (Table 3), compatible with the findings reported by Kojima et al. [16]. Regarding epidemiological characteristics, two cases were identified in women (66.7%) and one in men (33.3%), with a mean age of 24.6 years and lesion duration around 24.6 months (Table 2). This finding in younger people was also evidenced by Kojima et al. [16], in which patient age was at average 24 years in 14 LH cases, but with a higher frequency in men.

Chronic sclerosing sialodenitis (CSS), also known as "Küttner's tumor" [18], is an inflammatory disease that affects the salivary glands, with the submandibular gland being the most commonly affected. It is now known that this lesion is part of an alteration known as multifocal fibrosclerosis disease, related to Ig-4. In histopathological examinations, acinar atrophy with a lymphocytic infiltrate and a dense fibrosis area are observed. According to these findings, chronic sclerosing sialodenitis may present as four degrees of severity: Grade 1—focal sialoadenitis; Grade 2—diffuse lymphocytic sialoadenitis with glandular fibrosis; Grade 3—chronic sclerosing sialoadenitis with glandular sclerosis; and Grade 4—chronic progressive sialoadenitis with "cirrhosis" sclerosis of the salivary glands [19]. In the present study, only two cases of CSS were observed, located on the floor of the mouth, in male patients with an average age of 56.5 years (Table 2). According to the findings reported by Chang et al. [18], 21 CSS cases were observed, predominantly affecting men with mean age above 54 years. However, reports of this condition in younger patients are also available, as described by Gontarz et al. [20], in a 30-year-old patient, and by Melo et al. [21], in an 11-year-old child.

Regarding the histopathological analysis of CSS cases (Fig. 1d) and taking into account the degrees of severity described by Adouly et al. [19], one of the lesions observed in the present study was categorized as belonging to Grade 1 and the other to Grade 2. Metaplasia with ductal proliferation was also evidenced.

Angiolymphoid hyperplasia with eosinophilia (AHE) is a rare disease, and was observed herein in only one case, in a male patient (100%), mean age of 50 years with duration of about 84 months. Guinovart et al. [22] describe this lesion as being an unusual benign disorder, with uncertain pathogenesis, although it is considered a reactive disorder induced by various stimuli, such as vascular malformations, trauma and pregnancy. Clinically, it presents as nodular formations of varied staining located predominantly in the head and neck region [23]. Histopathologically, AHE presents as endothelial cells with a rounded morphology and abundant cytoplasm that surrounds the numerous vascular spaces present in the lesion, as well as the presence of a significant inflammatory component composed of lymphocytes, plasmocytes and numerous eosinophils (Fig. 1e). Due to these characteristics, it is also called epithelioid hemangioma [24].

Eosinophilic granuloma (EG) is a rare disease in the head and neck region characterized by an abnormal

proliferation of Langerhans cells, also known as Langerhans cell histiocytosis (previously known as histiocytosis X). Lichtenstein [25] gave a common terminology histiocytosis X for the triad of eosinophilic granuloma, Hand–Schuller–Christian, and Letterer–Siwe disease. A variable number of leukocytes, eosinophils, neutrophils, lymphocytes, plasma cells and multinucleated giant cells are present in these lesions, causing tissue destruction [26]. EG was described by Lichtenstein and Jaffe [27], who categorized the condition into three clinical forms, taking into account patient age when the first lesion appeared and lesion distribution as follows: chronic focal EG; chronic diffuse EG and acute disseminated EG, the latter being the fatal form. Angelini et al. [28] pointed out that EG affects children and adolescents in 80% of cases, can affect any bone in the skeleton and presents uncertain pathogenesis. Viruses, such as Epstein–Barr, human herpesvirus 6 (HHV-6), bacteria and genetic factors have been implicated in this condition. In the present study, only one case of EG was identified, with 1 month duration in an 8-year-old male patient, located in the lower retro-molar region, with 1 month of evolution and symptomatic and sessile implantation, evidencing the condition in young patients as described in the literature. Categorizing the case according to the Lichtenstein and Jaffe [27] criteria, the identified case was classified as chronic focal EG (Fig. 1f).

An unusual cystic lesion found in the present study was oral lymphoepithelial cyst (OLEC). This is an uncommon developmental lesion, often discovered during routine examinations. It clinically presents as a dome-shaped lesion, with a non-ulcerated surface, exhibiting a coloration ranging from rosy yellow to white and a cheese-like consistency when palpated. It mainly affects men in the 4th decade of life [29]. Of the 16 OLEC cases identified herein, 13 (81.2%) were present in females and three (18.8%) in males (Table 2), on the tongue in 56.25% of the cases, in agreement with the study performed by Sykara et al. [30]. The mean age in the present study was of 46 years, similar to that reported by Khelemsky and Mandel [29].

With regard to the etiopathogenesis of these lesions, the widely accepted theory is the one proposed by Knapp [31], which states that OLECs are actually pseudocysts that do not arise from lymph nodes, but originate instead from lymphoid aggregates located in the submucosa of the buccal floor, ventral surface of the tongue and soft palate. Microscopically, OLECs are characterized by the presence of a cystic cavity containing keratin that is circumscribed by a parakeratinized stratified squamous epithelium that exhibits a flat interface with the lamina propria, and a usually thick capsule presenting large numbers of lymphocytes arranged in lymph nodes, sometimes presenting germinal centers [32]. Herein, the typical characteristics of these lesions were noted during the histopathological findings of the present study (Fig. 2a) and the presence of germinal center lymphoid follicles was verified in ten cases (Table 3).

Benign lymphoepithelial lesion (BLEL), also known as lymphoepithelial sialoadenitis, lymphoepithelial lesion, myoepithelial sialoadenitis or Sjögren sialoadenitis, is considered an autoimmune disease, and approximately 50–84% of BLEL patients may manifest clinical characteristics of Sjögren's syndrome (SS), increasing the risk of developing lymphomas [33]. BLEL, also known as Mikulicz's disease, was originally defined as a bilateral asymptomatic increase of the submandibular, parotid and lacrimal glands [34]. The underlying conditions were shown to be heterogeneous, such as SS, which is considered the main cause of BLEL due to the histopathological similarities between the two disorders. However immunohistochemical studies have indicated that a prominent IgG-4 positive plasmacytic infiltrate in salivary and lacrimal glands is pathognomonic for BLEL [36]. Histopathologically, this condition is characterized by marked lymphocytic infiltration with the presence of epimyoepithelial islands (consisting of hyperplastic and metaplastic ducts) and acinar degeneration [33]. These characteristics were verified in the present analysis of this type of lesion (Fig. 2b), and the presence of lymphoid follicles with evidence of germinal centers was also observed (Table 3). In the present clinical epidemiological survey, only one case of BLEL was detected, in a 54-year-old female patient with a lip lesion lasting 3 months, with no clinical relation to SS (Table 2). This case is similar to that described in the literature, since it affects predominantly middle-aged and female adults [36].

Warthin's (WT) tumor, also known as papillary lymphomatous cystadenoma, is a lesion that affects the parotid gland and rarely involves extraparotid sites, including submandibular, sublingual and minor salivary glands, nasopharynx, larynx and cervical lymph nodes [37]. With regard to the involvement of minor salivary glands in WT, an analysis of 22 case reports between 1960 and 2011 indicated a higher prevalence of this condition in the jugal mucosa, hard palate and lip [38]. In the present study, the three identified WT cases were related to minor salivary glands located on the hard palate, lower lip and vestibule fundus.

Historically, it has been conceptualized that WT is a neoplasm that develops in salivary ducts confined within lymphoid tissue, and the most widely accepted explanation is that it is a metaplastic process with abundant secondary reactive lymphoid tissue [2, 37]. A critical examination of the lymphoid component is important, since the literature reports mantle lymphoma arising from the lymphoid stroma of a WT [39]. This lesion is more prevalent in men, but there is a progressive change in gender distribution, with a higher peak in men around the 7th decade of life, while in women the peak occurs during the 6th decade [37], due

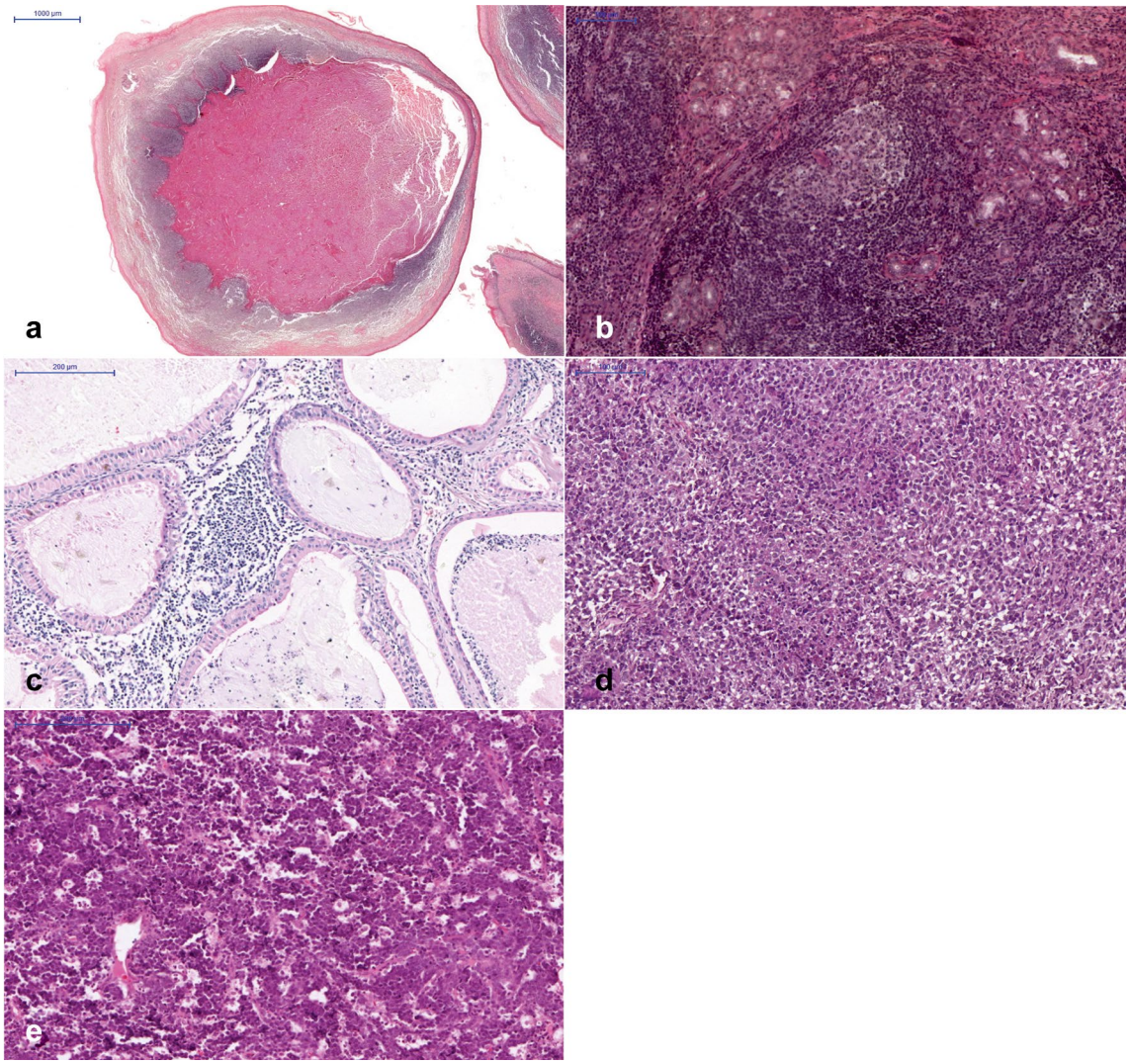

Fig. 2 Histopathologic analysis of oral lymphoepithelial cyst (**a**), benign lymphoepithelial lesion (**b**), Warthin tumor (**c**), non-Hodgkin lymphoma (**d**) and Burkitt lymphoma (**e**) (hematoxylin–eosin stain; Pannoramic Viewer)

to an increase in the population of women smokers, since smokers are eight times more likely to develop WT [2]. This fact was evidenced in a study on WT in the USA, in which 90% of the cases were associated with smoking [40]. In the present study, this condition was detected in two females (66.7%) and one male (33.3%), mean age of occurrence of 51.3 years, with an average evolution time of 16 months, with all patients presenting smoking habits. These findings corroborate the progressive change in sex distribution described previously, indicating a greater involvement of women and a correlation with smoking. With regard to age, the male patient was 63 years old and the female patients were 60 and 31 years old, demonstrating that younger people may eventually present with this condition (Table 2).

Histopathological WT characteristics include the presence of an epithelium of oncocytic nature, forming uniform columns of cells that surround the cystic spaces. These cells display an eosinophilic, slightly granular cytoplasm arranged in a double layer, the inner luminal layer, consisting of high columnar cells with a central nucleus, slightly hypercorated and palisade. Below this epithelium is a second layer of cuboidal cells with a more vesicular nucleus and the presence of numerous papillary projections projecting into the cystic spaces. This epithelium is maintained by a lymphoid stroma that frequently exhibits the presence of germinal centers [39]. In the histopathological analysis of the detected WTs, typical characteristics of the epithelial component were observed (Fig. 2c), although a more focal lymphoid stroma without evidence of lymphoid follicle formation was also verified (Table 3).

Non-Hodgkin's lymphomas (NHL) have a wide histopathological and clinical presentation, making diagnosis

difficult. This condition originates predominantly from B lymphocytes (85–90% of cases), while the others originate from T or NK lymphocytes. This diverse group of malignancies usually develops within the lymph nodes, but may occur in almost all tissues, ranging from an indolent to a more aggressive follicular lymphoma, such as large B-cell lymphoma and Burkitt's lymphoma [41].

In addition to age, several other risk factors are associated with NHL, such as primary or acquired immunodeficiency; autoimmune diseases (Sjögren's syndrome, systemic lupus erythematosus, among others); Infectious agents (EBV associated with African Burkitt's lymphoma, HHV8 associated with Kaposi's sarcoma, HCV, *H. Pilori* associated with peptic ulcer or gastric MALT lymphoma), exposure to harmful chemical agents and hereditary factors. Chromosomal translocations also play a crucial role in NHL pathogenesis, determining the activation of oncogenes or inactivating tumor suppressor genes, triggering a disorder in the genomic rearrangement mechanism of lymphoid cells [42].

Clinically, NHL occurs primarily in adults, although children are also affected. The condition develops most commonly in lymph nodes, but can also be observed in so-called extranodal lymphomas. In the oral cavity, lymphoma usually presents in soft tissues as a painless and diffuse volume increase that most commonly affects the oral vestibule, posterior hard palate and gingiva [43]. When this condition affects the bone tissue, mild pain or discomfort can arise, sometimes mimicking a periapical lesion [44]. Ferlay et al. [45], on the number of NHL cases for 2012 in Europe, estimated higher incidence and mortality of this condition in men. On the other hand, a study by Fetica et al. [46] on NHL in Romania indicated a slight preference for females (52.7%) compared to males (47.3%). In addition, 47.4% of the cases occurred in patients over 60 years old, and an increase in the prevalence of NHL was observed after the age of 40 years. Herein, only two NHL cases were identified, one in a female (50%) patient and one in a male (50%), with a mean age of 27 years (Table 2).

Histopathologically, NHLs are characterized by a proliferation of apparently lymphocytic cells that may show varying degrees of differentiation (Fig. 2d), depending on the type of lymphoma, and can be classified as aggressive (high grade) NHL, comprising less differentiated cells, and indolent (low grade) NHL comprising small and well-differentiated lymphocytes. Aggressive NHLs, if left untreated, rapidly lead to death, but in many cases are potentially curable with prompt immuno-chemotherapy. Indolent lymphomas, on the other hand, are generally incurable: although they are generally very receptive to initial therapy, they follow a course of repetition characterized by increased resistance to therapy and shorter duration of response to each successive treatment [47].

Burkitt's lymphoma (BL) is a malignancy originating from B-lymphocytes, representing an undifferentiated lymphoma classified into two categories, endemic and sporadic, with another classification regarding the form associated with immunodeficiency [48]. The endemic condition involves the jaws and abdominal region of children in equatorial Africa, while the sporadic form presents as an abdominal mass in adult patients from North America and Europe. However, the variant associated with immunodeficiency presents clinical similarity to the sporadic subtype, rare orofacial involvement with facial asymmetry, swelling, cutaneous ulceration, tooth mobility and alveolar bone destruction with root resorption and lamina dura loss in the affected site [49].

Approximately, 50–70% of the cases of endemic BL occur in the gnathic bones, with a higher prevalence in children at around seven, and a predilection for men, with the maxilla being more affected than the mandible, and, sometimes with the four quadrants presenting neoplastic involvement [50]. In the study performed by Rebelo-Pontes [49], seven cases of BL were reported, more prevalent in males with a mean age of 17.1 years, involving the maxillo-mandibular complex in 100% of the cases. This preference for gnathic bones was also evidenced in a study performed by Mohtasham et al. [51]. In the present survey, two cases of BL were identified, affecting male children with a mean age of less than 6.5 years, with evolution lasting 1 month and a half (Table 2). One case occurred in the mandible, asymptomatic, sessile implantation, tooth mobility and alveolar bone destruction was evidenced, while location information was not available for the second case.

Histopathologically, this condition is characterized as a small, undifferentiated, non-cleaved, B-cell lymphoma. A classic starry sky pattern is often present, caused by the presence of macrophages with abundant and lightly stained cytoplasm within the neoplastic tissue. Thus, these cells tend to stand out as "stars" against the "dark sky" of intensely hyperchromatic neoplastic lymphoid cells [52]. In the present study, typical histopathological BL (Fig. 2e) characteristics of were observed through hematoxylin–eosin staining (Table 3).

In view of the findings reported herein and according to a literature review, this study concludes that OLLs exhibit clinical and histopathological heterogeneity, involving a broad spectrum of lesions that share the presence of the lymphoid component, which, in turn, must be properly analyzed, even in if they present indolent behavior, since this component may eventually be responsible for the appearance of a lymphoma.

Funding The work was supported by Oral Pathology Post-Graduation Program, Dentistry Departament, Federal University of Rio Grande do Norte, Natal, RN, Brazil.

Compliance with ethical standards

Conflict of interest The author Juliana Campos Pinheiro declares that he has no conflict of interest; author Caio César da Silva Barros declares that he has no conflict of interest; author Larissa Santos Amaral Rolim declares that he has no conflict of interest; author Leão Pereira Pinto declares that he has no conflict of interest; author Lélia Batista de Souza declares that he has no conflict of interest; author Pedro Paulo de Andrade Santos declares that he has no conflict of interest.

References

1. Greaves W, Wang SA (2011) Selected topics on lymphoid lesions in the head and neck regions. Head Neck Pathol 5:41–50
2. Ellis G (2007) Lymphoid lesions of salivary glands: malignant and benign. Med Oral Patol Oral Cir Bucal 7:479–485
3. Ho P, Kyu J, Young K, Baik C, Woo M (2008) Histiocyte-rich reactive lymphoid hyperplasia of the liver: unusual morphologic features. J Korean Med Sci 23:156–160
4. Pereira A, Nonaka C, Santos P, Medeiros A, Galvão H (2009) Unusual coexistence of oral lymphoepithelial cyst and benign migratory glossitis. Braz J Otorhinolaryngol 75(2):318
5. Jham B, Binmad N, Scheper M, Zhao X, Koterwas G, Kashyap A et al (2009) Follicular lymphoid hyperplasia of the palate: case report and literature review. J Craniomaxillofac Sug 37:79–82
6. Jaffe ES (2012) Lymphoid lesions of the head and neck: a model of lymphocyte homing and lymphomagenesis. Mod Pathol 15(3):255–263
7. Doyle JL, Weisinger E, Manhold JH Jr (1970) Benign lymphoid lesions of the oral mucosa. Oral Surg Oral Med Oral Pathol 29(1):31–37
8. Seifert G (1980) Lymphoid lesions of the oral cavity. Path Res Pract 167:179–203
9. Ye Q, Harmsen MC, van Luyn MJA, Bank RA (2010) The relationship between collagen scaffold cross-linking agents and neutrophils in the foreign body reaction. Biomaterials 31:9192–9201
10. Shahrabi-Farahani S, Lerman MA, Noonan V, Kabani S, Woo SB (2014) Granulomatous foreign body reaction to dermal cosmetic fillers with intraoral migration. Oral Surg Oral Med Oral Pathol Oral Radiol 117:105–110
11. Owosho AA, Bilodeau EA, Vu J, Summersgill KF (2014) Orofacial dermal fillers: foreign body reactions, histopathologic features, and spectrometric studies. Oral Surg Oral Med Oral Pathol Oral Radiol 117:617–625
12. Florin W, Mandel L (2012) Foreign body reaction to facial dermal fillers: case report. J Oral Maxillofac Surg 70:2352–2355
13. Anjomshoaa I, Bulford LA, Dym H, Woo SB (2013) Florid follicular lymphoid hyperplasia of the hard palatal mucosa managed with intralesional steroids: a case report and review of the literature. J Oral Maxillofac Surg 71:1202–1208
14. Taguchi K, Kuroda S, Kobayashi T, Tashiro H, Ishiyama K, Ide K et al (2015) Pseudolymphoma of the liver: a case report and literature review. Surg Case Rep 1:107
15. Kolokotronis A, Dimitrakopoulos I, Asimaki A (2003) Follicular lymphoid hyperplasia of the palate: report of a case and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96:172–175
16. Kojima M, Nakamura S, Shimizu K, Iijima M, Murayama K, Ohno Y et al (2005) Reactive lymphoid hyperplasia of the lymph nodes with giant follicles: a clinicopathologic study of 14 Japanese cases, with special reference to Epstein–Barr virus infection. Int J Surg Pathol 13(3):267–272
17. Villa N, Redaelli S, Lissoni S, Saccheri S, Sala E, Crosti F et al (2014) Lymph node hyperplasia: clonal chromosomal and genomic rearrangements. Report of two new cases and literature review. Cancer Genetics 207:12–18
18. Chang DH, Wu PS, Wang YC, Lin CH, Li WY, Ma H et al (2016) Clinicopathology of Immunoglobulin G4-related chronic sclerosing sialadenitis: a single-center study. Otolaryngol Head Neck Surg 155(6):974–981
19. Adouly T, Adnane C, Housni Y, Rouadi S, Abada R, Roubal M et al (2016) Uncommon situation and presentation of chronic sclerosing sialadenitis. Int J Pediatr Otorhinolaryngol 83:22–24
20. Gontarz M, Wyszyńska-Pawelec G, Zapała J, Gałązka K, Tomaszewska R, Lazar A (2016) IgG4-related disease in the head and neck region: report of two cases and review of the literature. Pol J Pathol 67(4):370–375
21. Melo JC, Kitsko D, Reyes-Múgica M (2012) Pediatric chronic sclerosing sialadenitis: Küttner tumor. Pediatr Dev Pathol 15:165–169
22. Guinovart RM, Bassas-Vila J, Morell L, Ferrándiz C (2014) Angiolymphoid hyperplasia with eosinophilia: A clinicopathologic study of nine cases. Actas Dermosifiliogr 105(2):e1–e6
23. Tchernev G, Taneva T, Ananiev J, Cardoso JC, Gulubova M, Velev V et al (2012) Angiolymphoid hyperplasia with eosinophilia—an incidental finding after surgical excision. Wien Med Wochenschr 162:448–451
24. Tenório JR, Gonzaga AKG, Gonçalves PGP, Oliveira DHIP, Queiroz LMG (2016) Angiolymphoid hyperplasia with eosinophilia: a rare case in the oral cavity. J Vasc Bras 15(4):317–321
25. Lichtenstein L (1953) Integration of eosinophilic granuloma of bone, Letterer–Siwe disease and Schuller-Christian disease as related manifestations of a single nosologic entity. Arch Pathol 56:84–102
26. Mani V, Vinod VS, George A, Sivaprasad KK (2015) Eosinophilic granuloma of mandibular condyle: resection and complete regeneration. J Maxillofac Oral Surg 14(1):107–110
27. Lichtenstein L, Jaffe HL (1940) Eosinophilic granuloma of bone with a report of a case. Am J Pathol 16:595–604
28. Angelini A, Mavrogenis AF, Rimondi E, Rossi G, Ruggieri P (2017) Current concepts for the diagnosis and management of eosinophilic granuloma of bone. J Orthop Traumatol 18:83–90
29. Khelemsky R, Mandel L (2010) Lymphoepithelial cyst of mouth floor. J Oral Maxillofac Surg 2010; 68:3055–3057
30. Sykara M, Ntovas P, Kalogirou EM, Tosios KI, Sklavounou A (2017) Oral lymphoepithelial cyst: A clinicopathological study of 26 cases and review of the literature. J Clin Exp Dent 9(8):e1035–e1043
31. Knapp MJ (1970) Pathology of oral tonsils. Oral Surg Oral Med Oral Pathol 29:295–304
32. Castro JGL, Ferreira GM, Mendonça EF, Castro LA (2015) A rare occurrence of lymphoepithelial cyst in the palatine tonsil: a case report and discussion of the etiopathogenesis. Int J Clin Exp Pathol 8(4):4264–4268
33. Jeong HS, Lee HK, Ha YJ, Kim DH, Suh IS (2015) Benign lymphoepithelial lesion of parotid gland and secondary amyloidosis as concurrent manifestations in Sjögren's syndrome. Arch Plast Surg 42:380–383
34. Li QJ, Zhao PX, Zhang XJ, Yi Y, Chen DY, Ma JM et al (2017) Association of the macrophage migration inhibitory factor promoter polymorphisms with benign lymphoepithelial lesion of lacrimal gland. Int J Ophthalmol 10(8):1229–1232
35. Uehara T, Ikeda SI, Hamano H, Kawa S, Moteki H, Matsuda K et al (2012) A case of Mikulicz's Disease complicated by malignant lymphoma: a postmortem histopathological finding. Intern Med 51:419–423
36. Metwaly H, Cheng J, Suzuki M, Takata Y, Saitoh C, Hayashi T et al (2004) Benign lymphoepithelial lesion of minor salivary

gland: report of a case involving the palatal mucosa. Oral Oncol EXTRA 40:113–116
37. Raghu AR, Rehani S, Bishen KA, Sagari S (2014) Warthin's tumour: a case report and review on pathogenesis and its histological subtypes. J Clin Diagn Res 8(9):ZD37–ZD40
38. Iwai T, Baba J, Murata S, Mitsudo K, Maegawa J, Nagahama K et al (2012) Warthin tumor arising from the minor salivary gland. J Craniofac Surg 23(5):e374–e376
39. Arcega RS, Feinstein AJ, Bhuta S, Blackwell KE, Rao NP, Pullarkat ST (2015) An unusual initial presentation of mantle cell lymphoma arising from the lymphoid stroma of warthin tumor. Diagn Pathol 3(10):209
40. Sagiv D, Witt RL, Glikson E, Mansour J, Shalmon B, Yakirevitch A et al (2017) Warthin tumor within the superficial lobe of the parotid gland: a suggested criterion for diagnosis. Eur Arch Otorhinolaryngol 274:1993–1996
41. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F (2017) Non-hodgkin lymphoma. Lancet 390:298–310
42. Inchingolo F, Tatullo M, Abenavoli FM, Marrelli M, Inchingolo AD, Inchingolo AM et al (2011) Non-hodgkin lymphoma affecting the tongue: unusual intra-oral location. Head Neck Oncol 3:1
43. Varun BR, Varghese NO, Sivakumar TT, Joseph AP (2017) Extranodal non-hodgkin's lymphoma of the oral cavity: A Case Rep. Iran J Med Sci 42(4):407–411
44. Pereira DL, Fernandes DT, Santos-Silva AR, Vargas PA, Almeida OP, Lopes MA (2015) Intraosseous non-hodgkin lymphoma mimicking a periapical lesion. J Endod 41:1738–1742
45. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H et al (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 49:1374–1403
46. Fetica B, Achimas-Cadariu P, Pop B, Dima D, Petrov L, Perry AM et al (2017) Non-hodgkin lymphoma in Romania: a single-centre experience. Hematol Oncol 35:198–205
47. Ninkovic S, Lambert J (2017) Non-hodgkin lymphoma. Medicine 45(5):297–304
48. Amoils M, Truong MT (2016) Burkitt lymphoma presenting as facial nerve paresis. Int J Pediatr Otorhinolaryngol Extra 13:9–12
49. Rebelo-Pontes HA, Abreu MC, Guimarães DM, Fonseca FP, Andrade BAB, Almeida OP et al (2014) Burkitt's lymphoma of the jaws in the Amazon region of Brazil. Med Oral Patol Oral Cir Bucal 19(1):e32–e38
50. Zongo N, Sanou/Lamien A, Konsegré V, Ouédraogo A, Randé N, Goumbri/Lompo O et al (2011) Burkitt lymphomas: epidemiological and pathological aspects in Ouagadougou (Burkina Faso) Afr J Cancer 3(1):16–19
51. Mohtasham N, Babakoohi S, Sarraf-Yadzy M, Sadr B, Ghaffarzadegan K, Shiva A et al (2011) Oral and jaw lymphoma in an Iranian population. J Craniofac Surg 22:868–870
52. Bilodeau E, Galambos C, Yeung A, Potluri A, Collins B (2012) Sporadic Burkitt lymphoma of the jaw: case report and review of the literature. Quintessence Int 43:333–336