High Incidence of Epithelial Dysplasia in Oral Leukplakia: A Retrospective Study

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Authors’ contributions

This work was carried out in collaboration between all authors. Author NN designed the study, wrote the protocol, managed the literature search and wrote the first draft of the manuscript. Author MRZ managed the analyses of the study and edited the first draft. Author SR performed the statistical analysis. All authors read and approved the final manuscript.

ABSTRACT

“Oral leukoplakia” alludes to white keratotic plaques having excluded other known lesions and etiologic factors except smoking. Due to the potential of malignant transformation of this epithelial lesion, the purpose of the present case-series was to determine the clinical and histologic precancerous features of this lesion. The study was conducted at the oral medicine department at the dental faculty, Kerman. Demographic, clinical and histopathologic characteristics of biopsy proven oral leukoplakia cases were collected from the documented records from 1999 to 2017 and registered in pre-designed charts. Finally, out of the 47 patients, the consistency rate between the clinical and histologic diagnosis of this lesion was 85.1%. The incidence of epithelial dysplasia was 48.9% (38.3% mild, 8.5% moderate and 2.1% severe) whereas 53.2% of the lesions were non-homogenous and 66% of the patients were smokers. Inasmuch as dysplasia was reported in the approximately half of the cases, right diagnosis of leukoplakia should be done by the dentist to prevent malignant transformation. Proper understanding, recognising, identification and differentiating this lesion are necessary for proper treatment.

Keywords: Oral leukoplakia; epithelial dysplasia; histopathologic features; malignant transformation.
1. INTRODUCTION

The term "oral leukoplakia" refers to a white keratotic patch or plaque that, based on its histopathological or clinical profile, cannot be attributed to any diseases or causes, other than smoking. However, this term is often used as a clinical term and the definite histopathological changes in the relevant tissue are not taken into consideration as much as the clinical changes [1]. The global prevalence of leukoplakia is estimated to be nearly 1.5-4.3% (2.6% on average). Leukoplakia occurs among men ageing above 50 years old. Approximately 70% of the oral leukoplakia cases are observed on the vermilion of lips as well as buccal and gingival mucosa [1,2]. The incidence of leukoplakia on the oral mucous leads to the increased transformation rate of malignancy into SCC (squamous cell carcinoma), which is the most prevalent type of oral cancers, compared to the one in normal mucosa [3]. Leukoplakia lesions have various clinical manifestations, including homogenous and non-homogenous. The homogenous types often have no symptoms; thus, the lesions are discovered by dentists accidentally during the clinical examinations. Thickening of the leukoplakia surface is usually a reason of referral of patients to the dentist with complaint of mucosal coarseness. However, the emergence of red points and non-homogeneity of leukoplakia result in the increased probability of incidence of the symptoms among patients. These symptoms mainly emerge as a sense of burning when eating spicy foods [1-3]. After all, definite aetiology of leukoplakia is not known yet [4,5].

The major challenge of a clinician while encountering leukoplakia is the existing potential for malignant transformation of the disease. It is of great importance to prevent incidence of the malignant transformation in leukoplakia, since if leukoplakia has been developed and transformed into SCC, in most cases, prognosis of this malignancy will be very poor; thus, it will cause a serious threat for the patient’s life. Leukoplakia accounts for 85% of the oral precancerous lesions and also more than one third of oral carcinomas have a close affinity to leukoplakia [6-10]. Incidence of epithelial dysplasia (which is the prelude of SCC incidence) is mostly related to some clinical characteristics of leukoplakia (site, surface, colour, and size). Those types of leukoplakia, which do not exhibit epithelial dysplasia in their histopathological profile, make clinicians assured of non-transformation of the lesion into SCC to a large extent. However, the reports on mild, moderate, and severe dysplasia in leukoplakia cases usually result in worries, at the same proportion, about its progression and transformation into SCC [11-15]. Since demographic characteristics vary in different societies, assessment of these characteristics along with the clinical and histopathological characteristics of the reported leukoplakia cases will yield better detection of the approximate risk of its transformation into SCC for each society. Moreover, such important epidemiologic data can be eventually used to prevent the incidence of SCC and save the patients. On this basis, the present study was aimed to conduct a retrospective investigation of cases definitely increasing knowledge about the specialised epidemiologic data would be a practical tool for better diagnosis, and this study is the first retrospective study for illustration of clinical features of leukoplakia in Iran.

2. MATERIALS AND METHODS

The present study was conducted via retrospective case-series method. In this study, the archive of Oral Medicine Department, Faculty of Dentistry, Kerman University of Medical Sciences, which contained complete records of the patients with oral diseases since 1999, was reviewed and investigated. The time interval for including the records in the review was considered from the formation date of the archive until early 2017. The reviewer investigated the clinical diagnosis section of all the records found in the archive. All of the records, in which the clinical diagnosis of leukoplakia had been recorded by a specialist in oral diseases, were collected. In terms of clinical diagnosis of leukoplakia, there was a consensus among the oral disease specialists who had visited the intended patients, since they had made their diagnoses based on the definition provided by the WHO for this disease [16]. In the present study, through the census, the data of all the patients who, based on their records in the archive, were diagnosed with oral leukoplakia were included in the study. On the other hand, the patients with incomplete demographic, clinical, or histopathological data, those with a final diagnosis of any lesion other than leukoplakia, and those with any kind of systemic disease were excluded from the study. The patients’ data, including demographic (age, gender, tobacco use, and alcohol use), clinical (site, size, number of focuses or focal points, and homogeneity or non-homogeneity),
and histopathological (final diagnosis as well as presence and severity of the reported dysplasia) were extracted and, then, recorded in separate forms for each patient.

Homogenous leukoplakia refers to a lesion emerging as a plaque with fissured and corrugated surface, clear and well-defined boundary edges, and uniform white colour [2]. All the sampling processes were performed through surgical and incisional methods by specialised assistants of oral diseases and under the direct supervision of oral disease specialists. Once data extracted from the patients' records of Oral Medicine Department were collected, the researcher referred to Oral and Maxillofacial Pathology Department, Faculty of Dentistry. In this stage, the patients' histopathological data were divided between the archives of the two departments; then, the shortcomings and deficiencies, if any, were resolved and eliminated. Afterwards, the collected data were imported into SPSS.V.23 software for the statistical analysis. For descriptive statistics of the obtained results, the indices of dispersion and central tendency were used. Furthermore, Chi-squared test was used to find the significant relationships between the demographic, clinical, and histopathological components. The extracted personal information of the patients was kept confidential from the beginning until the end of the work.

3. RESULTS

The present case-series study was conducted on 47 patients, 23 (70.2%) of whom were male. The mean age of the studied patients was 49.5±11.1, ranging from 32 to 78 years old as the lowest and highest recorded ages, respectively. In accordance with the frequency distribution of age of the patients with leukoplakia, 24 individuals (51%) were assigned to the "below 50 years old" group, 19 (40.4%) to the "50-70 years old" group, and 4 (8.6%) to the "above 70 years old" group. Smoking was mentioned by 31 patients (66%), while only 5 (10.6%) mentioned alcohol use, all of whom were smokers as well. Among the patients studied in this case-series, the agreement between the clinical and final diagnosis was observed in 40 patients (85.1%). The histopathological findings showed that the incidence of dysplasia had been reported in 23 cases (48.9%), 18 of whom had mild dysplasia (38.3%), 4 moderate dysplasia (8.5%), and only 1 had severe dysplasia (2.1%).

The male patients with leukoplakia used to smoke significantly more than the female ones (P=0.035). Besides, in the smoker patients, the lesions had occurred in significantly more than a single site (P=0.023).

Table (1) represents the clinical information of the studied patients in the present case-series. As can be seen, the presented information included site or place of lesion, number of lesion focal points, homogeneity or non-homogeneity, size of lesion, the presence of symptoms and history of previous treatment for the lesion. Figs. (1) and (2) demonstrate two cases of homogenous and non-homogenous leukoplakia from among the studied patients.

![Homogenous leukoplakia in buccal mucosa](image)

**Fig. 1. Homogenous leukoplakia in buccal mucosa**
Table 1. Clinical characteristics of 47 patients with oral leukoplakia

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Frequency (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td></td>
</tr>
<tr>
<td>Lip mucosa</td>
<td>2(4.3)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>26(55.3)</td>
</tr>
<tr>
<td>Lateral border of the tongue</td>
<td>2(4.3)</td>
</tr>
<tr>
<td>Ventral border of the tongue</td>
<td>1(2.1)</td>
</tr>
<tr>
<td>Floor of the mouth</td>
<td>6(12.8)</td>
</tr>
<tr>
<td>Gingiva</td>
<td>3(6.4)</td>
</tr>
<tr>
<td>More than one location</td>
<td>7(14.9)</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td></td>
</tr>
<tr>
<td>Unifocal</td>
<td>29(61.7)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>18(38.3)</td>
</tr>
<tr>
<td><strong>Surface</strong></td>
<td></td>
</tr>
<tr>
<td>Homogenous</td>
<td>22(46.8)</td>
</tr>
<tr>
<td>Non-homogenous</td>
<td>25(53.2)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 15</td>
<td>15(31.9)</td>
</tr>
<tr>
<td>≥ 32</td>
<td>32(68.1)</td>
</tr>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13(27.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>34(72.3)</td>
</tr>
<tr>
<td><strong>Previous Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18(38.3)</td>
</tr>
<tr>
<td>No</td>
<td>29(61.7)</td>
</tr>
</tbody>
</table>

4. DISCUSSION

Nowadays, leukoplakia is diagnosed far too frequently than before, which is attributed to the clinicians' increased knowledge of this disease rather than to the actual increase in its prevalence. The present study is among the very few case-series on oral leukoplakia. The majority of the published valid studies on this type of lesion are methodologically case-report works; thus, they were not taken into consideration in order for comparing their results with the findings of the present work due to the lower level of evidence for this type of research method in the evidence-based pyramid. In fact, some researchers have pointed to rarity of the clinical characteristic of such lesions in their reports on leukoplakia, among which the two works conducted by Gupta et al. [17] and Vandana and Spana [18] can be mentioned.

The present case-series included 47 patients and its comparison with studies conducted via similar methodology indicated that the sample size of
the present work was larger than that of most of these studies and smaller than only a single study conducted by Bagam [16] (which included 55 cases) [19-21]. Lack of case-series studies with larger samples sizes on this type of lesion is seemingly due to the difference of the diagnostics criteria applied for this purpose. Accordingly, in some studies, leukoplakia is composed of white keratotic lesions on the mouth mucosa with origins other than smoking, so that such cases have been thereby recorded and reported as other types of lesions. Petti and Downer [22] expressed that the global prevalence of leukoplakia has been estimated less than what is actually expected and its underestimated report has been related specifically to the developing countries. Similarly, in a study conducted in Iran, Jahanbani [20] has estimated the prevalence of leukoplakia equal to 3.7%. However, in a comprehensive national study conducted by Scheifele et al. [23] on 16128 individuals in the USA, the prevalence of leukoplakia was shown to have a decreasing trend. Hence, the global statistics of the prevalence of leukoplakia around the world appears to be changing and fluctuating over time, which can be attributed to the changes in patterns of smoking habits in different societies over time.

In the present study, the majority of the reported cases belonged to males (70.2%), which was similar to other studies [3,20,22,23]. Nevertheless, results of some studies have indicated considerable prevalence of leukoplakia among females (especially those studies conducted in geographical regions, in which women highly used to smoke). The difference in the prevalence of leukoplakia among males and females is probably due to the difference of smoking rate among the two genders. Results of Petti’s systematic review (2003) indicated that leukoplakia was significantly more prevalent among males than females (prevalence ratio 3.2) [3].

The mean age of the patients with leukoplakia in the present study was 49.48 years, which was almost equal to 50 years old stated in other relevant works [3,20,22,23]. In another case-series in this regard, Bagam et al. [16] mentioned the mean age of 61.69 years old; in fact, the patients at this age had PVL (Proliferative Verrucous Leukoplakia) and the demographic characteristics of PVL could not be compared with those of leukoplakia with certainty. Furthermore, in the present study, the minimum age reported for leukoplakia was 32 years old, which was consistent with the fact about the rarity of incidence of this disease at ages below 30 years old [3].

In the present study, the most common area for the incidence of leukoplakia was reported to be the buccal mucous; whereas, similar studies have mentioned the vermilion of lips and gingiva, in addition to the buccal mucous, as the most common sites for the incidence of leukoplakia [3,20,22,23]. In the present work, no cases of leukoplakia were reported to be observed on the vermilion of the lips, while the floor of the mouth and the tongue were referred to as the most common sites for malignant transformation of leukoplakia [6-10]. Furthermore, in this study, the floor of the mouth ranked the second common site for the incidence of leukoplakia lesions [10].

In the present study, nearly 66% of the patients with leukoplakia used to smoke. Jahanbani [20] demonstrated the significant relationship between smoking and morbidity rate of oral leukoplakia in his work, whereas such a relationship was not found in the present work. On the other hand, in the present investigation, the male patients with leukoplakia used to smoke significantly more than the female ones, which was consistent with the findings of Petti’s systematic review (2003), indicating the higher rate of smoking among male patients with leukoplakia than the female ones. It should be noted that such gender-related difference has been estimated as 50% versus 9% in developed countries and 35% versus 22% in developing countries, which represents the higher difference in developing countries [3].

Although the presence of epithelial dysplasia is reported in 5-25% of the sample cases with leukoplakia [9,24], it was observed in the present study to be at a considerable rate, which was higher than other similar works [2,9,24]. Moreover, the reported high share of the non-homogenous types of this lesion (for increasing the risk of epithelial dysplasia) in the present work is noteworthy. However, based on the systematic reviews conducted by Warna Kulasuryia and Ariya Wardana [25], only three valid works have demonstrated a statistically significant relationship between the degree of dysplasia and malignant transformation, which has been mostly associated with the moderate and mild forms of dysplasia. The above-mentioned findings notwithstanding, in the present study, the pathologist reported the “mild"
degree for 78.2% of the dysplasia cases. Therefore, it is very difficult to draw a definite conclusion about the malignant transformation rate of oral leukoplakia based on the retrospective studies. In order to complete the reliable data, it is proposed to conduct further prospective research on the relationship of clinical forms of leukoplakia with dysplasia and malignant transformation in the future.

Among the major limitations of the present study, a multiplicity of the pathologists who examined the patients’ slides can be mentioned, since such multiplicity along with lack of a calibrated definition of a phenomenon such as dysplasia can misrepresent and distort the certainty of the relevant reported values to some extent. Consistently, Pagin et al. [26] pointed out the importance of selecting an appropriate area for taking the specimens from non-homogenous leukoplakia.

5. CONCLUSION

Results of the present study, on the one hand, confirmed the previously reported values (e.g. higher prevalence of leukoplakia among men and on buccal mucous as the most common site for incidence) and, on the other hand, represented considerable values for the high number of non-homogenous leukoplakia and epithelial dysplasia cases, the importance of which could be associated with the necessity of early diagnosis and effective follow-ups in the case of encountering this lesion. Shortage of theoretical knowledge and lack of sufficient diagnostic skills among dentists in terms of early diagnosis of such lesions must be tackled by providing proper theoretical and practical education for them in the general doctorate courses and refresher programs [27].

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


