

A histopathological Study of the Oral White Lesion Cases in Benghazi.

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Original Research Article

ABSTRACT

Background: The white lesions of the oral cavity are clinically common. They represent a large number of cases diagnosed as diseases with different severity, such as dysplasia and traumatic keratosis, and may lead to squamous cell carcinoma (SCC).

Aim: The study was to determine the types of oral white lesions in all patients who presented to the Oral Pathology Department at the Faculty of Dentistry in Benghazi in the period from 1999 to 2019.

Method and Materials: This study was a retrospective and descriptive type. The data were taken from the records of 149 cases with white lesions in the oral cavity and squamous cell carcinoma derived from white lesions. Statistical analysis and SPSS program were used.

Results: showed that most of the cases were more than forty years old. In general, more women than men were affected. The site of lesion was unilateral buccal mucosa in most cases. More than 56% were diagnosed as lichen planus, followed by leukoplakia (10.7%), simple keratosis (10.7%), frictional hyperkeratosis (6.7%), lichenoid reactions (3.4%), lupus erythematosus (3.4%), and white sponge nevus (2.0%). This study showed that the most common oral lesions, most commonly involved sites, age range and gender predilection were consistent with most published research in the literature, with the possibility of transformation of these lesions into dysplasia and SCC.

Conclusion: These lesions were associated with many systemic diseases. Awareness, early diagnosis and treatment will minimize disease further development.

KEYWORDS: oral white lesion, lichen planus, leukoplakia.

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INTRODUCTION

The oral cavity is exposed to external environmental insults in addition to systemic diseases that initially appear in the mucosa of the oral cavity, leading to oral lesions. The oral white lesions (OWL), which are commonly found on the oral mucosa, might be benign (may not require treatment), pre-malignant or malignant conditions.

Leukoplakia was mostly demonstrated as precancerous cases of the oral cavity, and the OWL is a medical manifestation of oral cancers; so a distinctive diagnosis of these lesions is essential. Also, the appearance of dysplasia in the pathology of OWL is clinically important (1) & (2). In a study of oral white lesion in Iran, the cases of white lesions were about 20.9% of the study population. The idiopathic lichen planus (ILP) was the most common lesion (3).

Lichen planus is commonly found in the mucosa of the oral cavity. OLP is an inflammatory immune-mediated disorder. This was followed by leukoplakia in which speckled leukoplakia and verrucous type were more common (4).

In Hungary, about 27% of the study sample had dysplasia showing characteristic changes in the epithelial thickness due to the increased cell proliferation (hyperplastic epithelial dysplasia). It is also associated with parakeratosis. These findings may be understood as a probable cause to the changes of epithelial and connective tissue layers in leukoplakia (5).

So far, no work has been done to evaluate all the types of oral white lesions among the Libyan population. This study aimed to shed light on the incidence of white lesions of the oral cavity over the past twenty years in Benghazi. All the information available in the files of oral white lesion patients was collected and evaluated. The results and possible risk factors were discussed in relation to previous results in the literature.

AIMS OF STUDY

This research was conducted to:

1. Study the types of oral white lesions in all patients who presented to the oral pathology department in

the Faculty of Dentistry in Benghazi, and their residences.

2. Identify the number of cases with special concern to the age, sex, site of lesion, grade of dysplasia and diagnosis.

3. Evaluate the cases of squamous cell carcinoma derived from these white lesions.

MATERIAL AND METHODS

The study was a cross-sectional, retrospective type. About 149 cases, included in this study, were diagnosed with oral lesions in the department of oral pathology, Faculty of Dentistry in the period from 1st January 1999 to 31st December 2019.

All the patients' information, including: sex, age at diagnosis, site of lesion, histopathological type, and grade of dysplasia, was extracted from medical file records.

Inclusion criteria:

All the white lesions in the oral cavity, including lingual, buccal, labial mucosae, palate, and floor of mouth, with special concern to dysplasia and OSCC caused by OWL.

Exclusion criteria:

Nicotine stomatitis, neoplastic lesions, actinic cheilitis, and actinic keratosis were excluded from the study.

H&E stained tissue sections of lesions were collected and examined under a light microscope. Different histopathological changes and dysplasia grades were established.

Statistical analysis:

The data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics, including frequency, percentage, and mean $\pm$ standard deviation, were obtained for all variables as appropriate. A P value of less than 0.05 was considered statistically significant. Microsoft Word, SPSS, and Excel were used to create tables and graphs.

RESULTS

During the period of twenty years, there were 149 patients with OWL. About 84 cases (56.4%) were diagnosed as lichen planus, then leukoplakia 16

cases (10.7%), simple keratosis 16 cases (10.7%), frictional hyperkeratosis 10 cases (6.7%), lichenoid reaction 5 cases (3.4%), lupus erythematosus 5 cas-

es (3.4%), white sponge nevus 3 cases (2.0%) & Squamous cell carcinoma developed from white lesions were 10 cases (6.7%).

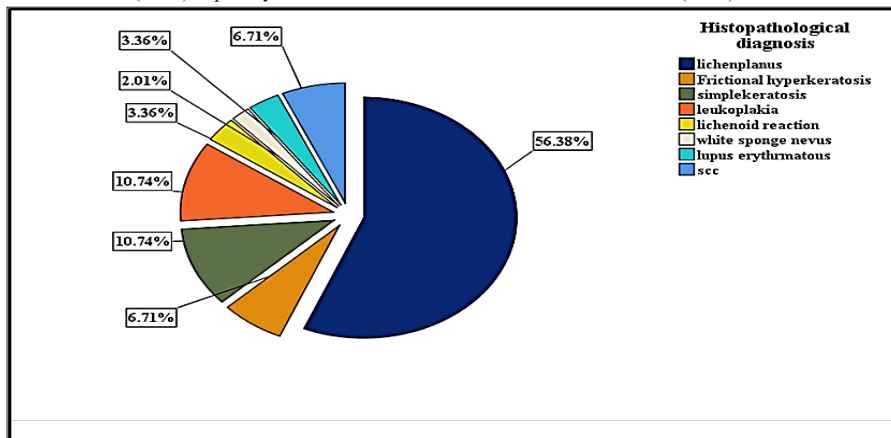


Figure (1): Histopathological diagnosis

Histopathological diagnosis according to age:

The majority of the OWL cases were above 40 years = 109 (73.2%). The cases under 40 years old were 40 (26.8%).

Most of the cases of the lichen planus, leukoplakia, simple keratosis, squamous cell carcinoma and lichenoid reaction were over forty years old, while more cases of frictional hyperkeratosis, white sponge nevus and lupus erythematosus were under forty years old.

Table (1): Age groups according to histopathological diagnosis, p value= 0.001 highly significant

	age groups	
	< 40 yrs. No. (%)	≥ 40yrs No. (%)
Lichen planus	21 (52.5%)	63 (57.8%)
Frictional hyperkeratosis	6 (15.0%)	4 (3.7%)
Simple keratosis	5 (12.5%)	11 (10.1%)
Leukoplakia	1 (2.5%)	15 (13.8%)
lichenoid reaction	0 (0.00%)	5 (4.6%)
white sponge nevus	3 (7.5%)	0(0.00%)
lupus erythematosus	3 (7.5%)	2 (1.8%)
Squamous cell carcinoma	1 (2.5%)	9 (8.3%)
Total	40 (100%)	109 (100%)

Histopathological diagnosis according to gender:

The number of female cases in general was higher, 78 (52.3%), than male cases, 71 (47.7%). The lichen planus cases were higher in females, in addition to lichenoid reaction. In the male category, simple keratosis, leukoplakia, lupus erythematosus, and white sponge nevus were higher.

P value = 0.318 (not significant)

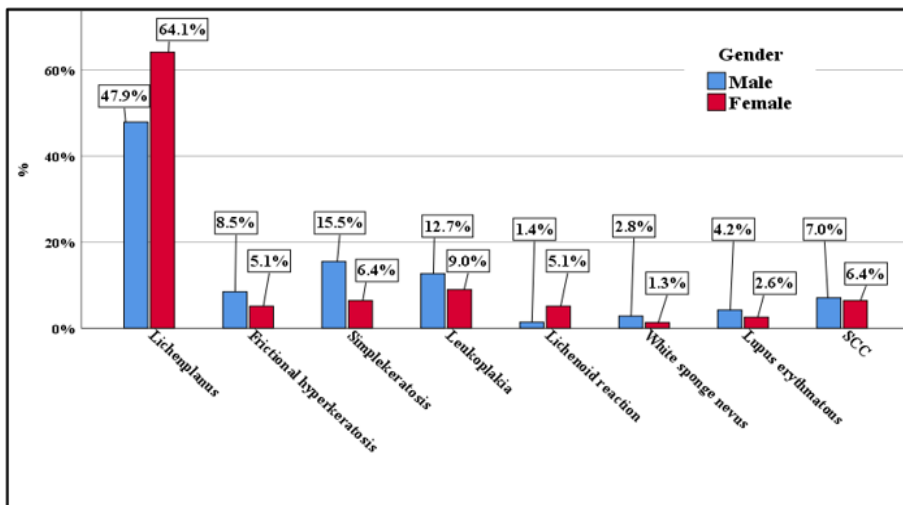


Figure (2): Histopathological diagnosis according to gender

The site of lesion distribution:

In oral white lesion cases, the buccal mucosa showed the highest number of cases, 81 (54.4%) patients, followed by multiple sites 20 (13.4%), labial

18 (12.1%), tongue 16 (10.7%), palate 12 (8.1%), and the least was the floor of the mouth in 2 (1.3%) cases.

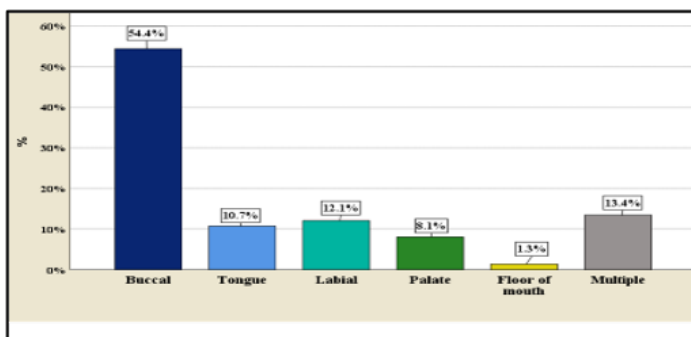


Figure (3): Site of lesion.

The number of patients according to grades of dysplasia:

Concerning the dysplasia of oral white lesions, about 24.2% of the oral white lesion cases devel-

oped dysplasia with different grades. Out of 36 dysplasia cases, 26 (72.2%) were mild, 8 (22.2%) were moderate, & 2 (5.6%) were severe.

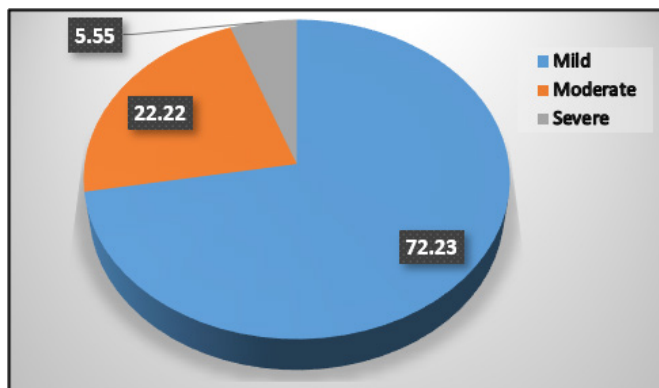


Figure (4): Distribution of dysplasia and grades.

Distribution of lichen planus cases according to clinical subtypes:

OLP subtypes; most of the cases were diagnosed as erosive 36 (42.9%), bullous cases were 5 (6.0%),

reticular were 4 (4.7%), & the least was atrophic 2 (2.4%) cases. About 37 (44%) of patients were recorded without a subtype in the files.

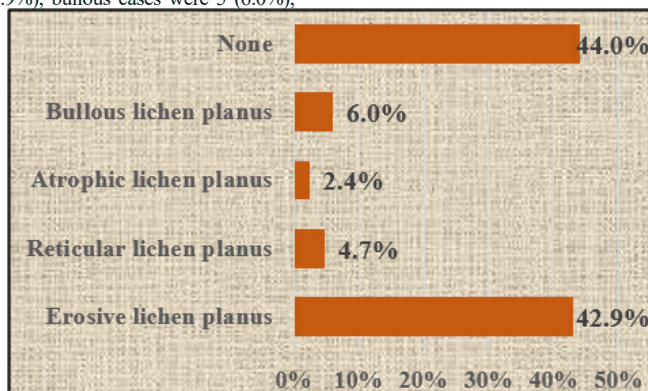


Figure (5): OLP cases distribution according to clinical subtypes

The numbers of oral leukoplakia cases according to clinical subtypes

There were 16 patients with leukoplakia. Verrucous leukoplakia accounted for 13 (81.3%) cases, and

candida leukoplakia accounted for 3 (18.7%) cases. There were no recorded cases of homogenous or hairy leukoplakia.

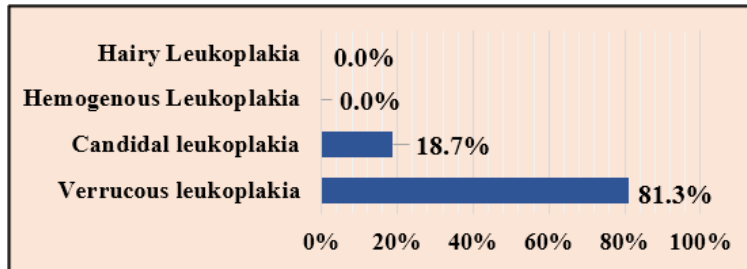


Figure (6): leukoplakia cases and clinical subtypes

Distribution of oral SCC according to clinical presentation (N=10)

The number of OSCC cases that progressed from OWL was 10 patients, with more patients having white than white & red lesions. The predominant grade of OSCC was well to moderate with 6 (60%) patients and 4(40 %) cases were of well grade. The grades were well in which white and red & white were equal at 2 cases each (50%), and well to moderate where white was higher with 4 cases (66.6%) than white & red with 2 cases (33.3%).

p value = 0.691 not significant

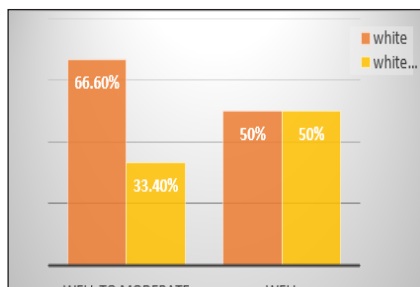


Figure (7): Distribution of clinical feature of oral SCC according to Grade

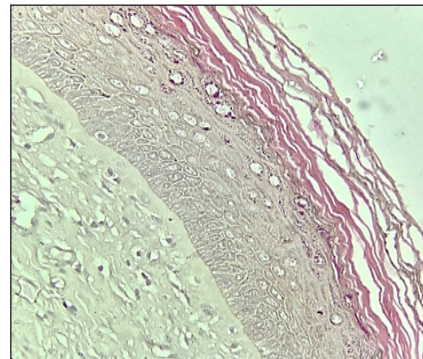


Figure (8): (frictional hyperkeratosis) The section showed hyperkeratosis (black arrow) with thick squamous epithelial layer and mildly inflamed stroma (blue arrow) H&E (10X)

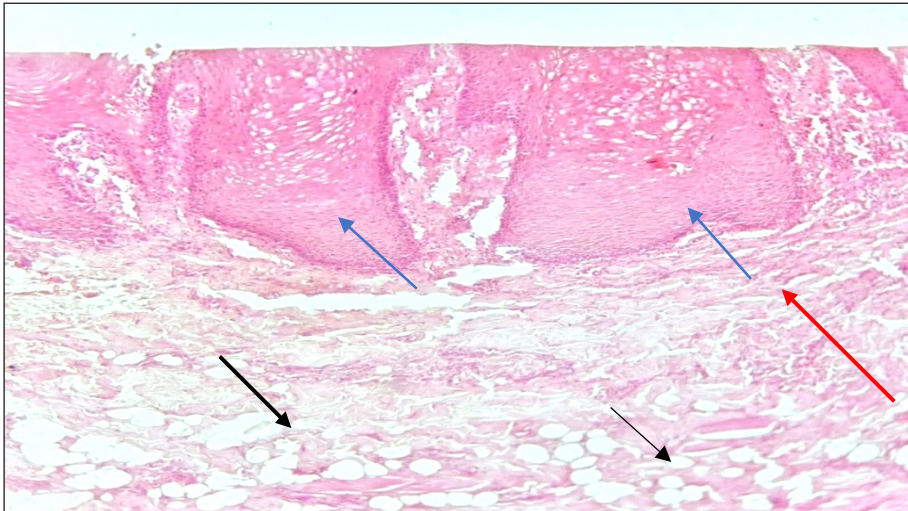


Figure (9): (white sponge nevus) The section showed severe acanthosis with formation of large blunt rete ridges (red arrow) and spongiosis. Extensive vacuolation of squamous epithelium (blue arrows); the underlying tissue showed loose congested fibrous tissue (black arrows), H&E (X10)

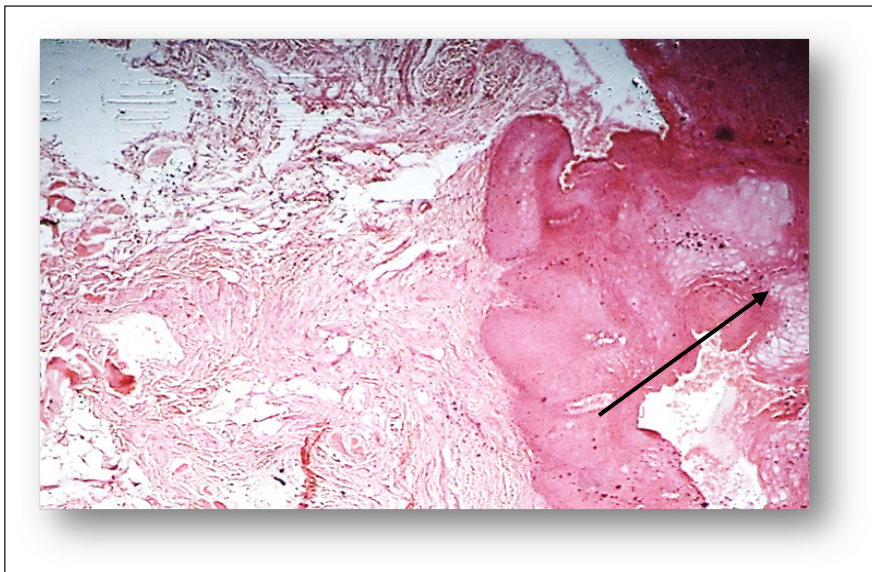


Figure (10) (hyperplasia lichen planus) There is irregular epidermal hyperplasia with balloon degeneration of squamous epithelium also there in a few inflammatory cells in the lower stroma (black arrow) H & E (X10).

DISCUSSION

The oral cavity lesions represent a large number of different clinical features. Most of these lesions are benign, some are premalignant and/or malignant at the time of clinical presentation.

The results of this study showed that most of the cases were more than forty years old. In general, more females were affected than males (Figure.1 & 2), (Table 1). The site of infection in most cases was unilateral buccal mucosa (Figure. 3). Most cases were lichen planus, followed by leukoplakia, simple keratosis, frictional hyperkeratosis, lichenoid reactions, lupus erythematosus, white sponge nevus, and SCC. The grades of SCC ranged between well to moderate (60%) and well (40%). The dysplasia of OWL was found in 24.2% of our patients, with a mild grade in the majority of the cases, some moderate, and a few severe cases (Figure. 4).

The age range of our patients was in agreement with previous results in different countries (6, 7, 8, 9, 10). In general, more females were affected, probably related to hormonal changes and autoimmune diseases. Others found that OWL was higher among males due to khat/tobacco chewing habits ($P < .001$). The number of oral keratotic white lesions was more prominent in males.

It was noticed that the OLP patients were middle-aged (57.8%), with females (64.1%) (Figure.5), whereas males were 47.9%, which agrees with previous studies on the incidence of lichen planus and its age and gender distribution in Tripoli (6) and in Iran (7). Others reported that Idiopathic LP cases were more common, with 63.5% female and 36.5% male, but OLP was higher among females in Serbia ($P < 0.001$) (8).

The OLP affected 0.5–2.0% of the general population (11, 12, 13). Other workers believed that the pathogenesis of OLP was due to immune-modulated events (14). The pathogenesis of OLP includes psychological factors and the genetic background of the patient (15, 16). Systemic conditions such as thyroid dysfunction, hypertension, hepatitis, and diabetes (17, 18) are also associated.

Among the various comorbidities observed in another study, 10.5% of the cases had diabetes mellitus, 8.9% had hypertension, 5.0% had thyroid dysfunction, 2.8% were in an immunocompromised state, 0.8% were anemic, and 25.7% were due to oral abusive habits (18, 19).

The OLP and Hashimoto's thyroiditis (HT) are both autoimmune diseases mediated by T cells. OLP is due to apoptosis in the basal cells of the oral epithelium triggered by cytotoxic CD8 + T cells. Hashimoto's thyroiditis (HT) is due to perforin release by the same lymphocytes, damaging the thyroid cells. A meta-analysis concluded that among OLP patients, the thyroid disease was high. In addition, the risk for women is about 10 times higher than for men because it is triggered by autoimmunity, which is more commonly found in women than men (20, 21). In Libyan patients, 25% of the diabetic cases had hypothyroidism. In another study, similar results were found. Thyroid problems and female gender were risk factors. These cases were more prominent in females (22.5%) than males (2.5%) (22).

In Alwahat Libya, similar conclusion was reached concerning the gender distribution in thyroid diseases (23).

In OLP subtypes, erosive LP was the most prevalent (42.9%). Most ELP patients were between 50–80 years old, with a higher number of females than males (24).

Other subtypes included bullous lichen planus (BLP) (6.0%), reticular lichen planus (RLP) (4.7%), and atrophic lichen planus (2.4%). Notably, no subtype information was available in the medical records for about 44% of the OLP patients. OBLP rarely affects the oral mucosa. OBLP was usually present with blisters occurring over typical lesions of lichen planus. The blisters are more generalized and extensive.

EOLP is symptomatic, causing painful ulcerations. Although it is less common, it is more clinically significant (24, 25).

Unlike ELP, reticular OLP is incidentally found on the oral mucosa, characterized by white lace-like lesions known as Wickham striae. Infiltration of lym-



phocytes in the lamina propria and hyperkeratosis were important histological findings.

Direct immunofluorescence (DIF) can localize fibrinogen deposits and IgM-positive bodies may also be seen, as well as deposits of complement C3, IgG and IgA (26).

The atrophic LP is not common. It forms plaques with an atrophic center. The oral mucosa is frequently affected and these eruptions are much more chronic, and can lead to an OSCC if not followed carefully (26).

The Oral lichenoid lesion (OLL) was diagnosed in only 3 of our patients, most of whom were females over forty years old. Allergic responses to drugs and dental material may cause inflammatory lesions, such as graft-vs-host disease (GVHD); in addition, those suffering from systemic conditions, e.g., chronic hepatitis C (27, 28) and hepatitis B vaccinated (30). The inflammatory mediators may stimulate epithelial cell proliferation, increasing the epithelial thickness. However, the connective tissue cell number was higher in OLP than in OLL, and the presence of a band of basal lamina with strands into the connective tissue provides the basis for the differentiation between OLP and OLL (29, 30, 31). Earlier, some cases were reported as a drug-induced lesion due to the exposure to medications and drugs. The implicated agents are angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs (32, 33, 34, 35).

Since LP is multifocal in more than 60% of females and more than 70% of males, it was concluded that LP with mucosal involvement should be considered and managed as a systemic disease, insisting on the need for a multidisciplinary clinic to ensure optimal care and treatment.

Leukoplakia cases were 10.7% in our patients (Figure. 6). They showed older age but different gender distribution than LP cases with 12.7% males and 9% females. But the age distribution confirmed that the majority of cases occur in individuals over 40 years old. It is defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease (35). The Idiopathic

leukoplakia is recognized as a rare, potentially malignant lesion, primarily located on the tongue, with a greater risk of malignancy than the tobacco-associated variety (36, 37). This risk escalates with age. Clinically, diagnosis can be quite challenging, as it involves excluding other conditions that could cause hyperkeratosis.

Our results were in accordance with research reporting an annual frequency of 6.6% for oral leukoplakia. The gender ratio was male predominant at 7.5:1, with most reported cases occurring in individuals from the 1st to the 8th decade of life, peaking in the 4th to 6th decades (38).

Robert A et al reached different results concerning the gender distribution with predominant female cases (39). This might be due to the predominance of homogenous leukoplakia over smoking-related leukoplakia, as most patients were non-smokers, and smoking is more strongly associated with males. They also found that non-homogeneous leukoplakia was associated with non-smoker status. This supports our findings, where non-homogeneous was higher among our patients.

Leukoplakia can be subtyped, with Proliferative Verrucous Leukoplakia (PVL) (40) accounting for 81.3% of Leukoplakia patients, while candidal leukoplakia comprises about 18.7%. Further studies have shown that PVL with a high recurrence rate along with a significant rate of malignancy occurring in about 74% of cases, often with multi-centric foci (40) which aligns with our findings.

Leukoplakia may be caused by smoking, some components of toothpaste, mouthwash, ultraviolet radiation, microorganisms, and viruses.

Tobacco use was considered an important risk factor related to the triggering of OL and OSCC. Tobacco carcinogens are responsible for chromosomal aberrations affecting the normal process of DNA repair and the cell cycle, leading to aneuploidy (41).

The genetic disorder is the mutation of the tumor suppressor gene p53. These genes regulate the normal processes of apoptosis and cell turnover. Patients with smoking history constitute about 80% of leukoplakia cases (42).

In Libya, smoking is a common habit among male SCC patients (43) and diabetic patients (44). Other studies concluded that smoking, age, and gender were widely related to OWL. These findings were in agreement with others published in Iran (9), and also supported by a Saudi study that 88.8% of the tobacco users had oral lesions (45).

About 18.8% of our leukoplakia patients were diagnosed with candida leukoplakia (CL). It is a candidiasis variant caused by a fungal pathogen. Clinically, the lesions can be treated with antifungals. But if not properly treated, it may transform into dysplasia and carcinoma.

In our study 6.7% of the cases had frictional hyperkeratosis in younger males (Figure. 8). The age of most of the cases occurred in the individuals below 40 years old with a notable gender distribution leaning towards males (8.5%), compared to females (5.1%).

Frictional keratosis (FK) is a repeated trauma, initiated by sharp dentures, oral habits (biting the cheek), chemical, heat or physical irritants leading to a reaction of the mucosa in the oral cavity. Over-keratinization of the non-keratinized areas (e.g. buccal mucosa) and in those keratinized (e.g. hard palate); in the latter the lesion is called frictional hyperkeratosis (Figure; 8).

The lesions more or less extended in proportion to the traumatized area, with a translucent, white appearance to which erythematous areas could also be associated. The lesions were smooth or wrinkled, totally asymptomatic, and surrounded by healthy, pink-colored mucosa. Frictional hyperkeratosis appears whiter in color, with a thicker stratum spongiosum (acanthosis) that absorbs fluid, forming a pseudo-membrane. White lesions are mostly benign, a few are considered malignant disorders (46). If the lesion does not disappear, a biopsy and histopathological examination is required.

The simple keratosis cases were approximately 10.7% of all cases. The majority of cases occur over 40 years, with a notable gender shift toward males (15.5%) compared to females (6.4%).

White sponge nevus (WSN) is a rare genetic disorder of the oral mucosa (Figure.9) that appears as whitish, spongy, thickened plaques (47, 48). The mutations occur in the genes for Keratin 4 or 13, which code for intermediate filaments (48).

Our results included 2.0% of total cases of OWSN. The age distribution shows the majority of cases occur under 40 years, with a notable gender distribution of more males (2.8%) than females (1.3%).

Lupus erythematosus (LE) is an autoimmune disorder. It upsets the oral mucosa with varied prevalence (49, 50). It is affecting 3.4% of our patients. It also showed more cases among younger male individuals. The gender distribution was different from the published reports, but in agreement concerning the site, where the unilateral buccal mucosa was the most common site (54).

Discoid lupus erythematosus refers to an oral discoid lesion with pathologically characteristic features that can be confused with lichen planus.

Concerning the site distribution of the oral white lesions (OWL), the buccal lining (54.4%) was identified as the most common site, with 59.7% unilateral, while the remaining 40.3% were bilateral buccal mucosae, compared to the rest of the oral mucosa. This was in accordance with previous studies (14), while the floor of the mouth had the least occurrences, with only 1.3% (Figure. 3). Similar results were found by other workers (40).

This study revealed that 24.2% of cases with OWL were diagnosed with dysplasia. These were categorized into different grades. Notably, 72.2% of these cases exhibited mild dysplasia, while 22.2% had moderate dysplasia and 5.6% were classified as severe dysplasia. These results were similar to those found by Gurung (4)

Moreover, within 54 cases of homogeneous leukoplakia, 40.7% were found to have mild dysplasia, and 3.7% showed moderate dysplasia. Speckled leukoplakia cases displayed varying grades of dysplasia—mild, moderate, and severe—while two cases of VL were diagnosed with dysplasia between moderate and severe, which corroborates our study findings (Figure. 4). The term “epithelial dysplasia”



denotes significant histologic abnormalities, indicating a greater risk of malignancy that might develop from oral leukoplakia (51, 52, 53).

Approximately 10 OSCC cases arose from oral lesions. Among these, about 6 patients (7.5%) had white lesions, and 4 patients had both white and red lesions. The most common grade of OSCC observed was well to moderately differentiated, with 42.5% of patients falling into this category (Figure. 7). When considering the relationships between the types of lesions and their grades, well-differentiated SCC arose from white lesions in 2 cases and the same number from red and white lesions. Additionally, 4 cases of well to moderately differentiated SCC originated from white lesions, while 2 cases were associated with red and white lesions (Figure. 7). Concerning the age distribution, most of our OSCC patients were more than forty years old, with a ratio of male to female of 1.63:1. Similar results were found by Japer MA (42).

Tobacco, alcohol, and human papillomavirus (HPV) cause lesions and may lead to malignant disorders and consequently OSCC (55). Genetic mutations may inactivate oncogenic signaling and suppressor signaling, increasing uncontrolled proliferation of OSCC cells. About 80%-90% of head and neck SCC (HNSCC) cases were due to expression of epidermal growth factor receptors (EGFR). These receptors promote OSCC cell proliferation, metastasis, and apoptosis resistance.

Tobacco use is a major risk factor for OSCC (56, 57). Smoking was reported in 79% of patients. These habits affect the incidence of OSCC in many sub-sites of the oral cavity such as the palate, while in the other forms of tobacco use, OSCC often occurs in alveolar sulcus or gingiva (48).

In our results, the lining of the lateral sides of the oral cavity was mostly affected, with fewer cases involving multiple sites, the palate, and the floor of the mouth.

A multidisciplinary team of specialists in surgery, oncology and nutrition is required to deal with these cases (49, 51, 57, 58).

CONCLUSION

The oral cavity is exposed to external environmental insults in addition to systemic conditions that initially appear in the oral cavity, leading to oral lesions. White lesions are common findings in the oral cavity. These lesions might be benign (and may not require treatment), pre-malignant or malignant conditions.

RECOMMENDATION

- Improvement in public awareness, lifestyle and regular dental examination.
- Early detection and diagnosis can improve access to affordable treatment and palliative care.
- A complete medical history, including habits, drug history, and duration of disease, is required.

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