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Review Article

Oral leukoplakia

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ABSTRACT

Oral leukoplakia is defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; however, the lesion must be confirmed histopathologically by biopsy in order to discuss malignant transformation of oral leukoplakia. 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%. In this review were described some datas about the frequency, etiology and pathogenesis of oral leukoplakia. Clinical symptoms and treatment methods were described. The basic information sources were up to date articles. The author's results were retrospectively analysed.

Keywords: *Dysplasia, oral leukoplakia, treatment*

Introduction

Oral leukoplakia is defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; however, the lesion must be confirmed histopathologically by biopsy in order to discuss malignant transformation of oral leukoplakia. 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%. Some reports found a high incidence of malignant transformation in older patients. Chewing tobacco and smoking are distinct risk factors particularly among males in certain countries; however, other countries have noted that females or non-smokers may be at risk of malignant transformation. HPV has been detected in oral dysplasia lesions and cancer in non-smokers. 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. [1]

According to Sdubba JJ [2] reflective of the biology of leukoplakia is the concept of cellular atypia and epithelial dysplasia. The potential etiologic role of Candida albicans has been stressed, as well as its possible role in carcinogenesis. A new binary system to grade dysplasia was proposed by WHO, but the biological significance in predicting malignant transformation risk is unknown. According to the definition of OL, "A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer", the exclusion criteria were as follows:

- Any patient without the initial histopathologic examination of OL and development of oral squamous cell carcinoma (OSCC) during a follow-up period by biopsy or surgery.
- Any patient with the clinical history and histopathologic changes of oral white or predominantly white oral benign diseases, for example, linea alba, leukoedema, leukokeratosis; and oral precancerous conditions such as discoid lupus erythematosus and lichen planus.
- Any patient with diagnosis of OL concomitant OSCC at the first visit.
- Any patient with a follow-up period of less than 12 months.

Based on these criteria, 218 patients with OL were selected to be retrospectively reviewed in the cohort. This study was approved by the institutional review board of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. The architecture (a total of 7 scoring) and cytology (a total of 9 scoring) criteria for epithelial dysplasia were as follows:

Architecture:

- Irregular epithelial stratification;
- Loss of polarity of basal cells;
- Drop-shaped rete ridges;
- Increased number of mitotic figures;
- Abnormally superficial mitoses;
- Premature keratinization in single cells;
- Keratin pearls within rete ridges.

Cytology:

- Abnormal variation in nuclear size;
- Abnormal variation in nuclear shape;
- Abnormal variation in cell size;
- Abnormal variation in cell shape;
- Increased nuclear-cytoplasmic ratio;
- Increased nuclear size;
- Atypical mitotic figures;
- Increased number and size of nucleoli;
- Hyperchromasia.

Liu W. [3] reclassified all lesions as low-risk dysplasia and high-risk dysplasia. A low-risk lesion was based on observing less than four architectural changes or less than five cytological changes. A high-risk lesion was based on observing at least four architectural changes and five cytological changes. Liu W. [3] were investigated 218 patients, with a mean follow-up period of 5.3 years. Of these, 39 (17.9%) patients developed invasive oral cancer, with the mean time of malignant transformation of 5.2 years.

For all the subjects, the gender ratio was equal (110 males: 108 females). The average age at diagnosis was 52.7 years old (range 21-84). The peak incidence was fifth decade of life (33.0%). Tongue was affected in 51.4% patients with OL, followed by buccal mucosa (32.6%). Few lesions were located on the floor of mouth and lip. There were 12.8% patients with spicy dietary habit. The history of smoking and ethanol intake were observed in 29.8% and 6.9% cases, respectively. Liu W[3] found 180 (82.6%) OL cases were low-risk dysplastic lesions and 38 (17.4%) OL cases were high-risk dysplastic lesions. High-risk dysplasia was a significant indicator for OL malignant transformation. It is thus import to detect early malignant events of OL with the diagnosis of high-risk dysplasia in rigorous followed-up in the first 2-3 years. [3] According to Amagasa T, Yamashiro M, Ishikawa H. [1] leukoplakia has different clinical features: type I of the maxillary gingiva showing fl at white patch, type II of the tongue showing white patch and plaque with erosion, type III of the buccal mucosa showing slightly elevated white plaque, and type IV of the buccal mucosa showing markedly elevated white plaque with partly granular appearance. (Fig. 1)

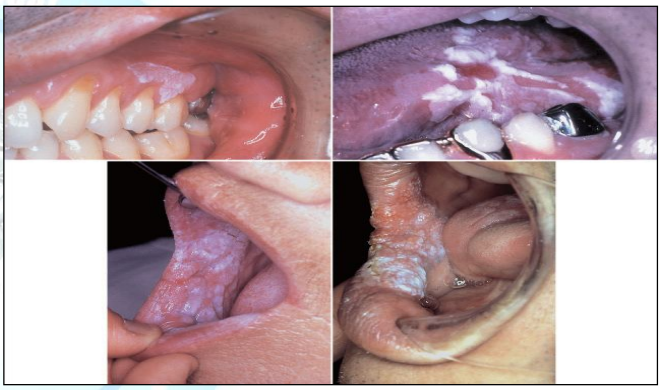

Fig. 1 Different clinical features of leukoplakia (Source: Amagasa T, Yamashiro M, Ishikawa H)

Interleukin 37 (IL-37) has been reported to play a significant role in innate immune response and to be involved in several kinds of cancers. However, the investigation of association between IL-37 and oral mucosa carcinogenesis hasn't been clearly established. The aim of the study was to assess IL-37 expression and explore its role in oral mucosa carcinogenesis. What's more, overexpression of IL-37 in RAW264.7 cells remarkably reduced the pseudopodia, vacuolization and the expression of IL-6, TNF-α, and IL-1β. Lin L, Wang J, Liu D, Liu S, Xu H, Ji N, et al. [4] were found IL-37 and its receptor IL-18Rα but not its binding partner IL-18BP have similar tissue location and expression trend in different stages of oral mucosa carcinogenesis. Overall, IL-

37 can be used as a biomarker for early oral tumorigenesis and for malignant transformation risk assessment of premalignant lesions. (Fig. 2)

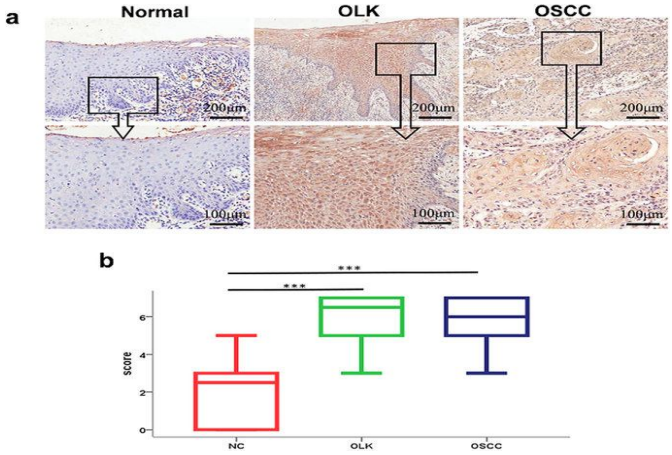

Fig. 2: (a) Immunohistochemical analysis of IL-37 expression in human healthy oral mucosa, OLK and OSCC lesions. (b) Comparison of the staining score between these groups (P < 0.001).
(Source: Lin L, Wang J, Liu D, Liu S, Xu H, Ji N, et al)

Treatment methods

There are few clinical trials using non surgical management like topical bleomycin, laser therapy, photodynamic therapy etc., but use of antioxidants is more common. Vitamin A, E, C and lycopene are the most commonly used antioxidants in treatment of oral leukoplakia to assess the outcome measures such as clinical resolution, adverse effects, recurrence and malignant transformation. Reactive oxygen species like malondialdehyde (MDA), nitroxide (NO), lipid peroxidation, and decreased activities of antioxidants including glutathione (GSH), ascorbic acid (AA), glutathione peroxidise (GPx), glutathione reductase (GR), superoxide dismutase (SOD), and catalase associated with tobacco users and potentially malignant disorders, produce both phenotypic and genotypic alterations which may progress to cancer. Thus the use of antioxidants at early stages becomes utmost essential for prevention of malignant transformation. Review had proved the significance of retinoids versus placebo in leukoplakia in most of the trials with successful outcome measures. [5] Singh M., Krishanappa R., Bagewadi A., Keluskar V. [6] evaluates the efficacy of lycopene in the treatment of oral leukoplakia and compares two different doses with a placebo. Fifty-eight clinically and histologically diagnosed patients of oral leukoplakia were selected. They were randomly divided into three groups. Group A: (*n*=20; 8 mg lycopene/day), Group B: (*n*=20; 4 mg lycopene/day) and Group C: (*n*=18; placebo). The duration of the therapy was three months. Outcome was assessed clinically as well as histologically. Post-treatment patients were on follow-up for two months. Clinically the patients in Groups A, B, C had a mean response of 80%, 66.25% and 12.5% respectively. Histological evaluation too had similar results. Patients receiving lycopene in both regimes show highly significant difference in response as compared to placebo (Group C). The observed effect of lycopene suggests that it can be effectively and safely used for the management of oral leukoplakia.

By treating leukoplakia in its incipient stage, the risk of occurrence of oral carcinoma can be prevented. In this aspect, photodynamic therapy (PDT) can serve as a useful treatment modality. The aim of the study is to treat patients with OL using PDT in which 5-aminolevulinic acid (ALA) is used as a photosensitizer. Selvam NP, Sadaksharam J, Singaravelu G, Ramu R. [7] were included five patients with OL. They were treated with 10% ALA mediated PDT (light source: Xenon lamp, power: 0.1 W, wavelength: 630 ± 5 nm, total dose: 100 J/cm 2 per session) for 6-8 sessions. Follow-up was done for a period of 1 year.

The results are: one month (4 weeks) after ALA-PDT, the response was evaluated based on clinical examination. It was as follows: Complete response: Two patients; partial response: Two patients; and no response: One patient. There was no recurrence in any of the cases. The conclusion is following: There was satisfactory reduction in the size of the OL lesion without any side-effects. Thus, ALA mediated PDT seems to be a promising alternative for the treatment of OL.

Although OL lesions can be eradicated by surgical excision, laser surgery, and photodynamic therapy, cryotherapy is also an effective and

alternative treatment modality for OL lesions. Cryotherapy is a method that locally destroys lesional tissues by freezing in situ. It has several advantages including being a bloodless treatment, has a very low incidence rate of secondary infections, and has a relative lack of scarring and pain. Cryotherapy can be carried out with either a "closed" or an "open" system. Closed-system cryotherapy offers a greater degree of temperature control but requires complex, delicate, and expensive equipment. Open-system cryotherapy involves directly applying the cryogen to the lesion with either a cotton swab or a portable spray apparatus such as a cryogun (Brymill Corp., Ellington, CT, USA). Cheng SJ, Chen HM, Chiang CP. [8] were found that topical 5-aminolevulinic acid-mediated photodynamic therapy (topical ALA-PDT) is very effective for oral erythroleukoplakia and oral verrucous hyperplasia lesions, but is less effective for OL lesions. However, when topical ALA-PDT is combined with cryotherapy, the combination therapy may be an effective treatment modality for OL lesions. Compared to topical ALA-PDT or combination therapy, cryogun cryotherapy is a simple, easy, cheap, less-painful, effective, and acceptable treatment modality for OL lesions. Cryogun cryotherapy can serve as the first-line treatment of choice for OL lesions.

One of the preferred treatment options for oral mucosal lesions (eg, leukoplakia and lichen planus) is excision, with or without the use of a coverage agent. Platelet-rich fibrin(PRF) membranes are popular fibrin scaffolds with entrapped platelets that release various growth factors and cytokines to support and enhance wound healing. The results suggest that PRF membrane is a successful coverage agent that aids in the healing of superficial oral mucosal wounds. [9]

Praveen KNS, Veeraraghavan G, Reddy RS, Kotha P, Koneru J, Yelisetty K. [10] were evaluated the effectiveness of 810-nm diode LASER in the management of patients with oral leukoplakia. Their study revealed that usage of diode LASER may indeed be the best choice in the management of oral leukoplakia.

There are different kinds of treatment for this lesion, but using high power laser has some advantages like less pain, swelling, prevention of metastasis, edema, less bleeding (dry surgery) and infection. Using Carbon Dioxide Laser (CO2) with average power is set on 6.2 W, frequency 20 Hz., non-contact irradiation mode in the treatment of oral lesions has many advantages like selective removal of the affected tissues and minimal damage to surrounding tissue, lseading to excellent wound healing with no or minimal scar and good functional results. (Fig. 3) [11]

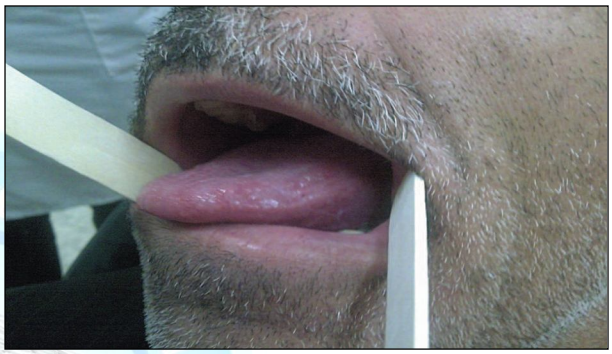

Fig. 3 The follow up session after 3 months (Source: Chiniforush N. et al)

Vivek V, Jayasree RS, Balan A, Sreelatha KT, Gupta AK. [12] were found that the Nd:YAG laser had the advantage of precise delivery of laser through fibre-optic cable. The surgical sites showed excellent wound healing, with no scarring and minimal postoperative pain. The cure rate of 89.28% (25/28 patients) after 3 years is much better than that of other surgical treatment modalities. Absence of complications, such as bleeding, paresthesia or anaesthesia, very low recurrence rates and excellent healing make laser treatment superior to other methods of treating oral leukoplakia.

Conclusion

In dentistry, early detection and accurate diagnosis of the leukoplakia is of paramount importance for successful treatment. Therefore, the dentist must have knowledge of the biological and histological behavior of leukoplakia and her frequency to ensure early detection, accurate diagnosis and proper treatment.

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