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Oral Leukoplakia: Report of two cases and Review on Its Potential for Malignant Transformation

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ABSTRACT

Oral leukoplakia (OL) is a precancerous mucosal condition as it is considered the most common potentially malignant disorder (PMD) affecting the mucosa of the oral cavity. It is especially prevalent in older males as a result of persistent irritation, such as ill-fitting dentures, smoking, or excessive alcohol consumption. Typically, this disease is treated by removing the source of irritation, such as quitting tobacco chewing, smoking, or repairing dental abnormalities. Leukoplakia patches can be surgically removed by a dentist or oral surgeon using a scalpel, electrocauterization, laser ablation, or cryosurgery. To date, there is no evidence of effective treatment that may prevent a recurrence. there is an exciting possibility suggesting a potential role for antioxidants as adjuvant in cancer therapy. Antioxidant vitamins and some phytochemicals selectively induce apoptosis in cancer cells and prevent angiogenesis and metastatic spread.

Keywords:

leukoplakia, dysplasia, antioxidant, potential malignant lesions

Introduction

Oral leukoplakia (OL) is a frequently encountered premalignant lesion with a variety of clinical manifestations that is not associated with any specific histologic disease.[1,2] Leukoplakia may be associated with a number of histologic disorders ranging from epithelial hyperkeratosis, hyperplasia, and dysplasia to cancer [3]

Tobacco consumption is a significant causative factor in OL[4,5]. OL has been found to be six times more prevalent in smokers than in non-smokers, [6] this was related to the presence of certain carcinogenic chemicals in tobacco smoke in the form of NOO- radicals. [7] Additionally, alcohol is a significant risk factor for OL. Although the human papilloma virus (HPV) is yet unknown as an etiologic factor for this condition, it has been identified as one of the etiologic causes for OL.[6,7]

Many studies have documented molecular profiles of oral dysplasia and the risk of progression of dysplastic lesions to malignant disease.[8-10] These molecular markers include loss of heterozygosity often at *3p*, *9p*, *17p*, 8q, *11q*, and *13q* and other makers, such as*p53*. These findings about the progression of oral lesions to dysplasia and carcinoma may aid in the identification of lesions for treatment, serve as intermediate markers for interventions, and may result in the development of novel treatment techniques.[3]

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Many factors are responsible to increase the chance of the OL becoming malignant, Warnakulasuriya et al. indexed the following as the increased risk for malignant transformation from a premalignant disease.[11]

1. Gender – female more than male
2. Duration – long-lasting leukoplakias have bad prognosis than recent
3. Idiopathic OL – nonsmokers with OL have an increased rate of malignant transformation in relation to OL in smokers
4. Site – OL located on the floor of the mouth, soft palate, and tongue are considered as high-risk lesions, while, in other areas, they may be considered as of low malignancy risk
5. Size – measuring >200 mm2
6. Type – Non-homogeneous OL lesions have a mixed color of white and red alterations, and an exophytic, papillary, or verrucous aspect; regardless of treatment, they exhibit a high recurrence rate and often eventually transformation to squamous cell carcinoma
7. Histopathologically – the occurrence of *Candida albicans* with OL with moderate and severe dysplastic lesions had a significantly higher risk of developing a squamous cell carcinoma than OL without epithelial dysplasia or with mild epithelial dysplasia.

Prior to initiating treatment for OL, the extent of epithelial dysplasia must be determined. Surgical therapy is recommended in the presence of moderate or severe epithelial dysplasia. When mild to moderate dysplasia is present, other factors such as location, size, and, in the case of smokers, the patient's commitment to smoking cessation should be considered[12]. Surgical resection may be considered for lesions that are localized and easily accessible. Surgical removal is, however, contraindicated in patients with significant lesions, lesions that include sensitive anatomic structures, such as the ducts of major salivary glands, or lesions that return following repeated excision .[2,13]

However surgical intervention does not appear to be effective in preventing oral leukoplakia from becoming cancer. Additionally, surgery is not done on individuals who come with surgery-related high-risk medical conditions or who refuse surgical intervention.[14]

It is worth noting that medical treatment for OL is frequently desirable, particularly in order to avoid leukoplakia from progressing to cancer. Despite their insufficient production, chemopreventive agents such as Vitamin A and retinoid, carotenoids, tea extract, bleomycin, curcumin, and Vitamin C have been employed.[15,16]

The goal of this case report is to provide two cases of OL and to educate the reader about the many treatment options available for OL in order to further prevent its malignant progression.

Cases description:

First case

A cancer phobic 47-year-old Egyptian male patient referred to the Faculty of Dentistry, Tanta University, Oral Medicine Department in June 2019, complaining of a white patch on his left side cheek mucosa. His past medical history including his family history was unremarkable except for his tobacco dipping habit (which is called GAT) for a long time when he was working in Saudia Arabia. The patient didn't complain from pain only discomfort, roughness and rigidity of the buccal mucosa. Intra-oral examination showed a 3.0 x 3.0 cm white leathery non-scrapable and with well-defined margins irregular texture patch on the left side cheek mucosa related to the posterior teeth and retromolar area surrounded by mild redness fig (1). There was no any rough margin or sharp edge in the teeth related to the lesion. The regional lymph nodes were non-palpable. The lesion was previously small and had gradually increased to the present size over the past 4 months. An excisional biopsy was performed and the excised tissue was sent for histopathological analysis. (fig3a).

Histopathologic features

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Histopathological examination revealed hyperkeratotic epithelium with dysplastic characteristics such as basilar hyperplasia and hyperchromatic cells extending to the epithelium's lower third, changed nuclear to cytoplasmic ratio, and dyskeratosis. In the juxtaepithelial region, the stroma was composed of collagen fibers and plump to spindle-shaped fibroblasts, as well as a patchy distribution of inflammatory cells, predominantly lymphocytes and plasma cells (Fig 2). The lesion was characterized histologically as hyperkeratosis with moderate dysplasia.

Treatment and follow up

Subsequent to histological diagnosis patient instructed to quit smoking and tobacco dipping and to follow oral hygiene instructions and prescribed 400 IU of vit E and 1000mg vit C daily for 3 months. During this period, the patient was observed every 15 days to evaluate the clinical progress or recurrence of the lesion.
After three months of treatment, the patient was well and healthy with no sign of recurrence and he was instructed to keep on eating healthy food specially the antioxidant foods and good oral hygiene. (fig3b). The patient was observed monthly up to the end of the first year and then observed every 3 months then every 6 months with no any recurrence or any other lesions were noted. Each visit we had to make sure that the patient did not smoke again by asking his wife or his son.

The patient instructed to continue oral hygiene, continue quit tobacco dipping, and increase from antioxidant food like food rich in vitamin A, E and C. Throughout the maintenance phase, the patient's compliance was good. Regular follow-up examinations over a two-year period revealed no return of the white lesion, and the patient was satisfied with the therapy and results (fig 3 c).

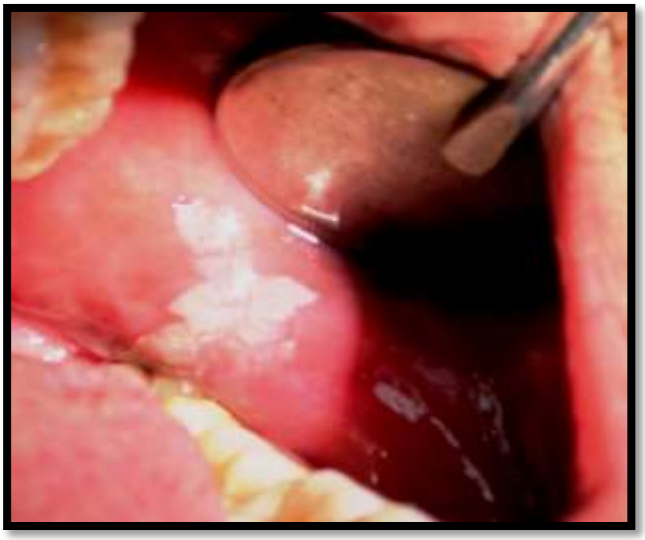

Fig (1): Intra-oral photograph showing white leathery, slightly raised lesion with a granular texture in left cheek and retromolar area measuring about 3x3 cm

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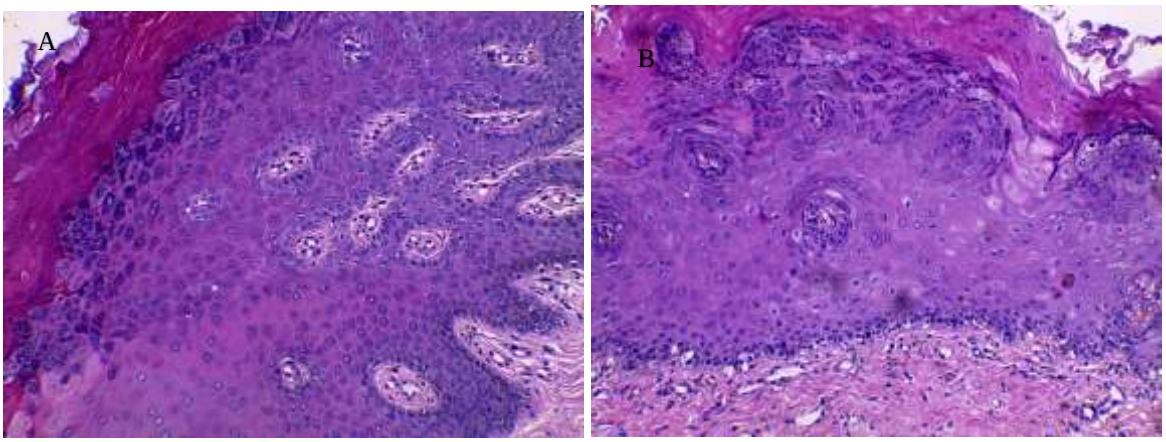

Fig (2): Photomicrograph of the lesion showing hyperkeratotic epithelium and dysplastic features like basilar hyperplasia and hyperchromatic cells (AX40, B x100)

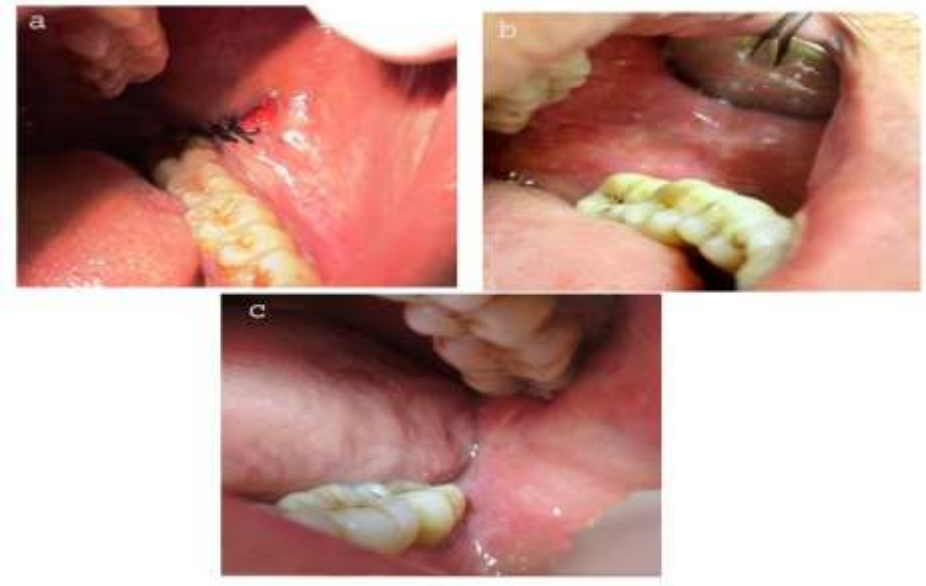

Fig (3): a) complete removal of the lesion. b) Show the clinical state of the patient 3 months after removal of the lesion. c) The clinical state of the patient 2 year after

Second Case:

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A 40-year-old male patient came to the Department of Oral Medicine and diagnosis faculty of dentistry, Tanta University in May 2020 complaining of rough surface in his right side buccal mucosa. He started to notice it accidentally when he visited one of the dental clinics for filling of a carious tooth and the dentist informed him about the lesion and that it is very serious and he must go to oral medicine department for biopsy. His past medical history and family history were unremarkable, and he gave a history of smoking a hookah and heavy cigarette smoking for a longtime.

Intra-oral examination showed diffuse irregular whitish plaque on the right buccal mucosa measuring approximately 4 cm × 3 cm at its maximum diameter extending 1 cm away from the commissure of the lip up to just before the retromolar region posteriorly, and it extends inferiorly to the buccal vestibule fig (4). The patient is very poor oral hygiene. Our provisional diagnosis is homogeneous leukoplakia. Patient motivation and instruction about tobacco cessation was done. Incisional biopsy was done after routine lab investigation and the specimen was sent for histopathological examination fig (5).

Histopathology

Histopathological examination revealed stratified squamous which was hyperkeratotic and acanthosis of the epithelium that shows dysplastic features like basilar hyperplasia, nuclear pleomorphism, abnormal mitotic activity, increased nuclear-cytoplasmic ratio. The basement membrane is intact. The underlying connective tissue shows collagen fibers interspersed with fibroblasts, and inflammatory cells infiltration, fig (6).

The patient was given the same instruction and line of treatment as with the first patient and stressed to quit tobacco, eating antioxidants and healthy foods, using Vit C and E, and practice good oral hygiene. The patient continued to follow up with us every month. After 6 months' patient come back for follow up with slight regression of the lesion size as shown in fig (7)

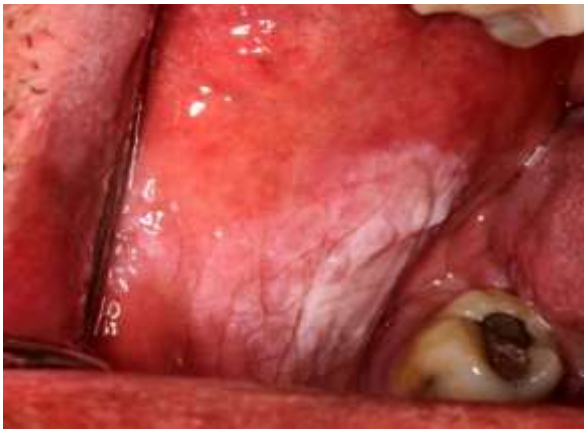

Fig (4): shows diffuse large white patch in the buccal mucosa

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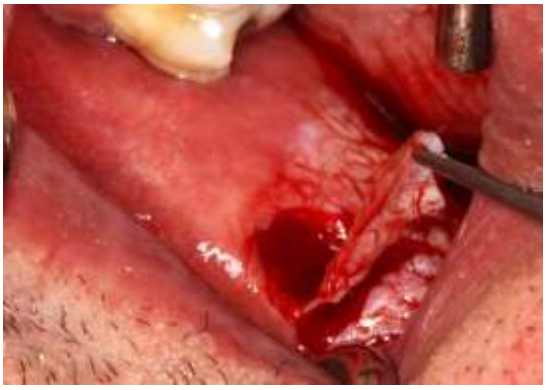

Fig (5): shows incisional biopsy was taken from the lesion for hitopathology evaluation

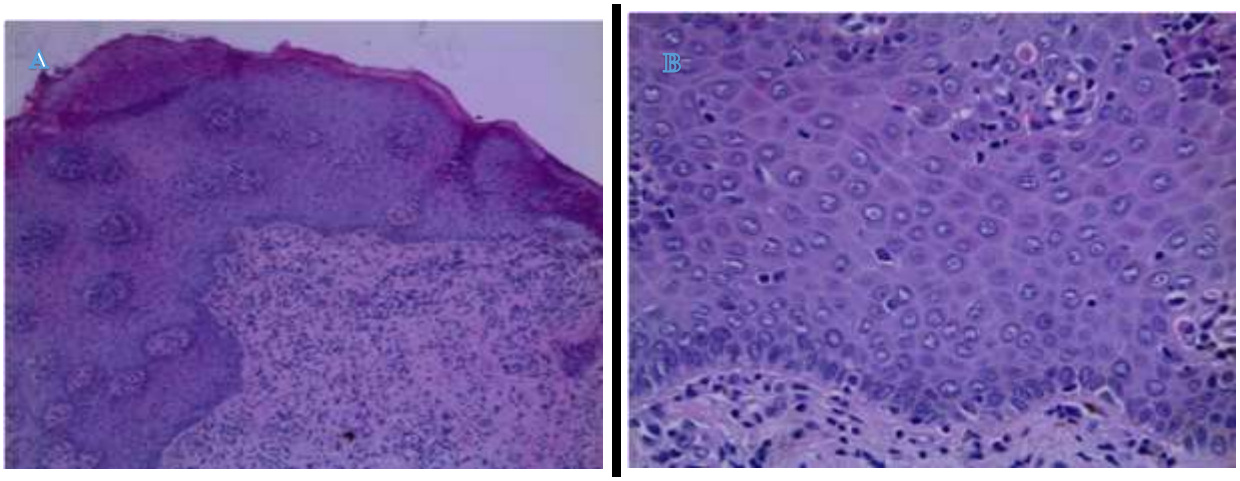

Fig (6): Photomicrograph of the lesion showing hyperkeratotic epithelium and dysplastic features like basilar hyperplasia and hyperchromatic cells, heavy infiltration of the connective tissue stroma with chronic inflammatory cells (AX40), (B x100)

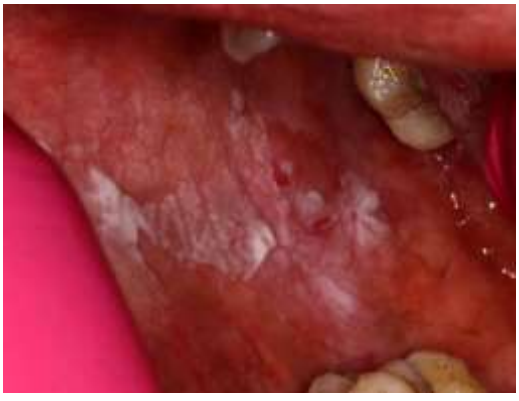

Fig (7): shows 6 months' post-operative follow up of the lesion, there was slight regression in the size of the lesion.

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Discussion

The treatment of OL continues to be a significant problem for clinicians who care for this patient population. Smoking and tobacco use have been shown as the primary etiological cause for OL. Other etiologic factors include alcohol consumption, candidiasis, human papilloma virus, prolonged mechanical trauma, UV exposure, and habit of chewing tobacco with betel quid and spicy food.[17] In the first case, patient had a habit of chewing tobacco and tobacco dipping and this the cause of his lesion, and when he stopped this habit and follow the instructions the lesion did not recur and he is in remission until now.

In the second case the patient had large size leukoplakia so we performed an incisional biopsy and we emphasized to the patient the importance of follow-up, quit tobacco and smoking and to follow the instruction by healthy live attitude, hence, the lesion in regression or at least stopped progression.

Conservative treatment has failed to prevent recurrence and malignant transformation according to many studies.[18,19] The first outcome of leukoplakia therapy must be the prevention of malignant transformation, so an early diagnosis is mandatory for good management.[20]

Prior to initiating therapy, a biopsy must be performed and a diagnosis established. Controlling risk factors such as smoking and alcohol intake is also critical to the success of treatment.[20,21]It is well established that leukoplakia in patients with tobacco use may be reversible if the patients discontinue smoking [5,22].

Oral epithelial dysplasia is the most important prognostic factor for assessing the probability of leukoplakia malignant transformation. When one or more of the following symptoms are present, a lesion may be considered malignant: ulceration, induration, elevation, fungation, and fixation are all terms that refer to the same thing.[23] The floor of the mouth, the tongue's lateral borders, and the soft palate/retromolar areas were identified as locations at high risk of malignant transformation and according to Liu et al.,[24] malignant transformation occurred at a high rate in patients with high-grade dysplasia over the first 2–3 years of follow-up.

Additionally, the overall survival and prognosis of patients are based on early detection and diagnosis, which determine whether a patient is at an increased risk than usual or if there is early infiltration prior to metastatic disease.[18]

Oral leukoplakia that is homogenous has a low risk of malignancy, however non-homogeneous speckled (mixed white and red lesions), nodular, or verrucous areas have a higher risk of malignancy. Nowadays, molecular markers have been created to aid in the early detection of premalignant oral lesions that proceed to squamous cell carcinoma.[25]

Multiple treatment modalities of OL starting from “watch and see”, conventional surgery, cryosurgery, CO2 laser, eletrocoagulation, photodynamic therapy. A systematic review done by

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Deliverska and Petkova stated that randomized controlled trials for nonsurgical treatment have not shown much of evidence in the prevention of malignant transformation and recurrence.[26] However, complete eradication of the lesion may not guarantee a cure, as certain studies have documented lesion recurrence following excision, and in some circumstances, carcinoma recurrence. As a result, patients must be observed on a regular basis.[27]

Nonsurgical treatment of OL that can prevent the malignant transformation include topical bleomycin, laser therapy, photodynamic therapy, and antioxidant medications. Antioxidants include beta-carotene, retinol, retinoids, ascorbic acid (vit C), and alpha-tocopherol (vitamin E). Antioxidants contribute significantly to the reduction of free radical reactions that can result in DNA mutations, changes in enzyme activity, and lipid peroxidation of cellular membranes.[17- 28]

Recent reports have documented beta Carotene's clinical success in the treatment of oral leukoplakia, both alone and in combination with other antioxidants and retinoids. Numerous studies have demonstrated an inverse association between low dietary and serum antioxidant levels and the likelihood of developing several forms of cancer.[29,30]

Additionally, Bhagat et al., 2018[31] showed that Curcumin can be used to treat oral potentially malignant disorders like OL, oral lichen planus, and oral submucous fibrosis.

Moreover, a systemic review done by Ribeiro et al 2010[17] reported that although retinoic acid and beta-carotene supplementation have some efficacy in resolving OL, there is little indication of efficacy in avoiding malignant transformation and recurrence. It reaffirms the importance of routinely monitoring OL following clinical resolution.

While antioxidants are useful in preventing malignant transformation to a certain extent when used alone, the combination of conventional surgical excision with postoperative antioxidant therapy has not been tested. This would have the obvious advantage of traditional surgical treatment combined with the antioxidant impact.

In the present case report, the patients were instructed to quit smoking and tobacco dipping and to follow oral hygiene instructions and prescribed 400 IU of vit E and 1000mg vit C daily for 3 months and they followed the instruction that is why they are safe and in remission until now for the first patient and in regression or stop progression for the second case.

Conclusion:

If feasible, leukoplakia should be completely eradicated. Patients should be instructed to avoid main risk factors for oral epithelial dysplasia, including cigarette and alcohol use, and should be examined routinely for any significant mucosal changes.

From the clinical cases we can report, the importance of periodical follows up of the patients, even after complete removal of the lesion.

The combination of conventional surgical excision with the possible protective effect of the administration of the antioxidants seemed to be effective in the prevention of recurrence and transformation.

Declaration of patient consent

All necessary patient consent forms were collected. The patient(s) has/have consented in this form for his/her/their photos and other clinical data to be published in the journal. Patients acknowledge that their names and initials will not be published and that reasonable attempts will be made to conceal their identities.

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