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REVIEW ARTICLE

Malignant Transformation Of Oral Leukoplakia: An Asian Scenario

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ABSTRACT:
Oral leukoplakia is the most common potentially malignant disorder of the oral mucosa. The prevalence increases with age, ranging from less than 1% in men under age 30 years to 8 % in men and women over age 70 years. There may be several routes to malignant transformation of oral leukoplakia, including transformations induced by carcinogenesis due to betel quid chewing or smoking, or by HPV infection. The only significant factors associated with it are clinical type and size of lesion. Although epithelial dysplasia is an important predictive factor of malignant transformation, it should be realized that not all dysplastic lesions will become malignant. This systemic review presents a retrograde analysis of malignant transformation of leukoplakia in the Asian scenario. The review was undertaken to address the objective of demographic and clinicopathologic factors involved in malignant transformation of oral leukoplakia.

Key words: Oral leukoplakia, Malignant transformation, Epithelial dysplasia.

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INTRODUCTION

The term cancer, by itself has evoked a sense of morbidity and mortality among the medical fraternity as well as in general population.[1] Cancer of the head and neck region is a serious condition and in the oral cavity the appearance of cancer is preceded by other lesions which may show various tissue morphological changes and histopathological cellular changes that point towards the possible subsequent development of malignancy.[1] Oral squamous cell carcinoma could be preceded by OPMDs (oral potentially malignant disorders). Among these OPMDs, oral leukoplakia is the most commonly encountered entity in clinical practice. It is a precancerous or potentially malignant lesion, which means that in this morphologically altered tissue, cancer is more likely to occur than its apparently normal counterpart.[2] Oral leukoplakia has recently been redefined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some oral leukoplakia will transform into cancer (Axell T, 1996).[2] It is used to designate a clinical white patch or plaque on the oral mucous membranes that cannot be removed by scraping and cannot be classified clinically or microscopically as another disease entity.[3] In a conference of Uppsala (1994), it was established that it would be the predominantly white lesion of the oral mucosa which could not be clinically or pathologically characterized as another specific entity.[4]

Global prevalence of oral leukoplakia has been estimated at 2.60% (95% confidence interval 1.72 – 2.74%).[5] Napier and Speight recently reviewed clinical predicators of malignant transformation in oral leukoplakia, such as age, gender and lesion site, but the results from different study populations vary.[6] Most leukoplakias are caused by tobacco, alcohol and betel quid use resulting in sequential evolution of the disorder; few are genetically destined and referred to as idiopathic leukoplakias.[7] Butlin (1885) related these lesions to smoking and considered smokers patch to be an early stage of a more advanced white raised lesion that he called as leukoma.[8] Kramer had recognized the malignant potential of leukokeratosis and smokers patch and its relationship to pipe smoking.[9] Paget recognized an association between a white keratotic oral lesion and lingual carcinoma.[9] Brouns et al found the location of oral leukoplakia specified according to eight subsites: tongue, floor of mouth, lower lip, hard palate, buccal mucosa, upper alveolus and gingiva, lower alveolus, and gingiva and finally in multiple sites.[10] Leukoplakia occurred on two or more surfaces in 70% of the individuals.[3] The buccal mucosa was the most common site occurring in 46% of the patients, followed by gingiva (40%), palate (27%), tongue (26%), floor (22%) and lip (11%).[3] Over 30 year period, Bancozy identified a greater prevalence of leukoplakia among the

50-60 year old group, but the highest risk of malignant transformation was among the 60-70 year old group.[11] The onset of leukoplakia usually takes place after the age of 30 years; resulting in a peak incidence above the age of 50 years.[11]

Axell et al[4] and Pindborg et al[12] classified homogenous and non- homogenous leukoplakias into 4 subtypes for each other. Homogenous types were classified into flat, corrugated, wrinkled and pumice types, whereas non-homogenous types were classified as verrucous, nodular (speckled), ulcerated, and erythroleukoplakia type. Sugar and Banocky, using a different clinical classification, reported the association of leukoplakia erosive and leukoplakia verrucosa with epithelial dysplasia.

Sharp[13], Rotter et al[14] and Hahn et al,[15] reported that verrucous leukoplakia was often associated with epithelial dysplasia, and Ackermann and Johnson[16] and Shafer and Waldron[17] stated that a pinkish- gray or red granular appearance was often associated with epithelial dysplasia or carcinoma in situ.

Banoczy reported that erosive leukoplakia showed that highest potential of malignant transformation in comparsion to simplex leukoplakia.[18] In 2013, Brouns et al. in his study found that 52.7% had homogeneous leukoplakia and 47.27% cases had non-homogeneous leukoplakia.[8] This could be due to variation in availability of tobacco products, consumption of tobacco with or without slaked lime, duration and frequency to tobacco product combined with alcohol.[19]

Through this systemic review we present a retrograde analysis of malignant transformation of leukoplakia in the Asian scenario. The review was undertaken to address the objective of demographic and clinicopathologic factors involved in malignant transformation of oral leukoplakia.

STUDY REVIEW

Gangadharan and Paymaster [20] followed up leukoplakias of different anatomical locations for varying periods of time from 1941 to 1969 at Tata Memorial Hospital, Bombay, India. The buccal mucosa was the commonest site affected in all religious communities of Western India except Parsis. Majority of Parsis were non – smokers and non –chewers of tobacco, had leukoplakia more often on anterior two –third of the tongue. It was noticed that leukoplakia not associated with smoking habits had a greater chance of malignant transformation. Sixty – three carcinomas were observed in those 1411 patients during subsequent follow up with a malignant transformation rate of 4.46%.

Silverman et al [21] followed up 6718 industrial workers in Gujarat, India, during the period 1967 to 1971, and 4762 (71%) were re – examined after 2 years. The buccal mucosa was the predominant site of oral leukoplakia (91.5%). 98.3 % of these individuals had oral habits, with smoking alone or smoking in combination with pan or supari chewing accounting for 74.9% of habits forms. Thirty –five oral leukoplakia lesions (less than 1%) had epithelial dysplasia in their original biopsy. Of the total group, six individuals (0.13%) developed oral cancer. Out of these, females have shown a higher malignant transformation compared to males (males 0.1% and females 1.3%). This study confirmed the precancerous nature of leukoplakia.

Gupta PC et al [22] conducted a cohort's study in which 12,212 tobacco users were followed up annually to assess malignant potential of oral precancerous lesions in the Ernakulam district in Kerala India. A total of 19 new oral cancers were diagnosed over a period of 8 years and 15 of these arose from some pre existing precancerous lesion or condition. Nodular leukoplakia showed highest rate of malignant transformation (16% per year) as a 6 of 13 nodular leukoplakia underwent malignant transformation over a mean follow up period of 2.8 years. All these patients were tobacco users. Of the 12,212 individuals examined in the baseline survey, 98.5% were re-examined, atleast in 1 of the follow ups.

They conducted a large scale epidemiological study of oral cancer and pre cancer which was initiated in 1966 in several regions of India. Phase 1 of the study consisted of a cross – section survey to determine the prevalence of cancer and precancerous lesions while a phase II was a 10 year follow up survey to determine the incidence and natural history of oral pre cancer. Following these, an intervention study was started to try to pursue the subjects to give up tobacco and to measure the subsequent changes in the incidence and regression rate of oral precancer. In each study area, 12000 adult tobacco users was selected, examined and interviewed in a house to house survey. The population was reviewed after 1 year and the proportion of the subjects who had discontinued tobacco use were found to be 2% in Ernaklam, 1% in Bhavnagar, 5% Srikakulam, in Bhavnagar and Ernaklam; and the regression rate of leukoplakia was significantly higher among those who had stopped or reduced their tobacco consumptions.

Gupta et al [23] carried out a community based 10 year (mean 7 years) follow up study among Indian villagers. Nine of 410 individuals (2.2%) in Ernakulam district had developed carcinoma from existing oral leukoplakia and one of 302 individuals in Srikakulam district. Among them, there were 90 cases of biopsy proven dysplasia and 7% of which developed into carcinoma.

Saito et al [24] followed up 111 patients in Japan (1976-1996) for 7 months- 16 years (mean 4 years) to assess any differences in malignant transformation of widespread multiple oral leukoplakia excluding proliferation verrucous lesions leukoplakia . Among 99 patients with localised lesions, 5 (5%) developed oral cancer, whereas of 12 who had widespread oral leukoplakia, 3 (25%) had malignant transformation. Gingiva and tongue were major affected sites of leukoplakia in the localised patients where as gingiva and buccal mucosa were predominantly affected in widespread patients. Their results indicate that the widespread leukoplakia have a higher potential for the development of carcinoma than do the localised lesions. Saito et al.[25] reported that malignant transformation was higher in the group who had surgical exision (1/75) compared with those who did not have surgery (4/51)

which led them to conclude that surgical excision may reduce the risk of subsequent development of carcinomas. **Amagasa T et al** [26] conducted a study in Tokyo Medical and Dental University on oral leukoplakia related to malignant transformation in the year 1999. In their study, 7.9% out of 444 patients presented with malignant transformation under the observational period of 1- 29 years. The rate of malignant transformation may increase when patients are followed over a longer term or may decrease when the patients are lost early to follow up. The resulting rate of malignant transformation can therefore be unreliable. Malignant transformation rates of oral leukoplakia range from 0.13 to 17.5%, while the rates of five year cumulative malignant transformation range from 1.2 to 14.5%. Chewing tobacco and smoking are the two distinct risk factors particularly among males.

Hsue et al [27] studied 1458 patients with potentially malignant disorders in a Taiwan hospital among whom 423 had white lesions/leukoplakias. The average age at initial diagnosis was 47.5 years. 44 patients progressed to oral cancer in the same site as the initial lesions with an overall transformation rate of 30.2% and a mean follow up time of 42-64months. 8 of 166 patients with dysplastic lesions and 15 of 423 patients with hyperkeratosis or epithelial hyperplasia progressed to malignancy . Of these hyperkeratotic lesions, 15 transformed into cancer (3.6%) over the follow –up period.

Yen et al [28] in a cohort of Taiwan patients from Taipei city with leukoplakia (n=615) carried out a follow up study over a period of 20 years. The annual incidence rate (per year) of leukoplakia was estimated as 0.35% (95% Cl:0.22-0.48%). In their research, they modelled the effects of both duration and quantity of betel quid chewing and smoking on annual incidence rate of developing leukoplakia and average dwelling times (ADTs) staying in leukoplakia and erythroplakia. The ADTs were 24 years for leukoplakia and 7 years for erythroplakia. Annual incidence rate of leukoplakia with consumption and long duration of betel quid and smoking was higher. They reported a cumulative risk of malignant transformation of leukoplakia at 42.2% after a 20- year follow –up.

Liu W et al [29] in their research on malignant transformation of oral leukoplakia: a retrospective cohort study of 218 Chinese patients in 2010 reviewed their archived files along with clinical and histopathological diagnosis of oral leukoplakia (OL); from the Department of Oral Mucosal diseases, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine with the mean follow –up period of 5.3 years. In their study, they found that among 218 cases, 39 (17.9%) oral leukoplakia patients developed oral cancer, with a mean duration of 5.2 years. Cox regression analysis revealed that dysplasia was an independent risk factor for oral leukoplakia malignant transformation, but age, gender, lesion site, diet habit, smoking and ethanol intake were not risk factors. The average age at diagnosis was 52.7yrs old (range 21-84). The peak incidence was fifth decade of life (33.0%). Tongue was affected in 51.4% patients with oral leukoplakia followed by buccal mucosa (32.6%). Few lesions were located on the floor of mouth and lip. 180(82.6%) OL cases were low risk dysplastic lesions and 38(17.4%) OL cases were high risk dysplastic lesions. The utilisation of high risk dysplasia as a significant indicator for evaluating malignant transformation risk in patients with oral leukoplakia was suggested, which may be helpful to guide treatment selection in clinical practice.

Qasrdashti AB et al [30] conducted a study in Namazi and Khalili hospitals (Shiraz, Iran), which are two of the largest referral centres in southern Iran. They evaluated factors that affect the malignant transformation of leukoplakia in an Iranian population during a 20 year period from 1989-2009. Of 522 patients; 213 patients showed signs of malignant transformation. Female patients with malignant changes were mostly non smokers (76.4%), while male patients with malignant changes were mostly smokers (63.8% in non smokers)($P<0.001$). In univariate analysis, male sex and smoking showed lower chances for malignant transformation, while age above 50 above was a risk factor for malignant transformation(50.2%). According to this study most common site for malignant changes was on the tongue. Reason for high rates of malignant changes in Iranians as compared to other countries, could be related to cultural differences, for example many Iranians who have leukoplakia lesions undergo medical evaluation only when the lesion has advanced. It was concluded that a follow up program and further work up should be considered for Iranian patients who have leukoplakia lesions that are flat and are white patch or plaques with red components, and for patients who have lesions located on the tongue and non smokers who develops leukoplakia lesions.

CONCLUSION

A thorough knowledge on various aspects of these pre - cancerous entities shall render a clinician to make appropriate diagnosis or plan treatment. Age, gender, clinical type of the lesion and etiology were found to be important risk factors for malignant transformation. So, health education, counselling the individual and behavioural therapies is most essential methods of prevention at a primary level.

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