ORIGINAL RESEARCH

Analysis of Incidence of Clinically Diagnosed Oral Leukoplakia Patients Undergoing Incisional Biopsy Using Certainty Factor: An Institutional Study

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Abstract

Aim: The aim of the study is to evaluate the frequency of clinically diagnosed oral leukoplakia patients undergoing biopsy or rather not in their early visit and correlate that with the certainty factor (C-factor) classification of oral leukoplakia.

Materials and methods: This is a retrospective study performed at an institutional level that includes a total of $n = 96$ clinically diagnosed leukoplakia patients. The patients' demographic data and clinical details were retrieved from the institutional database and tabulated. The data of clinicopathologically confirmed cases of oral leukoplakia patients were correlated with the diagnostic C-factor C1–C4 using van der Waal's classification. The study parameters, clinical diagnosis, and biopsy history were statistically analyzed using Pearson's Chi-square test and descriptive statistics were also performed for all study parameters using SPSS software.

Results: The study results of $n = 96$ clinically diagnosed oral leukoplakia patients showed 90.6% had not undergone biopsy and 9.4% have done a biopsy. About 93.7% were males and 6.25% were females with 57.28% being >50 years of age and 33.28% being <50 years of age. About 66.5% of the population had at least one predisposing habit and 33.5% with no habit history. The histopathological evidence of 62.5% of patients showed grades of dysplasia. About 85.5% of the population had not reported for review after an initial provisional diagnosis. Statistical analysis revealed that incisional biopsy history and C-factor classification of oral leukoplakia have a correlation with a highly significant p-value = 0.000008 (p-value < 0.05).

Conclusion: The correlation between clinically diagnosed leukoplakia with the C-factor classification of oral leukoplakia in our study showed 86.50% of patients were under the C1 category which is indicative of investigations not been done in their early visits. Conversely, this emphasizes a delay in the biopsy would mean overlooking the lesion and its severity.

Clinical significance: Our study connotes the requirement of whether to biopsy the lesion or not which is imperative for determining further treatment plans in oral leukoplakia. The reason for early diagnosis and intervention in leukoplakia is an attempt to prevent malignant transformation.

Keywords: Certainty factor, Incisional biopsy, Leukoplakia.

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Introduction

Oral potentially malignant disorders (OPMDs) have a statistically increased risk of progressing to cancer, but the risk varies according to a range of patients or lesion-related factors.[1] The increased risk of malignant transformation is noticeable for OPMD lesions of the oral mucosa. World Health Organization (WHO) in 2005, the term oral potentially malignant disorder/lesion (OPMD/OPML) was propounded as a replacement for premalignant lesions or conditions.[2] The term "leukoplakia" is generally used as a clinical term. Oral leukoplakia is the most common OPML which is a white, irreversible, nonscrapable lesion of oral mucosa that can be characterized clinically or histopathologically as any other lesion/disease. Leukoplakia is a white plaque of questionable risk having excluded known diseases or disorders that carry no increase for cancer (WHO, 2005).[3] It is considered as an OPML with a malignant transformation rate of 0.13–34% and the clinicopathological prevalence in India being 0.2–5.2%.[4] Martorell-Calatayud et al. stated the prevalence of leukoplakia to be in the range of 0.4–0.7% annually.[5] Feller et al. approximated the annual prevalence of leukoplakia to be 0.5–3.46% with a malignant transformation rate of 0.7–2.9%. Over the decades, various classifications have been proposed in the literature for leukoplakia. The term leukoplakia can be used at different levels of C-factor as a clinical term only (C1 or C2) or as a clinicopathological term (C3 or C4), as shown in Table 1.[6] The WHO 2005 recognizes five histological stages in epithelial precursor lesion—squamous leukoplakia, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma *in situ*.[7] Verrucous carcinoma or invasive squamous cell carcinoma is quite difficult to be diagnosed with the clinical

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Table 1: Classification of C-factor of a diagnosis of oral leukoplakia

C1	Evidence from a single visit, applying inspection and palpation as the only diagnostic means (provisional clinical diagnosis)
C2	Evidence obtained by a negative result of the elimination of suspected etiologic factors. For example, mechanical irritation during a follow-up period of 2–4 weeks or in the absence of any suspected etiological factors (definitive clinical diagnosis)
C3	As C2, but complemented by incisional biopsy (provisional histopathological diagnosis)
C4	Evidence following excision and pathological examination of the resected specimen (definitive histopathological diagnosis)

presentation of leukoplakia, in such instances the histopathological diagnosis takes precedence over the clinical diagnosis of leukoplakia.[6] Oral leukoplakia is classified into two types, the nonhomogeneous type which includes speckled, nodular, and verrucous leukoplakia, and the homogeneous leukoplakia which is a uniform white thin area altering or not with normal oral mucosa. The malignant transformation rate for all types of leukoplakia is approximately 1% and much higher evidence of malignant transformation is seen in nonhomogenous type.[6] The prognosis is worse for the incidence of oral cancers due to malignant transformation from OPMDs especially oral leukoplakia.[8,9] Assessing the risk of the malignant change in OPMDs can be difficult because any decision at each stage of the management pathway is not binary, and the clinician may be faced with a number of options. There are three stages of evaluation—clinical history, clinical examination, and surgical biopsy with histopathological evaluation. It is a holistic approach that combines three stages of evaluation and that it achieves optimal outcomes in the risk assessment of oral leukoplakia.[1]

The clinical diagnosis algorithm of leukoplakia is an exclusion diagnosis with other white lesions correlating with the habit history and lifestyle of the patient. The assessment of surgical biopsy for the clinicopathological correlations of oral leukoplakia at a patient's early visit has been carried out to give a definitive diagnosis in a few studies. Brouns et al. in 2013 used the C-factor classification and found that it is acceptable to accept a diagnosis of leukoplakia based on a single oral examination (C1) for epidemiological studies. For studies on management and malignant transformation rate the recommendation of histopathological examination through biopsy, representing C3 and C4, respectively is necessary.[10] A previous study recognized that the clinical diagnosis is in accordance with the histopathological diagnosis in oral leukoplakia.[11] This study on oral leukoplakia quantifies the clinically diagnosed patients going for incisional biopsy at an institutional level in South India, Chennai. No other studies compared and analyzed the data of the reported cases in a time span at an institutional level.

The aim of our study is to evaluate the frequency of clinically diagnosed oral leukoplakia patients undergoing biopsy or rather not in their early visit and correlate that with the C-factor classification of oral leukoplakia which further emphasizes an early diagnosis and early intervention.

Materials and Methods

This retrospective study was conducted after getting approval from the institutional human ethical committee, Saveetha Dental College and Hospitals. The data of clinically diagnosed patients with oral leukoplakia in the Department of Oral Pathology and Microbiology were analyzed and collected from patients' records between July 2019 and March 2020 from the institution's management software. The details of the patient include age, gender, oral habits, relevant medical history, lesional site with the duration, investigation if done, a biopsy was done on which visit, clinical and pathological diagnosis, treatment done with follow-up history were retrieved and tabulated using Microsoft Excel 2013. The data of clinicopathologically confirmed cases of oral leukoplakia were included and cross-verified with the photographs to minimize the sampling bias. The cases under diagnostic C-factor C1–C4 using van der Waal's classification have been included in the study. The cases with no clinical images of the lesion, other white lesions excluded by histopathological diagnosis, and no follow-up after their first visit were all excluded from the study. This study included $n = 96$ clinically diagnosed oral leukoplakia patients.

Statistical Analysis

All the collected data were entered and statistically analyzed using statistical software SPSS by IBM version 20.0. Descriptive statistical analysis was performed for frequency tabulation and percentage of the parameters analyzed. Chi-square tests were performed to statistically identify the correlation between clinically diagnosed oral leukoplakia patients undergoing incisional biopsy and C-factor classification. p-value < 0.05 was considered statistically significant.

Results

The study included 96 clinically confirmed cases of oral leukoplakia cases ($n = 96$). Of these 96 patients, 57.28% of patients were above 50 years of age and 33.28% of patients were below 50 years of age. The age of clinically diagnosed leukoplakia patients was between 23 and 70 years of age. The age of the patients is further classified in Table 2.

Among $n = 96$ patients, 93.7% were males and 6.3% were females with a male:female ratio being 15:1 (Table 2). The majority of the male population has indulged in at least one predisposing habit. Among $n = 96$ patients, 35.3% of the affected population had a smoking habit, 13.5% had a *pan* chewing habit, 2.1% had *gutka*, and 1.1% had betel nut chewing habit. Also, 13.54% had multiple habit histories. We have also observed that 33.5% of patients had no habit profile out of which 31% are male population and 1.5% are female population (Table 2). Among 6.3% of the affected female population, almost all of them had a habit history. Of $n = 96$ patients, 9.40% of patients had undergone incisional biopsy and 90.60% of patients had not undergone any investigation. Out of 9.40% of patients, 8.10% of patients had undergone incisional biopsy investigation in their early visit (first and second visit) and 1.30% of patients had undergone incisional biopsy investigation in their late visit (fourth to tenth visit). The later visit biopsies showed unresponsiveness of the previous drug recommended for clinically diagnosed leukoplakia up to 5 months of the initial lesion. The investigation visit history has been summarized in Table 3. The histopathological examination 8.10% of patients showed 1.04% hyperkeratosis with mild dysplasia, 2.08% showed hyperkeratosis with moderate epithelial dysplasia, and verrucous hyperplasia in 1.04%. Also, 2.08% showed an atypical diagnosis. But still, the atypical diagnosis in our study had no effect on the clinically diagnosed leukoplakia patients. The histopathological diagnosis has been summarized in Table 4. Among $n = 96$ patients, after

clinical diagnosis, 25% of the affected population has been advised for habit cessation, 38.5% have been prescribed vitamin A, 8.3% lycopene and aquasol, and 19.79% have been advised multiple interventions. Of the total, 14.5% of cases had been reported for review and 85.5% of cases have not been reported for review after initial treatment interventions. The treatment and follow-up history are summarized in Table 5.

The C-factor classification distribution of the clinically diagnosed oral leukoplakia patients is C1—86.5%, C2—6.3%, C3—7.3%, and C4—0% (Table 3). The study population in majority is present in the C1 category which indicates that majority of clinically diagnosed leukoplakia patients have not undergone any biopsy investigation even when required.

The Chi-square results showed that the correlation between inncisional biopsy and the C-factor classification of oral leukoplakia showed statistically significant results with a *p*-value greater or equal to 0.05. *p*-value = 0.000008 (highly significant) (Table 3).

Discussion

Some of the white lesions may clinically mimic oral leukoplakia such as oral candidiasis, lichen planus, etc. may be easily misdiagnosed as oral leukoplakia.[12] However, leukoplakia has been associated with the use of tobacco or areca nuts as mentioned in recent past literature. The impairment of epithelial differentiation has been thought to be the pathogenesis of oral leukoplakia.[13] Even though there has been considerable progress in the development of diagnostic tools for the diagnosis of oral precancer including oral leukoplakia, biopsy, and histopathological examination remain the gold standard in their diagnosis.[11]

The results of our study showed that oral leukoplakia is more observed in the middle age population of 45–65 years of age. Vázquez-Álvarez et al.[14] stated that the mean group of the affected population is between 50 and 70 years. Waldron and Shafer et al.[15] found that leukoplakia chiefly occurs in the 5th–7th decades of life. There is a slight deviation in the age prediction of our study that may be due to the minimum sample size *n* = 96 and also due to difference in the geographic region of the study conducted. This is consistent with other literature. But in contradiction, Mishra et al. observed that the maximum percentage of patients were seen in the 3rd decade which is not in concordance with other literature. The discrepancy could be due to the use of tobacco, lime, and betel quite prevalent among the younger population in our country. This is because the oral habits start at a young age because of recklessness and that the habits decline as people mature and take on more responsibilities with manifestations of lesions more prevalent in middle or later adulthood due to prolonged use of tobacco from a younger age.

The male-to-female ratio in the study was observed as 15:1 which denotes that the incidence of leukoplakia is more in the male population than the female. Several other works of literature have also shown leukoplakia to be predominantly affecting males.[14] Mustafa et al. observed that male predilection is more in oral leukoplakia.[16] Nagao et al.[17] stated the age-adjusted incidence

Table 2: The frequency table showing the distribution of demographic data (age, gender, and habits) among the affected population (oral leukoplakia) within the study group (*n* = 96 patients)

		Frequency	*Percentage*
Age	<50 years	55	57.28%
	>50 years	41	42.72%
Gender	Male	90	93.80%
	Female	6	6.20%
Habits	Smoking	35	36.50%
	Pan chewing	13	13.50%
	Gutka	2	2.10%
	Betel nut	1	1%
	Multiple habits	13	13.50%
	No habits	32	33.33%

Table 3: The table showing the frequency distribution of incisional biopsy history and C-factor classification among the affected population (oral leukoplakia) within the study group (*n* = 96 patients) and the Chi-square results showing the correlation between the above-mentioned parameters, respectively

		Frequency	*Percentage*
Incisional biopsy	Biopsy not done	88	91.70%
	One visit	3	3.10%
	Two visits	3	3.10%
	Four visits	1	1%
	Ten visits	1	1%
C-factor	C1	83	86.50%
	C2	6	6.30%
	C3	7	7.30%
	C4	0	0%

Chi-square test = *p*-value 0.000008 (<0.05 highly significant)

rate for oral leukoplakia in males is more compared with females. This can be attributed to the increased indulgence of males in tobacco chewing or smoking habits. The gender differences vary in magnitude across cultures and across different habitual patterns, it is also very likely that gender differences in oral habitual behavior are modified by cultural or historical and not biological factors. Self-restraint of tobacco/alcohol habits by women in some cultural settings may demonstrate their roles as social guardians and restraining influences on male recklessness.

In the current study, the habit profile of the patients is widely distributed with a majority being smoking tobacco followed by *pan* chewing (smokeless tobacco). The patients with habits are slightly more than those patients who do not have a habit history in our study. Hallikeri et al.[18] found that the prevalence of oral leukoplakia is more associated with different forms of tobacco. Kumar and Muniyandi[19] observed positive effects of tobacco use in the prevalence of leukoplakia. Holmstrup et al.[20] stated 85% of oral leukoplakia cases have been associated with a tobacco habit. Fisher et al.[21] also stated that the incidence of oral leukoplakia is more in smokeless tobacco. This result is concordant with the other literature. The concept of oral habits is more prevalent because the social culture and norms, lifestyle, and habitual practices that are being practiced may vary remarkably in different parts of the globe and within different sectors in the country, especially in India. The other major reason for the increased habitual profile is because of the easy availability of tobacco at a cheaper rate.

Our study includes 90.6% of clinically diagnosed leukoplakia population who have not undergone biopsy investigation at all and 9.4% of cases had done biopsy with only 3.1% of cases undergoing biopsy at an early visit. No other similar study has been done to justify the visit of biopsy history.

The histopathological evidence of the patients undergone biopsy in our study showed dysplasia in 62.5% of cases. The general frequency of epithelial dysplasia in leukoplakia varies between 1 and 30%.[15,22,23] The presence of dysplasia in this lesion is one of the most important predictors of malignancy[24] that emphasizes the need for early biopsy in all these lesions. Mutalik et al.[11] showed the agreement on clinical and pathological diagnosis and found 6.95% sure evidence of malignancy.[25] Weilu et al. showed 20.8% malignancy in oral leukoplakia cases studied. Waldron and Shafer[15] showed evidence of malignancy in 3.1% of cases. With this literature evidence, it is seen that anticipating evidence of malignancy in clinically diagnosed leukoplakia cases is not uncommon. Oral lesions are more common but can also have multiple challenges in clinicopathological diagnosis.[26] Hence it is advisable to undergo a biopsy of the lesion at the initial appointment. An incisional biopsy is a gold standard, but the practice of it is not quite widespread in dental practice. It is important to alert the clinicians about the clinical falls arising preoperatively and postoperatively that may affect the histological assessment and the diagnosis. Indication of biopsy and histopathological diagnosis can either refine the clinical diagnosis or show concordance with the clinical diagnosis. Although clinical characteristics can raise suspicion, a biopsy of the lesion at an early appointment is required to establish a definitive diagnosis that in turn quantifies the need for early intervention if required.

Vitamin A supplements are preferred and prescribed for patients diagnosed with oral leukoplakia in our study and also have counseled for habit cessation. This is in accordance with Nagao et al.[27] who found evident regression of oral leukoplakia lesion with vitamin A (beta-carotene) supplements. Sankaranarayanan et al.[28] found that a 5.2% significant remission of leukoplakia is seen with vitamin A supplements, also the patient has to be periodically reviewed. This vitamin A is proven to exert an anti or dekeratinization effect on normal or hyperkeratotic oral mucosa.[29]

In this current study, 85.5% of the affected population has not reported for review after being clinically diagnosed for leukoplakia. van der Waal[30] emphasizes that noninvasive treatment of oral lookup like a patient has to be reviewed every 3–6 months after initial intervention. Bánóczy and Csiba[23] stated only 5.9% of cases have been reported for review after diagnosing oral leukoplakia. This is in concordance with the present study that almost 80–90% of leukoplakia patients do not report back for review this is due to

Table 4: The frequency table showing the distribution of histopathological diagnosis among the affected population (oral leukoplakia) within the study group (n = 96 patients)

	Frequency	*Percentage*
Biopsy not done	88	91.70%
Hyperkeratosis with moderate dysplasia	2	2.10%
Hyperkeratosis with mild dysplasia	1	1%
Atypical	2	2.10%
Hyperkeratosis with moderate epithelial dysplasia	2	2.10%
Verrucous hyperplasia	1	1%

Table 5: The frequency table showing the treatment modalities and follow-up history of oral leukoplakia patients within the study group (n = 96 patients)

		Frequency	*Percentage*
Treatment	Habit cessation	24	25%
	Vitamin A	37	38.50%
	Lycopene	8	8.30%
	Aquasol	8	8.30%
	Multidrug	19	19.79%
Follow-up	Nil	82	85.40%
	One visit	11	11.50%
	Two visits	1	1%
	Three visits	1	1%
	Four visits	1	1%

the lack of awareness and knowledge among the patients about the association with the risk factors, behavior, and severity of the lesion type.

This current study correlates clinically diagnosed oral leukoplakia patients undergoing biopsy or not in their early visit with C-factor classification of oral leukoplakia. The study results showed that the majority are in the C1 category followed by the C2 category which signifies the provisional and definitive clinical diagnosis. Brouns et al.[10] categorized the oral leukoplakia patients according to the C-factor classification and found the presented classification system to be valuable for comparing management results of patients with oral leukoplakia. No other literature evidence for evaluating the frequency of clinically diagnosed oral leukoplakia patients undergoing biopsy in their early visit and correlating that with the C-factor classification of oral leukoplakia at an institutional level.

The limitation of this study is that the availability of patients is minimum within the geographic region. This study is conducted at an institutional level. Oral potentially malignant disorders are less identified by patients, in that oral leukoplakia is a white lesion that can be diagnosed only by a dentist.[11] The clinical picture of oral leukoplakia can be deceptive which makes it necessary for biopsy at an initial appointment. It is an accepted fact that microscopic analysis is the gold standard for the diagnostic criteria.[31] If any suspicious lesion of the oral cavity persists for more than 2 weeks even after the initial intervention, biopsy should be performed. This quantifies the need for awareness of whether to biopsy or not among patients and dentists to make a necessary intervention at an institutional level. Also, further large-scale longitudinal studies are required to substantiate the findings obtained in this study.

Conclusion

The study showed statistically highly significant results for the correlation between incisional biopsy and C-factor classification of oral leukoplakia. About 86.50% of patients were under the C1 category which is indicative of investigations not being done in their early visits with a male preponderance of the age group (45–65 years) who had not undergone biopsy even when recommended. Hence utmost importance has to be given for assessing the need for biopsy, with advanced planning. Pathologists play a crucial role to facilitate the early diagnosis and hence a prompt treatment, thus preventing malignant transformation of leukoplakia to a great extent.

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