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Original article

Comprehensive Clinicopathological Analysis of Oral Reactive Hyperplastic Lesions Diagnosed in Libyan Population: Cross-Sectional Multicentric Study

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Abstract
Oral reactive hyperplastic lesions (ORHLs) are non-neoplastic tumor-like hyperplasia frequently developing in the oral mucosa due to chronic inflammation caused by many low-grade irritations. They are relatively common, and their clinical appearance resembles neoplastic proliferations. This study aims to determine the prevalence and distribution of ORHLs based on WHO's head and neck tumor classification (2022) in the Libyan population over the last 20 years and compare the results with previous literature. In this retrospective study, all the records of histologically diagnosed ORHLs between 2002 and 2023 collected from the Tripoli University Hospital and Saray Salam Center in Tripoli, Libya, were reviewed. Information regarding the age at diagnosis, gender, site affection, and histopathological diagnosis was extracted and analyzed using SPSS statistical software (V.26) using the Chi-square test. ORHLs constituted 14.5% of the total diagnosed cases (335/3210) in registered oral and maxillofacial biopsies. Pyogenic granuloma (PG) was the most common type of ORHL (48%) followed by irritational fibroma (IF) (30%), and peripheral giant cell granuloma (PGCG) (8%). The peak incidence of ORHLs was in the third and fourth decades (37.6% and 32.8% retrospectively), with an overall age at onset of diagnosis (Mean ± SD 36.4±7). The relationship between the age categories and ORHLs was statistically significant (P=0.03). Female predominance was found in all lesions with a ratio (2:1). Gingiva was the most prevalent anatomical location for ORHLs, accounting for 31% of cases. There have been some similarities and inconsistencies between our findings and previous studies involving various populations. We found a clear geographic difference in the relative incidence of oral reactive lesions in each Libyan governorate. The occurrence of ORHRLs in different nations can be retrospectively evaluated to improve knowledge of ORHLs, which is critical for pathologists and oral and maxillofacial surgeons.
Keywords. *Epidemiology, Reactive Lesions, Oral Cavity, Prevalence, Clinicopathological Features, Histopathological Diagnosis.*

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Introduction

Oral reactive hyperplastic lesions (ORHLs) may arise from persistent low-grade irritation that provokes an excessive tissue healing response. The soft tissue growth caused by this excessive reaction has similarities to a wide variety of pathologic lesions. Because the growth might be suggestive of a variety of normal anatomic structures, inflammation, cysts, abnormalities of development, and even neoplasms, this response presents a diagnostic challenge (1). ORHLs have a clinical appearance of growth of tissue with fibrous or flabby consistency, reddish hue, sessile in nature, or pedunculated, and can occur in several intraoral locations. Typically, the gingiva is the most susceptible to irritation caused by biofilm, calculus, food impaction, inadequately suited restorations or prosthesis, and iatrogenic causes. Patients may report no symptoms, or symptoms ranging from mild pain to bleeding. Radiographic signs are typically absent; however, in rare cases of severe lesions, localized alveolar bone resorption may be observed (2).

Histopathologically, ORHLs have been categorized by several researchers as giant cell types, fibrous, vascular, or hemorrhagic (3, 4), and others suggest that at various developmental stages, all of these entities constitute the same lesion (5, 6). Currently, According to WHO's head and neck tumor classification (2022) and the novel classification system introduced by a study performed by Fathy et.al 2024 (7), this system took into consideration the clinical appearance of the lesions in the oral cavity as well as their characteristic histopathological features. The clinical pictures comprised 4 groups, mucosal colored swellings, red to purple swellings, verrucous papillary swellings, and ulcerative lesions. On the other hand, the histopathological features were based on the nature of the tissue showing the hyperplastic changes whether involving both epithelium and connective tissue which include Pyogenic Granuloma (PG), Peripheral Giant Cell Granuloma (PGCG), Peripheral Ossifying Fibroma (POF), Focal Fibrous Hyperplasia (FFH), Palatal

papillomatosis (PP) and Irritation Fibroma (IF), while lesions involving epithelium only including Squamous Cell Papilloma (SCP) and Verruca Vulgarise (VV), finally, lesions involving connective tissue only include Traumatic Neuroma (TN) and Traumatic eosinophilic ulcer (TEU) (7).
Few epidemiology studies have assessed the prevalence of reactive lesions worldwide, even though they are the most common type of oral mucosal lesions. Evaluating the prevalence of these lesions is crucial for raising practitioner awareness and allocating healthcare resources as effectively as possible (2). Early management and timely diagnosis depend on understanding the distribution of various ORHLs (8). Additionally, histopathological findings are crucial for accurate diagnosis and effective treatment planning to prevent recurrence (9). A tissue biopsy determines the definitive diagnosis of oral lesions based on certain histological characteristics. A tissue specimens can confirm or rule out clinical diagnosis, and aid in diagnostic and treatment options. Furthermore, biopsy findings have unassailable legal medical value. (10, 11). The American Academy of Oral and Maxillofacial Pathology (AAOMP) considers biopsy to be the gold standard diagnostic method, which ordinary dentists can do (12).
To the best of our knowledge, no comprehensive study has been conducted on the distribution and frequency of ORHLs in Libya. As a result, the current study aims to use the most recent classification of head and neck tumors (2022) to assess the prevalence and distribution of each type of reactive lesion of the oral cavity in a Libyan population over an extended period covering two decays and to compare the results with the previous studies. Demographic data, incidence, and histological characteristics of lesions can assist practitioners in making more accurate differential diagnoses and managing patients more efficiently.

Methods

Ethical Statement

This study was approved by the Scientific Research and Ethics Committee at the University of Tripoli, Tripoli, Libya, and then by the head of each center. It conformed to the World Medical Association Helsinki Declaration's procedures for human beings, revised in 2013.

Study Design

The study was conducted using a cross-sectional retrospective design in a multi-center setting, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (9).

Patient cohort and data Collection

All patient case records of orofacial specimen biopsies documented in the database of the Department of Anatomical Pathology at Tripoli University Centre, Tripoli, Libya, were retrieved for the duration from January 2002 to December 2023, exceeding 20 years, as well as from the database of Saray Salam Center, Tripoli, Libya, covering the period from May 2021 to December 2023. Two oral pathologists have reviewed reports for cases of oral cavity ORHLs.

Inclusion and exclusion criteria

Reports with available Hematoxylin and Eosin-stained slides that were reinvestigated by two Oral Pathologists and then classified as reactive hyperplastic lesions were included in this study. Patients from all genders and ages who had sufficient clinical data were included. The study removed reports with incomplete or ambiguous diagnoses and duplicate cases. These criteria were used to improve the precision of the research being conducted.

Clinicopathological data

Clinical data, including age, gender, size, anatomical location, and clinical appearance of the lesion (color, shape, surface, and consistency) was obtained from patient files. The sites involved were the lips, palate, tongue, buccal mucosa, and gingiva. It was determined that the histopathological characteristics were determined by the nature of the tissue that had hyperplastic changes. These changes could involve the epithelial and connective tissue components, which are grouped into: epithelium hyperplasia only, connective tissue component hyperplasia, and both epithelial and connective tissue hyperplasia (Fig, 1).

Statistical analysis

All data were subjected to statistical analyses using SPSS software version 26.0® (IBM Corporation, New York, USA). Descriptive statistics were used to display percentages and frequencies of categorical variables, while continuous variables were expressed as mean ± standard deviation (SD) or median range (in not

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normally distributed data). Pearson's Chi-squared test was used to determine the association between the categorical variables. P≤0.05 was considered statistically significant.

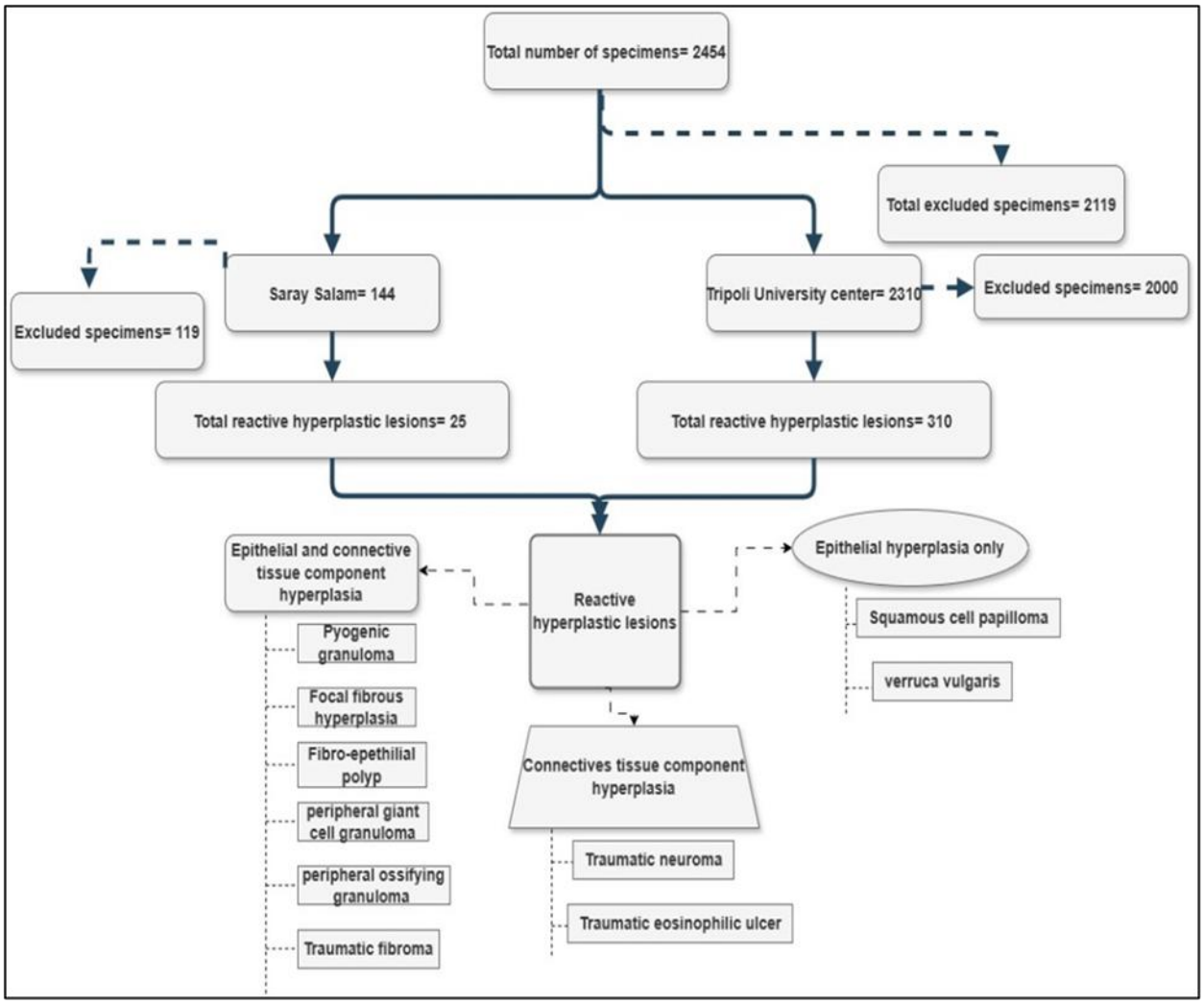

Figure 1: Screening process for the identification of Oral Reactive Hyperplastic Lesions

Results

Demographic and Clinicopathological Features of ORHLs

The comprehensive clinicopathological and demographic data are summarized in (Table 1). Total cases of 2310 specimens of orofacial lesions were examined by the Department of Anatomical Pathology at Tripoli University Hospital and Saray Salam Center, Tripoli, Libya, with 335 cases in which histological diagnoses were identified as ORHLs, resulting in a prevalence presented by (14.5%). Demographic analysis showed that ORHLs had females preferred, accounting for nearly two-thirds (63.0%) of all cases, compared to males at (37.0%), with a female to male ratio (F: M) 2: 1. The patient age at the diagnosis was ranged from 3 to 95 years, with an overall age (Mean ± SD 36.4±7 and a Median age of 33 years), with the highest frequency observed in the age group (20-35), (37.6%). On the other hand, the middle age groups (13-19) are less frequently affected (8.4%), as illustrated in (Fig, 2).

On the other hand, our findings showed that the hyperplastic changes that occurred in the subgroup of epithelial and connective tissue components constituted the largest and most common category, making up 311 (92.8%) of the total cases, then followed by a group of epithelial hyperplasia only, accounting for 21 (6.26%), and a type that is less frequently occurring is the connective tissue component hyperplasia group, comprising 3 (0.9) of cases, as illustrated in (Fig, 3).

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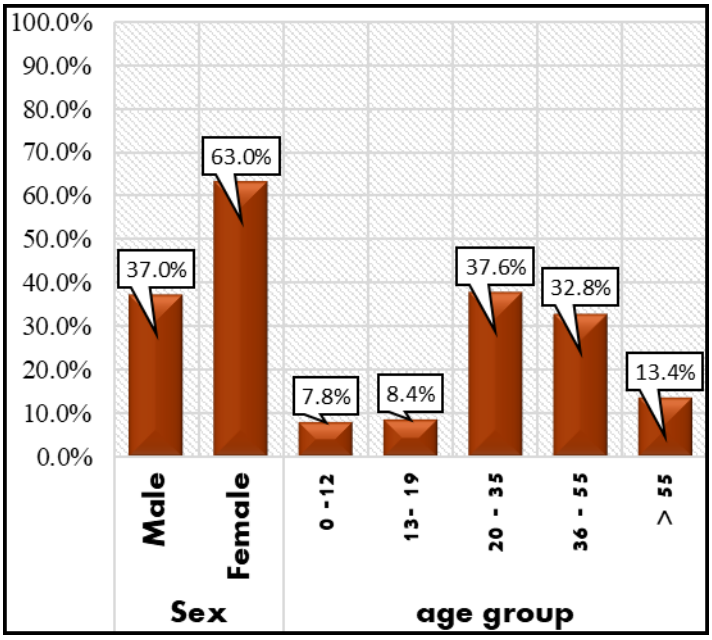

Figure 2. Distribution of Oral Reactive Hyperplastic Lesion by Six and Age Groups

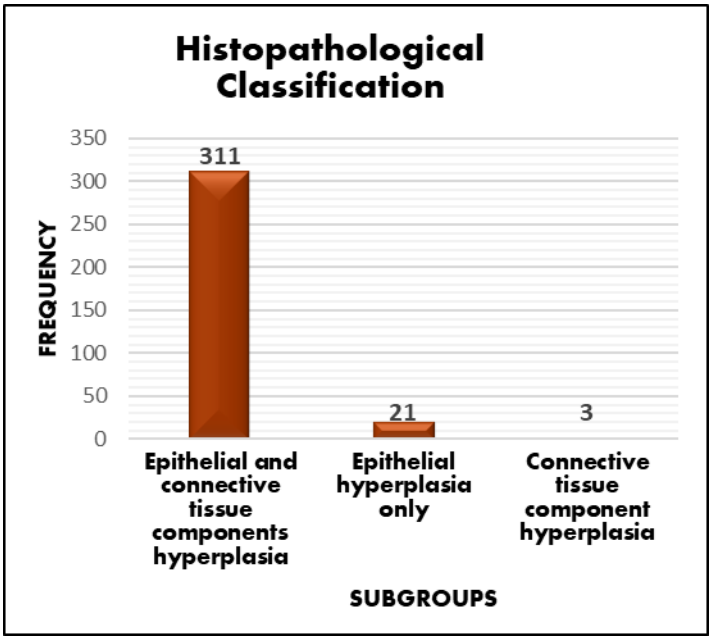

Figure 3. Histopathological classification of Oral Reactive Hyperplastic Lesions

Table 1. Summary of Demographic and Clinicopathological Features of ORHLs

Parameters		Frequency (N)	Percentage (%)
Age in years	Mean ± SD Range	36±17 (3-95)	
Age group category	0-12 13-19 20-35 36-55 > 55	26 28 126 110 45	7.8 8.4 37.6 32.8 13.4
Gender	Female Male	211 124	63.0 37.0

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Anatomical Site	Gingiva Tongue Buccal mucosa Lower lip Upper lip Palate Alveolar ridge	91 77 52 41 7 15 8	31.2 26.4 17.8 14.0 2.40 5.15 2.74
Gross size, cm	Mean (SD) Range	1.2 (2) (0.5-6)	
Color	White to gray swelling	203	60.6
	Mucosal colored swelling	103	30.7
	Red to purple swelling	29	8.7
Histopathological Classification	Epithelial and connective tissue components hyperplasia	311	92.8
	Epithelial hyperplasia only	21	6.3
	Connective tissue component hyperplasia	3	0.9

Relative Frequency of ORHLs by Histopathological Diagnosis (Final Diagnosis)

The Histopathological diagnosis analysis revealed that PG was the most predominant form of ORHL, making up 161 cases (48.1% of the sample). The next most common form was IF, which accounted for 102 cases (30.4%). Then comes PGCG, which comprised 27 cases, or 8.1% of the overall. SCP was found in 18 cases (5.4%). Followed by POF was observed in 11 patients, accounting for 3.3% of all cases and FFH was found in nine cases, or 2.7%. VV appeared in four cases, accounting for (1.2%) of the total cases investigated. TN and TEU were the least common diagnoses, with only two cases (0.6%) of TN and one case of TEU (0.3) shown in (Fig, 4).

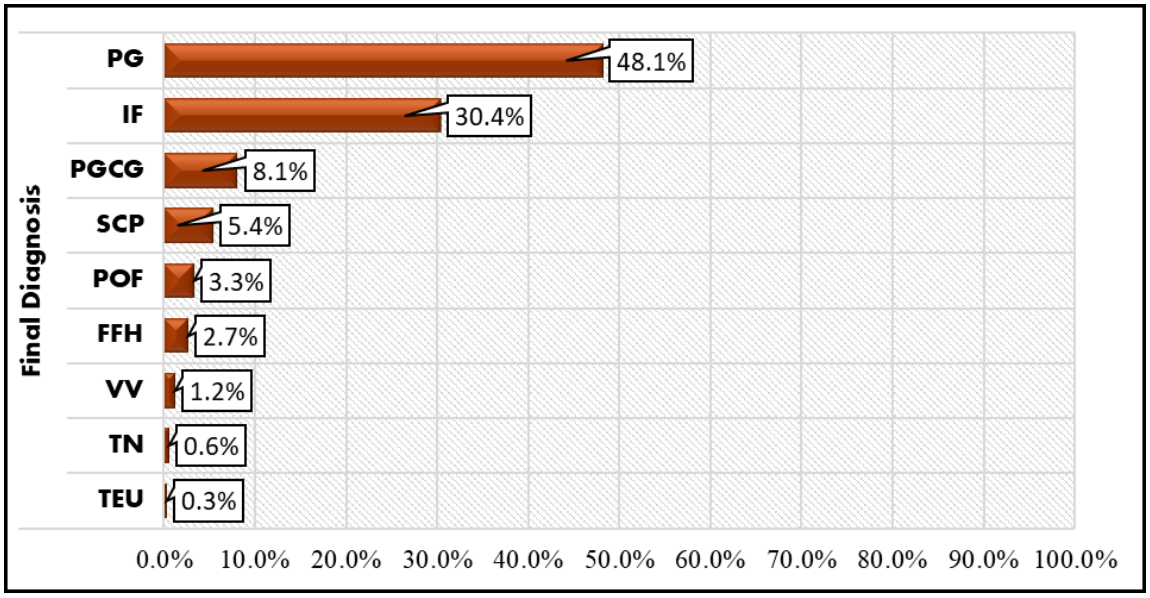

Figure 4. Distribution of ORHLs by histopathological diagnosis.
PG: Pyogenic granuloma, PGCG: Peripheral giant cell granuloma, POF: Peripheral ossifying fibroma, IF: Irritation fibroma, FFH: Focal fibrous hyperplasia, TN: Traumatic neuroma, VV: Verrucous vulgaris, SCP: Squamous cell papilloma, and TEU: Traumatic eosinophilic ulcer

Trends in Histopathological Classification of Diagnosed Cases from 2002 to 2023

The annual analysis showed that the number of cases of epithelial hyperplasia varied over the years, with a noticeable case gap from 2010 to 2021. Connective tissue component hyperplasia: Very few cases were noted, with none reported after 2010. Epithelial and connective tissue component hyperplasia: This category was the most frequently observed, peaking in 2006 and 2008. The incidence remained relatively high throughout the study period, with specific trends in a significant rise in 2023 (Fig. 5).

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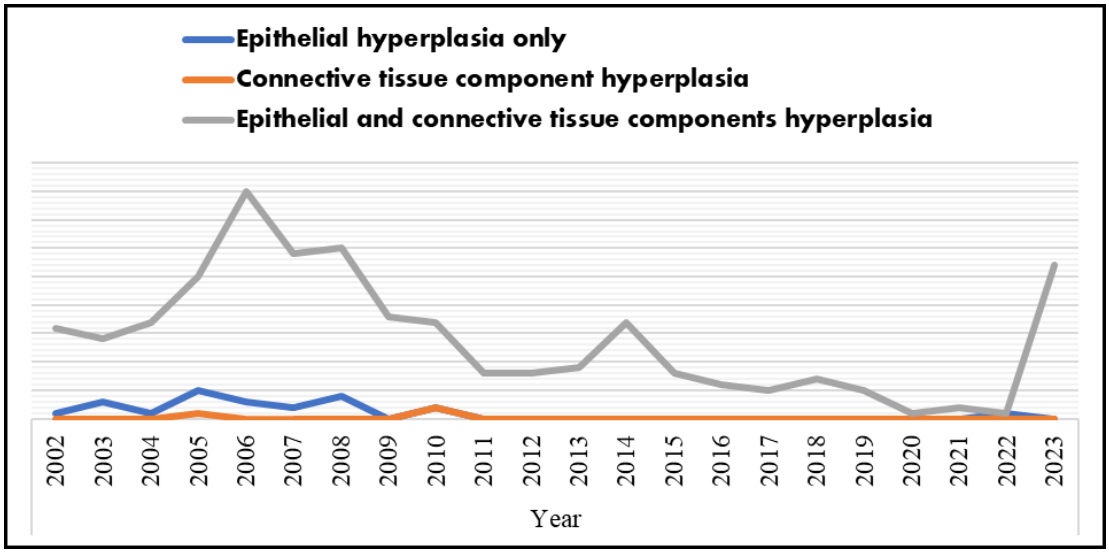

Figure 5. Trends in Histopathological Characteristics of Cases from 2002 to 2023

Analysis of ORHLs according to Sex and Age Group Categories

The distribution of ORHLs according to the patient's sex and age group has been presented in (Table 2) which revealed variety in results: PG is more common in females (31.6%) than in males (16.4%), with the largest frequencies identified in the age groups 20-35 and 36-55 (19.7% and 13.1%, respectively). The IF was virtually evenly distributed in two age groups: 20-35 and 36-55 years, with proportions of 11.3% and 11.9%, respectively, and it was more frequent in females (14.3%) than males (10.1%). In addition, PGCG commonly occurred in females (4.8%), while those aged 36 to 55 were more likely to have it (3.0%). The frequency of SCP was two times higher in females (3.6%) than males (1.8%) and the group aged 20 to 35 had the most common proportion (2.4%). However, POF was more frequent in females (0.9%) and had an elevated incidence in the 20-35 and 36-55 age groups with the same proportion (1.2%). FFH was greater in females (2.1%) and had a higher incidence in the age group 36-55 (1.5%). In contrast, VV and TN were all cases that affected males only (1.4% and 0.6% retrospectively), and the age group 20 to 35 was the more common category for them with the same percentage (0.2%). TEU was the latest form of lesions with only one case occurring in females (0.3%) and in the age group above 55 (0.3%). The Pearson Chi-square test indicated no statistically significant sex-based differences (x2 = 14.44; P = 0.150) but revealed statistically significant age-related variations in case distribution (x2 = 48.60; P = 0.03) (Table 2).

Table 2. Distribution of ORHLs by sex and age groups

*ORHL	Total N (%)	Sex		Age group (years)				
		Male	Female	3-12	13-19	20-35	36-55	>55
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PG	161 (48.1)	55 (16.4)	106 (31.6)	15 (4.5)	20 (6.0)	66 (19.7)	44 (13.1)	16 (4.8)
IF	102 (30.4)	41 (12.2)	61 (18.2)	2 (0.6)	6 (1.8)	38 (11.3)	40 (11.9)	16 (4.7)
PGCG	27(8.1)	11 (3.5)	16(4.8)	6(1.8)	0(0.0)	6(1.8)	10(3.0)	10 (21.7)
SCP	18 (5.4)	6 (1.8)	12 (3.6)	2 (0.6)	0 (0.0)	8 (2.4)	6 (1.8)	2 (0.6)
POF	11 (3.3)	3 (0.9)	8 (2.4)	0 (0.0)	2 (0.6)	4 (1.2)	4 (1.2)	1 (0.3)
FFH	9 (2.7)	2 (0.6)	7 (2.1)	1 (0.3)	0 (0.0)	0 (0.0)	5 (1.5)	3 (0.9)
VV	4 (1.2)	4 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)	1 (0.3)
TN	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
TEU	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
****P- value of sex = 0.15**				****P- value of age = 0.03**				

****ORHL: Oral reactive hyperplastic lesions, PG: Pyogenic granuloma, PGCG: Peripheral giant cell granuloma, POF: Peripheral ossifying fibroma, IF: Irritation fibroma, FFH: Focal fibrous hyperplasia, TN: Traumatic neuroma, VV: Verrucous vulgaris, SCP: Squamous cell papilloma, and TEU: Traumatic eosinophilic ulcer***
***** Pearson Chi-square***

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Analysis of ORHLs according to Anatomical Sites

The occurrence of ORHLs across diverse anatomical regions was analyzed and presented in (Table 3), indicating substantial differences. For those cases with available information, the preferential anatomic location was the gingiva (31.2%) of cases, followed by the tongue (29.4%) and buccal mucosa (17.5%). The lower lip with a proportion of (14.0%) has a higher affection for ORHLs than the upper lip, found only in (2.4%). Additionally, the upper lip and alveolar ridge showed lower percentages of all lesions with the proportions approximately near the same (2.4% and 2.7%, retrospectively). On the other hand, the most commonly observed lesion type was PG, which accounted for 35.1% of cases in the gingiva. This site also exhibited a notable occurrence of POF, which constituted 81.8% of lesions identified in that region. Conversely, lesions such as IF were predominantly found in the buccal mucosa (40.2%) and tongue (28.0%). The lower and upper lips demonstrated a more diverse distribution of ORHL types, although with lower overall frequencies; PG and IF were the most prevalent in these sites. The palate exhibited the least prevalence of ORHLs, with minimal representation from PG and IF. Additionally, the alveolar ridge showed a low percentage of lesions, with PGCG, PG, and POF reported in the alveolar ridge. The Pearson Chi-Square test results indicate a significant association between histological diagnosis and anatomical site, with (P= 0.001), this suggests that the distribution of histological diagnoses varies significantly across different anatomical sites.

Table 3. Distribution of ORHLs by the anatomical site

*ORHL	Gingiva	Tongue	Buccal Mucosa	Lower Lip	Upper Lip	Palate	Alveolar Ridge	**P-Value
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
PG	47 (35.1)	41 (30.6)	8 (6.0)	25 (18.7)	3 (2.2)	8 (6.0)	2 (1.5)	**0.001**
IF	15 (14.4)	26 (28.0)	42 (40.2)	13 (13.4)	1 (0.0)	5 (4.9)	0 (0.0)	
PGCG	13 (72.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.2)	
SCP	0 (0.0)	8 (61.5)	1 (7.7)	1 (7.7)	2 (15.4)	1 (7.7)	0 (0.0)	
POF	9 (81.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.1)	
FFH	5 (55.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
VV	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	
TN	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
TEU	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Total (%)	91(31.2)	76(26.4)	51(17.8)	41(14.0)	7(2.4)	14(5.15)	8(2.74)	

****ORHL: Oral reactive hyperplastic lesions, PG: Pyogenic granuloma, PGCG: Peripheral giant cell granuloma, SCP: Squamous cell papilloma, POF: Peripheral ossifying fibroma, IF: irritational fibroma, FFH: Focal fibrous hyperplasia, TN: Traumatic neuroma, VV: Verrucous vulgaris, SCP: Squamous cell papilloma, and TEU: Traumatic eosinophilic ulcer ** Pearson Chi-square***

Analysis of ORHLs according to Clinical Features

The detailed clinical features of ORHLs according to histopathological diagnosis were summarized in (Table 4) and (Fig, 6). Regarding surface texture, the distribution was as follows: smooth surface lesions were the most common at 44 % (125 cases), followed by irregular surface lesions at 40% (115 cases). Ulcerated surface lesions comprised 10% (27 cases), and papillary surface lesions were the least common at 6% (18 cases). Concerning consistency, soft lesions were most frequent at 56% (182 cases), second most common is firm lesions at 41% (133 cases), elastic lesions were less common at 2% (6 cases), and hard lesions were rare at 1.2% (4 cases). Based on the color of the lesion, red to purple swellings were predominant, constituting 44.1% (148 cases). Mucosal-colored swellings were present in 30.0% (100 cases), and white to gray swellings were the least common at 21.1% (71 cases). For lesion size, the majority were under 3 cm,
accounting for 89.0% (298 cases). Lesions between 3 to 5 cm constituted 8.1% (27 cases), and those over 5 cm were the least common at 3.0% (10 cases). For lesion size, the majority were under 3 cm, accounting for 89.0% (298 cases). Lesions between 3 to 5 cm constituted 8.0% (27 cases), and those over 5 cm were the least common at 3.0% (10 cases) (Fig, 6). The Pearson Chi-Square test results for all clinical features indicate that statistically significant differences between histological diagnosis and clinical features were accounted as the following: the size (x2 =55.72, P-value=0.001), the color (x2 =63.21, P-value=0.04), the surface texture (x2 =295.5, P-value=0.001), and the consistency (x2 =43.92, P-value=0.002). This result suggests that the distribution of histological diagnoses varies significantly across clinical features as found in (Table 4).

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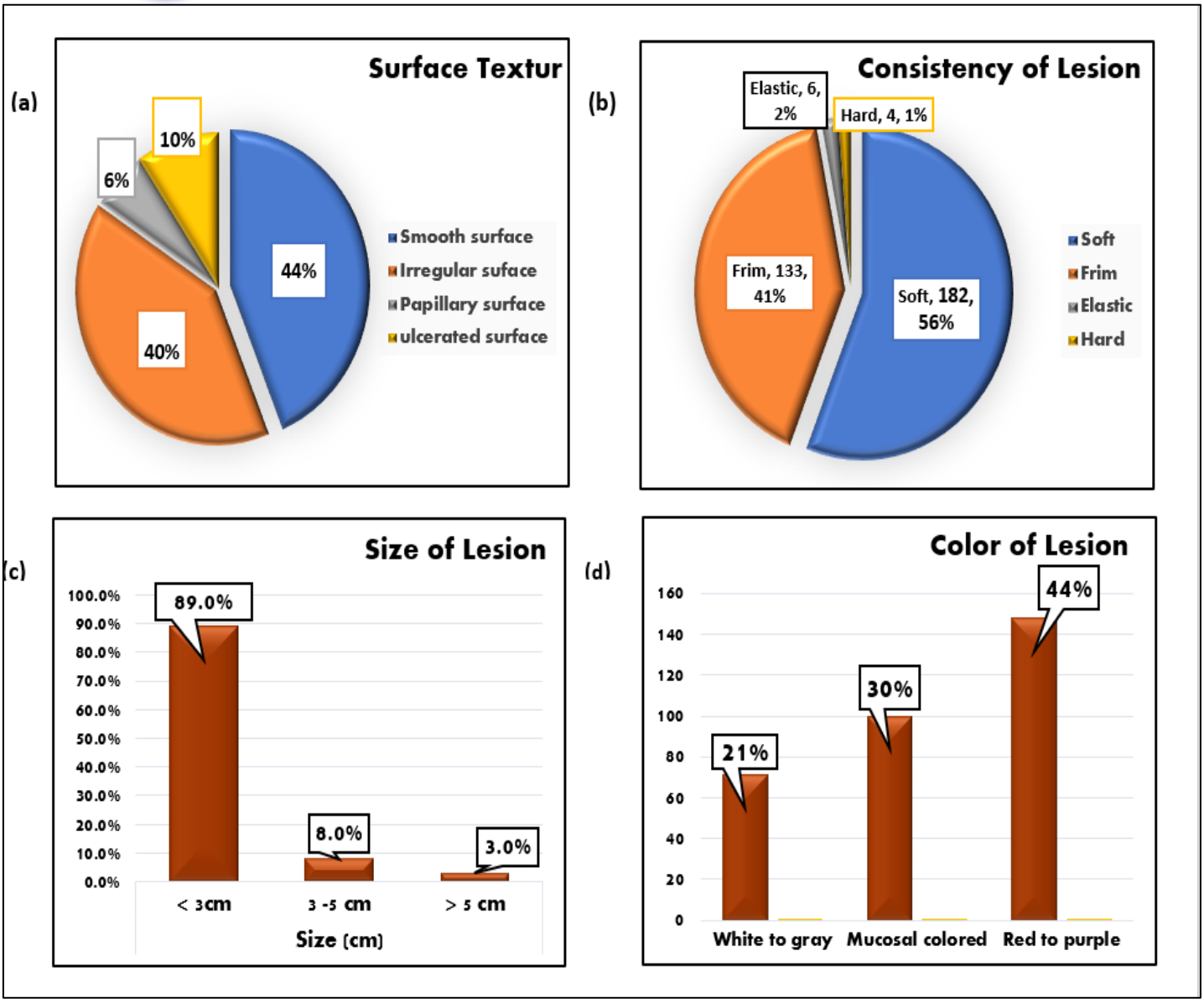

Figure 6: Distribution of Oral Reactive Lesions according to clinical features: a. Surface texture (smooth, irregular, papillary, or ulcerated surface), b. Consistency of lesion (soft, firm, elastic, or hard), c. Size of lesion (less than 3cm, 3-5, or more than 5cm. d. Color of lesion (white to gray, mucosal colored, or red to purple).

Table 4. Distribution of ORHLs according to Clinical Features

Parameter		Oral Reactive Hyperplastic Lesions N (%)								
		PG	IF	PGCG	POF	FFH	SCP	VV	TN	St. Test
Size (cm)	> 3	143 (52.7)	36 (10.8)	18 (5.4)	8 (2.4)	7 (2.1)	18 (5.4)	4 (1.2)	1 (0.30)	*P=0.001 **x2=55.7
	3-5	13 (3.9)	10 (3)	8 (2.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	
	<5	5 (1.5)	1 (0.3)	1 (0.3)	3 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.30)	
Color	Mucosal Colored	48 (15.0)	32 (5)	8 (2.5)	2 (0.6)	5 (1.6)	3 (0.9)	1 (0.3)	1 (0.3)	*P=0.04 *x2*=63.2
	White to gray	33 (10.2)	1 (0.3)	7 (2.2)	9 (2.8)	4 (1.3)	13 (4.1)	3 (0.9)	1 (0.3)	
	Red to purple	84 (25.3)	54 (16.9)	10 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Surface Texture	Smooth	47 (16.5)	53 (18.6)	4 (1.4)	5 (1.8)	1 (0.4)	2 (0.7)	0 (0.0)	1 (0.4)	*P=0.001 *x2*=295.5

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	Irregular	68 (23.9)	17 (6.0)	12 (4.2)	4 (1.4)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.00)	
	Papillary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (4.9)	4 (1.4)	0 (0.0)	
	Ulcerated	21 (7.4)	1 (0.40	4 (1.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Consistency	Soft	106 (32.7)	38 (11.7)	14 (4.3)	0 (0.0)	6 (1.8)	2 (0.6)	0 (0.0)	1 (0.3)	
	Firm	68 (20.9)	38 (11.7)	9 (2.8)	1 (0.3)	3 (0.9)	16 (4.9)	2 (0.6)	1 (0.3)	***P=0.002 *x2*=43.9**
	Elastic	1 (0.3)	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Hard	2 (0.6)	2 (0.6)	0 (0.0)	10 (3.1)	0 (0.00	0 (0.0)	0 (0.0)	0 (0.0)	

PG: Pyogenic granuloma, PGCG: Peripheral giant cell granuloma, POF: Peripheral ossifying fibroma, IF: irritational fibroma, FFH: Focal fibrous hyperplasia, TF: Traumatic fibroma, TN: Traumatic neuroma, VV: Verrucous vulgaris, SCP: Squamous cell papilloma. *P value ** Pearson Chi-square.

Analysis of ORHLs according to histopathological features

ORHLs were examined and analyzed based on their histopathological characteristics and detailed findings information can be found in (Table 5). The normal epithelial surface was a common comparison (56%) over half of the total cases of ORHLs (Fig, 7), especially in PG, which comprised 31% of the cases followed by IF in 14.9% of cases. Atrophic epithelium was rare across all lesion types (5%), while hyperplastic changes were less frequent in one-third of cases (32%). A strong association between epithelial surface features and and lesion type is indicated by Pearson Chi-square (x2=71.4, P=0.001). On the other hand, regarding the connective tissue component as shown in (Fig, 8), Inflammatory infiltration was the predominant feature found in (46%) of the total cases of the sample it was commonly present in PG (143 cases). Also, chronic inflammation was a dominant feature in PG and IF which was present in about (97 and 44 cases prospectively), while acute inflammation was less common (20.1% of PG lesions), However, the inflammation was a rare histological feature of VV which only accounted (for 0.3% of cases), and was absent on TN. The results demonstrated a significant statistical difference between inflammation and inflammation type and ORHLs (x2=75.5, P=0.001, and x2=25.0, P=0.001 retrospectively). Fibrous and blood vessel proliferation were notable, especially in PG (18.1% and 36.8% respectively). Mineralized tissue was common on POF and TF accounted similar proportion (1.6%) and was uncommon on the remaining types of ORHLs. However, the multinucleate giant cells were mainly found in PGCG comprised (7.6%). The Pearson Chi-Square test reported a statistically significant difference between the fibrous, blood vessel proliferation, and multinucleated cell features and various types of ORHLs as shown in (Table 7). Moreover, histopathologic images of some of these lesions were provided in (Fig, 9) for better understanding.

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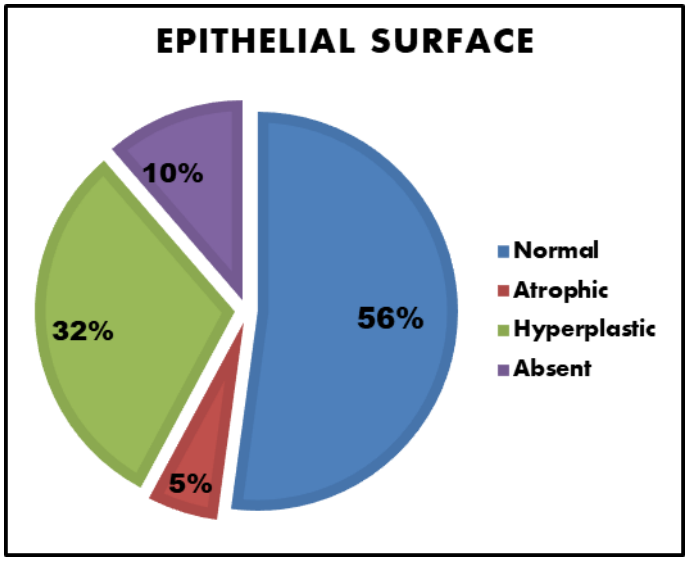

Figure 7: Distribution of the lesion according to histopathological features (epithelium surface)

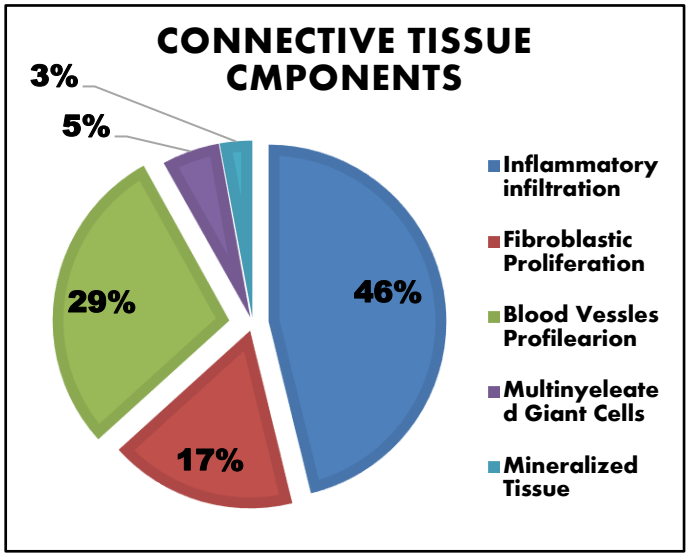

Figure 8: Distribution of the lesion according to histopathological features (Connective tissue components)

Table 5: Distribution of ORHLs according to Histopathological Features

Parameters		Oral Reactive Hyperplastic Lesions N (%)								
		PG	FFH	PGCG	POF	IF	SCP	VV	TN	St. Test
Epithelial	Normal	96 (31)	5 (1.6)	12 (3.9)	1 (0.3)	46 (14.9)	7 (2.3)	2 (0.6)	0 (0.0)	*P=0.001 **X2=71.4
	Atrophic	4 (1.3)	1 (0.3)	1 (0.3)	2 (0.6)	8 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	
	Hyperplastic	37 (12)	2 (0.6)	5 (1.6)	2 (0.6)	34 (11)	10 (3.2)	2 (0.6)	0 (0.0)	
	Absent	16 (5.2)	1 (0.3)	6 (1.9)	0 (0.0)	6 (1.9)	1 (0.3)	0 (0.0)	2 (0.6)	
Inflammation	Yas	143 (46.1)	8 (2.6)	15 (4.8)	4 (1.3)	47 (15.2)	10 (3.2)	1 (0.3)	0 (0.0)	*P=0.001 **X2=75.5
	NO	10 (3.2)	1 (0.3)	9 (2.9)	1 (0.3)	47 (15.2)	8 (2.6)	3 (1.0)	2 (0.6)	
Inflammation Type	Chronic	97 (42.4)	7 (3.1)	14 (6.1)	4 (1.7)	44 (19.2)	10 (4.4)	1 (0.4)	0 (0.0)	*P=0.001 **X2=25.0
	Acute	46 (20.1)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Inflammatory Intense	Mild	104 (45.4)	5 (2.2)	12 (5.2)	1 (0.4)	37 (16.2)	9 (3.9)	1 (0.0)	1 (0.0)	*P=0.001 **X2=30.8
	Moderate	17 (7.4)	3 (1.3)	1 (0.4)	0 (0.0)	4 (1.7)	0 (0.0)	0 (0.0)	1 (0.4)	
	Intense	22 (9.6)	0 (0.0)	2 (0.9)	3 (1.3)	6 (2.6)	1 (0.4)	0 (0.0)	1 (0.0)	
Fibrous	Yas	56 (18.1)	0 (0.0)	10 (3.2)	3 (1.0)	14 (4.6)	2 (0.6)	0 (0.0)	0 (0.0)	*P=0.001 **X2=40.5

Proliferation	**No**	97 (31.3)	9 (2.9)	14 (4.5)	2 (0.6)	80 (25)	16 (5.2)	4 (1.3)	2 (0.6)	
Blood vessels Proliferation	**Yas**	114 (36.8)	4 (1.3)	7 (2.3)	0 (0.0)	15 (4.9)	2 (0.6)	0 (0.0)	0 (0.0)	*P=0.001 **X2=116
	No	39 (12.6)	5 (1.6)	17 (5.5)	5 (1.6)	79 (25.2)	16 (5.2)	4 (1.3)	2 (0.6)	
Mineralized Tissue	**Yas**	3 (1.0)	0 (0.0)	2 (0.6)	5 (1.6)	5 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	*P=0.001 **X2=71.8
	No	150 (48.4)	9 (2.9)	22 (7.1)	0 (0.0)	89 (28.7	18 (5.8)	4 (1.3)	2 (0.6)	
Multinucleate Giant Cells	**Yas**	1 (0.3)	0 (0.0)	24 (7.6)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	*P=0.001 **X2=259
	No	152 (49.0)	9 (2.4)	0 (0.0)	5 (1.6)	92 (29.7)	18 (5.8)	4 (1.3)	2 (0.6)	
Hemorrhage	**Yas**	2 (0.6)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	*P=0.68 **X2=6.61
	No	151 (48.7)	9 (2.9)	22 (7.1)	5 (1.6)	92 (29.7)	18 (5.8)	4 (1.3)	2 (0.6)	

PG: Pyogenic granuloma, PGCG: Peripheral giant cell granuloma, POF: Peripheral ossifying fibroma, IF: irritational fibroma, FFH: Focal fibrous hyperplasia, TN: Traumatic neuroma, VV: Verrucous vulgaris, SCP: Squamous cell papilloma. *P value ** Pearson Chi-square.

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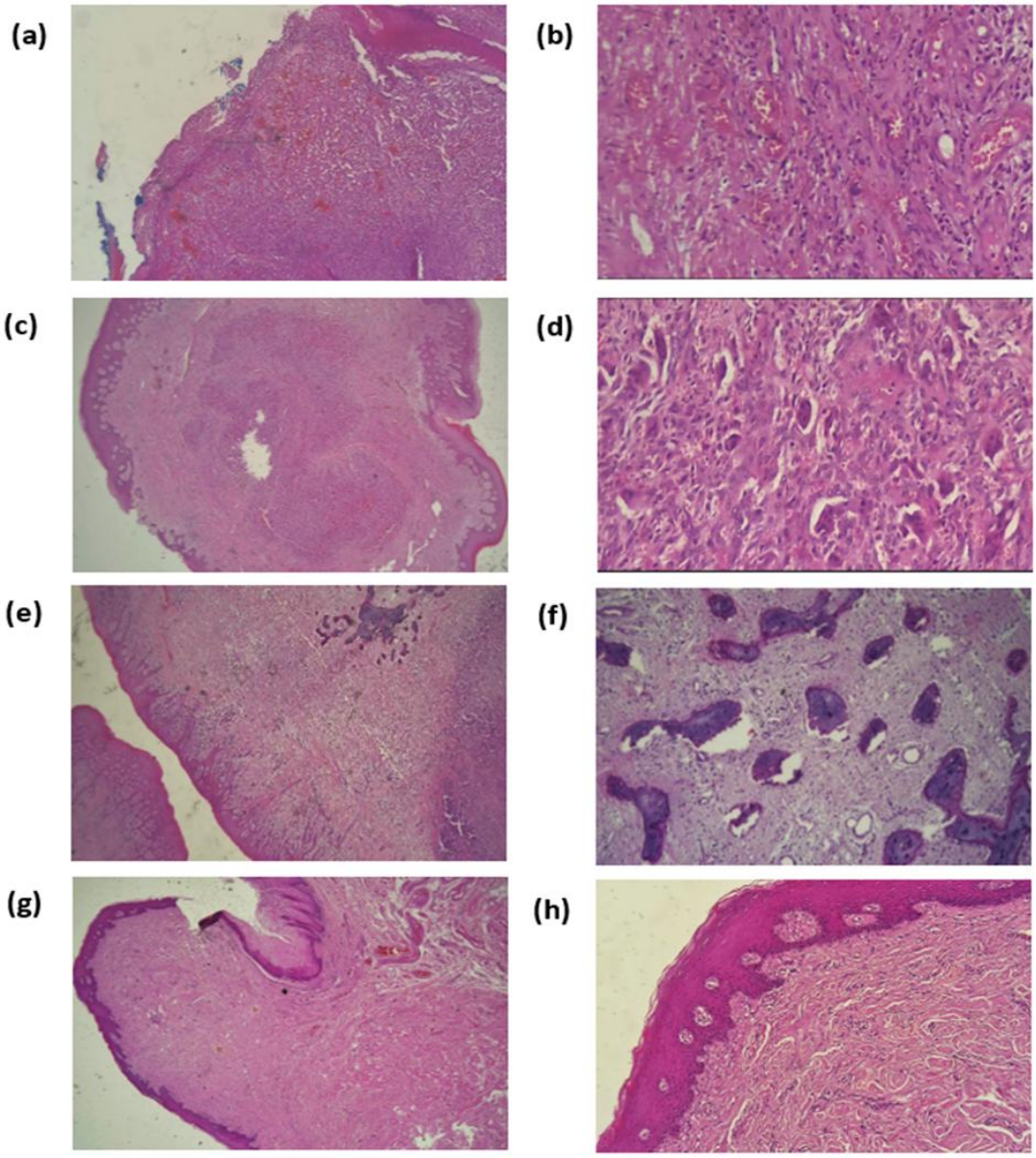

Figure 9. Representative Hematoxylin and eosin staining photomicrographs of histopathological features of ORHLs. (a) PG (40×) exhibits a lobated pattern the lesion is covered by an ulcerated thin layer of stratified squamous epithelium; (b) high magnification of the same case showing proliferation of endothelial cells and a large number of inflammatory cells (200×). (c) PGCG with thin and long epithelial projections (40×); (d) high magnification showed nodular prefiltration of multinucleated giant cells (200×). (e) POF with mineralized product in the connective tissue (40×); (f) high magnification of the same case demonstrating irregular bone trabeculae formed (200×); (h) IF showing hyperplastic epithelium with bundles of collagen fibers (40×); same case with high magnification showed connective tissue with chronic inflammatory cells (200×)

Discussion

A population-based prevalence or cross-sectional study is currently being conducted in Tripoli, Libya, to determine the frequency and clinicopathological features of ORHLs over 22 years. The current population sample is considered a suitable representation of the Libyan population in Tripoli, as the specimens were obtained from the Oral and Maxillofacial Department at Tripoli University Centre, one of Tripoli's largest and highly respected dental care hospitals. Additionally, every report specimen examined from the Saray Salam Center, Tripoli, Libya was included in the current study. Direct comparisons of histological diagnoses of lesions may be impossible due to heterogeneity in sample collection methods, patient age groups, and study design (13).

Out of a total of 2310 oral specimens, 14.5% had ORHLs. In agreement with our results, recent epidemiologic studies have revealed nearly similar to results conducted in Nigeria (14.2%) (14), Kuwait (13.9%) (15), and India (11.7%) (16). However, other studies conducted in different nations showed a higher incidence of ORHLs among oral lesions, Nepal (67.56%) (17), Iran (34.6%) (18), Egypt (33%) (7), and Brazil (22.25%) (2). On the other hand, a much lower prevalence approximates about half, and less of our prevalence observed in another research performed by Buchner et al., (6.7%) (19), Effiom et al., (5.6%) (20), and Motamedi et al., (5%) (21). Different terminology and classification systems may explain the difference in the frequency of reactive hyperplastic lesions among nations. In addition, differences in geography, lifestyle, race, study methodology, and sample size might have affected the results.

From point of-year trend analysis, the current study's prevalence of ORHLs by year revealed a significant variability over two decays, it shows a marked decline in ORHLs incidence between 2018 and 2020, which coincided with the start of the COVID-19 pandemic, which led to the closure of multiple institutions and the concentration and guidance of hospitals and medical personnel toward combating Corona, this observation also demonstrated by research conducted recently on Egypt (22). However, the prevalence of ORHLs significantly increased between 2022 and 2023, which might require additional research into the factors causing the increase in demand.

As demonstrated by our study, which had a female predominance (63%), the literature suggests that ORHLs have a stronger impact on female patients than male patients. (6, 15, 23, 24). Males were more prevalent in some studies (3, 25). The literature confirms that hormone imbalance, stress, and chronic irritation all contribute to an elevated risk of ORHLs and that female patients are more likely to observe and share changes in their oral cavity. The female predilection also supports these findings.

The age of onset is crucial for making a differential diagnosis of a lesion. In our study, the overall mean age of patients with various forms of ORHLs was 36.4±7 years, consistent with results published from other countries (4, 26). In addition, in line with research from Nigeria (14), Saudi Arabia (23), Iran (18), and Portugal (27), the average age of ORHLs in our study was discovered to be between the second and fourth decades. This could arise as a result of the middle-aged population's frequent exposure to trauma, low-grade inflammatory stimuli, or recurring irritation, which are believed to be the main risk factors for the majority of ORHLs.

In this study, gingiva was found to be the most commonly affected site for ORHLs, accounting for 31% of cases. This finding aligns with the results reported by Dutra et al., (2) and Nair et al, (28). In the same manner, Kadeh et al. (26) and Hunasgi et al. (29) suggested that the gingiva's frequent involvement may be due to its increased exposure to various irritants. Notably, our result found that PGCG and POF were exclusively localized to the gingiva or alveolar mucosa. This specific distribution is likely attributed to their origin from the periosteum or periodontal ligament which contains cells capable of generating bone and cementum, as Shadman et al. (30) and Wu et al. (31) proposed. This observation is further corroborated by several other studies, including those conducted by Ghandi et al., (32), Patil et al., (33), and more recently, Fligelstone and Ashworth (34).

The current study showed that PG was the most common prevalence lesion comprising (48.1%) of all ORHLs, consistent with the findings of other studies conducted on the issue (35-37). Whereas PG a had the second most common type of ORHLs in previously reported researchs (18, 23, 38). Our research revealed that the highest age of PG incidence occurred between the second and fourth decades of life, these observations support studies by (25, 39). It should be highlighted that in most of the studies, including ours, PG was more frequent in females (31.6%) (15, 17, 38, 40). Despite this, several authors noted a preference for men. (41, 42). Mishra and Pandey (43) demonstrated that gender prediction is not specified. Consistent with other studies, PG could be related to hormonal changes, specifically, to the vascular effects of female hormones. Furthermore, the gingiva was found to be the most common site for PG, which aligns with the results reported by several researchers, including Metwall et al., (22) Dutra et al., (2) Dakkam et al., (38) Amirchaghmaghi et al., (25), and Naderi et al (3). The predominant color observed among the lesions was reddish, accounting for (25.0%) of cases. This characteristic reddish appearance can be attributed to the typical histological structure of PG, which consists of highly vascularized granulation tissue containing numerous blood vessels.

Interestingly, IF was considered the second most prevalent lesion in our study with 102 cases (30.4%), this result is consistent and agrees with the findings in a few studies (26, 44). On the contrary, most of the prior studies have disagreed with our result, they reported that PG was the most prevalent lesion followed by IF, and they reported various prevalences at 57.4% (Reddy et al.,2012) (42), 69.3% (Vidyanath et al., 2015) (45), 37.4% (Sangle et al., 2018) (46), 72.09% (Dutra et al., 2019) (2), and 61% (Zhao et al., 2023) (47).This result can be explained by the fact that irritational fibroma has many terminologies utilized to describe these

lesions in the literature, including traumatic fibroma, fibroepithelial polyp, and inflammatory fibrous hyperplasia.

Regarding gender, IF occurs most frequently in females (18.2%) in accordance with the results of previous studies (15, 17, 38, 40). Despite this, a few authors observed a preference for males (3, 39, 44). Additionally, in agreement with findings from previous studies, our research showed that a high incidence of IF occurred between the third and fourth decades, with in agreement findings of researches (29, 38). However, other studies revealed that IF was more common in the elderly after the fourth decade of life (14, 23). Differences in oral health and the frequency and length of exposure to different kinds of irritation could explain the age disparity in IF between countries. Moreover, the location with the greatest prevalence was buccal mucosa (40.2%), followed by the tongue (28%), which is consistent with previous research (43, 48). According to Soyele et al. (14), Lakkam et al. (38), and Dutra et al. (2), the gingiva is the most commonly affected site.

In this current research, clinical features of ORHLs show remarkable variety; among the lesions evaluated, those shorter than 3 cm were much more common, accounting for 89.0% of cases. This result is consistent with several other global studies (49, 50), current research suggesting larger lesions could indicate a more severe or expanded reactive response, indicated by a statistically significant difference in size categories (P=0.001). The majority of ORHLs had smooth surfaces, comprising 125 cases (44%), followed by irregular surfaced lesions with 115 cases (40%) and ulcerated surface lesions with 27 cases (10%), and the least common was papillary surface only (6%). These findings were consistent with those shown by Kazmi et al, (51). Furthermore, many cases found with IF (53, 18.6%) and PG (47, 16.5%) exhibited smooth surfaces. The color of the lesion is another important factor, with red to purple lesions being the most commonly observed (44.1%), among these lesions, the majority of cases with PG (48, 15%) exhibited red color. This finding was comparable to that demonstrated by studies (44, 52). Where mucosal-colored lesions accounted for 30%, with statistical significance (P=0.04). This suggests that coloration may represent underlying vascular or inflammatory concerns pertinent to the clinical assessment of ORHL.

The current study found a high incidence of histological characteristics specific to each condition, including vascular growth in PG, mineralized material in POF, and multinucleated giant cells in PGCL. These characteristics were also observed in other groups' lesions, indicating some overlap in histological diagnostic criteria. This could explain the observed frequency disparities in the literature and support the theory that these diseases are caused by distinct tissue reactivity to similar trigger factors (53).

Surprisingly, the histological findings of ORHLs in this study provide useful information on their etiology. Our analysis revealed that almost all (92.8%) of the cases observed during the experimental period were characterized by hyperplasia of both epithelial and connective tissue components, which is commonly associated with chronic low-grade trauma. This finding is consistent with recent research conducted by Fathy et al 2024., (1). This finding explains why these etiological elements dominate the microscopic features of the lesions. Furthermore, the histological appearance corresponds to the nature of the stimuli, implying a reactive proliferation in response to chronic, low-grade irritation.

In contrast, all cases of ORHLs classified as epithelial hyperplasia are caused by the human papillomavirus (HPV). Successful HPV infection begins with entry and replication in stratified squamous epithelial cells, followed by differentiation, which results in epithelial hyperplasia alterations (Shafti-Keramat et al., (54); Rautava and Syrjänen, (55). In the current study, HPV-induced lesions (verruca vulgaris, Heck's disease, and condyloma acuminatum) accounted for fewer than 1% of the observed cases, indicating a restricted spread of the infection in the Libyan community.

Lastly, the reactive lesions in the category of connective tissue hyperplasia in this study comprised (0.9%) which is a significantly lower prevalence proportion such in TN (0.6%) and TEU (0.3%), these prevalences were consistent with results reported by a study done on the Egyptian population (22) where the prevalence was observed to be TEU (0.7%) and TN (0.2%).

Implications for practice

The statistical analysis in the current study confirmed strong associations between lesion types and their features, highlighting the importance of these findings for accurate diagnosis and treatment. Overall, the study enhances the understanding of lesion classification in clinical practice.

Limitations of the study

The current study had some limitations. One limitation is that the data was a retrospective study, and the records used were not created specifically for our research, which may impact the retrieved data quality. Another limitation is that there was not enough clinical data to identify the etiological factors related to the development of ORHLs. However, the present research was the first to analyze the frequency and pathology of biopsied reactive lesions of the oral cavity in a Libyan population.

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Recommendation
Based on the study's findings, several recommendations are made. Through educational programs, enhance awareness among healthcare providers about the higher incidence of oral reactive hyperplastic lesions in females and specific age groups. Implement regular oral health screenings, especially for individuals aged 20-35 and 36-55 years, to enable early detection and treatment. Conduct further research to explore genetic, hormonal, and environmental factors contributing to the higher incidence in these groups. Develop standardized diagnostic and treatment protocols to ensure consistent patient care. Educate patients on the importance of good oral hygiene and seeking prompt medical attention for oral lesions, providing information on common lesion types and their clinical features for early identification.

Conclusion
The study found that 14.5% of patients had ORHLs, with PG being the most common. The gingiva was the most common site of involvement, followed by the tongue. The study found a significant correlation between oral ORHLs and their histological categories. The shared characteristics may indicate distinct stages of the same traumatic/inflammatory etiology. Familiarity with common oral lesions helps with clinical diagnosis and differential diagnosis, allowing for accurate patient evaluation and management. Early detection and surgical excision can reduce complications. The study's variance in reactive lesions may be due to cultural differences and study design aspects, which require further research.

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Conflict of Interest
There are no financial, personal, or professional conflicts of interest to declare.

Data availability statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflict of interest. Nil

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المستخلص

الآفات التضخمية التفاعلية الفموية (ORHLs) هي تضخم غير ورمي يشبه الورم يتطور بشكل متكرر في الغشاء المخاطي للفم بسبب الالتهاب المزمن الناجم عن العديد من التهيجات منخفضة الدرجة. وهي شائعة نسبيًا، ويشبه مظهرها السريري التكاثرات السرطانية. تهدف هذه الدراسة إلى تحديد انتشار وتوزيع الآفات التضخمية التفاعلية الفموية بناءً على تصنيف منظمة الصحة العالمية لأورام الرأس والرقبة (2022) في السكان الليبيين على مدى السنوات العشرين الماضية ومقارنة النتائج بالأدبيات السابقة. في هذه الدراسة الاسترجاعية، تمت مراجعة جميع سجلات الآفات التضخمية التفاعلية الفموية التي تم تشخيصها نسيجيًا بين عامي 2002 و 2023 والتي تم جمعها من مستشفى جامعة طرابلس ومركز سراي سلام في طرابلس، ليبيا. تم استخراج المعلومات المتعلقة بالعمر عند التشخيص والجنس وموقع الإصابة والتشخيص النسيجي المرضي وتحليلها باستخدام برنامج SPSS الإحصائي (V.26) باستخدام اختبار مربع كاي. شكلت أورام اللثة المحيطة بالسن 14.5% من إجمالي الحالات التي تم تشخيصها (3210/335) في الخزعات المسجلة للفم والوجه والفكين. كان الورم الحبيبي القيحي (PG) هو النوع الأكثر شيوعًا من أورام اللثة المحيطة بالسن (48%) يليه الورم الليفي المهيج (30%) (IF) والورم الحبيبي الخلوي العملاق المحيطي .(8%) (PGCG) كان ذروة حدوث أورام اللثة المحيطة بالسن في العقدين الثالث والرابع (37.6% و32.8% بأثر رجعي)، مع عمر إجمالي عند بداية التشخيص (متوسط ± انحراف معياري 36.4±7). كانت العلاقة بين الفئات العمرية وأورام اللثة المحيطة بالسن ذات دلالة إحصائية .(P=0.03) وُجدت هيمنة الإناث في جميع الآفات بنسبة (2:1). كانت اللثة هي الموقع التشريحي الأكثر انتشارًا لأورام اللثة المحيطة بالسن، حيث مثلت 31% من الحالات. كانت هناك بعض أوجه التشابه والتناقض بين نتائجنا والدراسات السابقة التي شملت مجموعات سكانية مختلفة. لقد وجدنا اختلافًا جغرافيًا واضحًا في معدل الإصابة النسبي للآفات التفاعلية الفموية في كل محافظة ليبية. يمكن تقييم حدوث آفات الفم التفاعلية الفموية في دول مختلفة بأثر رجعي لتحسين المعرفة بآفات الفم التفاعلية الفموية، وهو أمر بالغ الأهمية لعلماء الأمراض وجراحي الفم والوجه والفكين.