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ORIGINAL RESEARCH

p53 as a Neoplastic Biomarker in Patients with Erosive and Plaque Like Forms of Oral Lichen Planus

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ABSTRACT

Aim: Unstimulated whole salivary p53 was assessed in patients suffering from erosive and plaque-like form of oral lichen planus (OLP).

Materials and methods: Eighteen patients with erosive form, 17 patients suffering from plaque-like form and 38 non-involvement subjects were enrolled. The unstimulated whole saliva p53 level was assayed by ELISA.

Results: The mean concentration of salivary p53 was significantly higher in patients with plaque-like form compared to both patients with erosive form and the control group.

Conclusion: We conclude that plaque like form of OLP is important in view of the potential for malignancy and is not safety form.

Clinical significance: It seems that all forms of OLP must be considered accurately, should be followed up with biannual examinations, and if possible, assessment of salivary p53 every year.

Keywords: p53, Oral lichen planus, Erosive, Plaque like, Saliva.

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INTRODUCTION

Lichen planus (LP) is prevalent in an estimated 1 to 2% of the population.[1,2] The disease occurs more frequently in women than in men, and is more common in the middle aged and elderly than in the young, but it may develop in individuals of all ages.[1-4] Oral lichen planus (OLP) is the most common non-infectious disease in patients referred to the Department of Oral Medicine, Faculty of Dentistry, TUMS after caries, gingival involvement and dry mouth.

Lichen planus commonly affects the oral mucosa, most often in the absence of skin lesions. Mucosal lesions are usually multiple and almost always have a bilateral, symmetrical distribution. In contrast to lichen of the skin, the course of cutaneous LP is variable and self-limited, OLP is usually of long duration without remission and does not respond particularly well to any form of therapy.[5,6]

p53 has a key role in the control of the cell cycle, the maintenance of genomic stability, cell differentiation, and apoptosis. Understanding the p53 pathway of oral carcinogenesis may help better predict the biologic behavior, and select the appropriate management strategy; it is also a valuable biomarker to predict malignant transformation in premalignant oral lesions.[7]

Several tumor markers are present in saliva;[8,9] therefore, its use as a diagnostic fluid could have significant diagnostic and logistical advantages when compared to serum. As a diagnostic medium, saliva has several advantages—its collection is safe, noninvasive, inexpensive, and simple, and it may be collected repeatedly without discomfort to the patient.[10,11]

The purpose of this study is to evaluate unstimulated salivary p53 among reticular and erosive forms of OLP and control individuals.

MATERIALS AND METHODS

Materials

The protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS), Iran and all patients and control subjects gave informed consent before participation.

Thirty-five patients clinically diagnosed with lichen planus (presence of bilateral lesions, and presence of reticular lesions elsewhere in the oral), and in histopathological examination (presence of well-defined band-like zones of inflammatory infiltration confined to the superficial part of the connective tissue, consisting mainly of mature lymphocytes vacuolar alteration of the basal layer of the epithelium), comprised the case group (15 men, 20

women; aged 28-74 years), and were selected from those referred to the Department of Oral Medicine, Faculty of Dentistry, TUMS. Eighteen of the patients with OLP were in erosive form (7 men, 11 women) and 17 were in reticular form (8 men, 9 women). Thirty-eight age and sex-matched healthy volunteers (17 men, 21 women; aged 23-67 years)—who did not have clinical signs of gingival inflammation-comprised the control group. In both groups, subjects with systemic and periodontal diseases (depth of gingival sulcus more than 3 mm), or who were taking medication (at all) at the time of the study, were excluded. Subject in case group had no bleeding.

Saliva Collection

Five milliliters of unstimulated whole salivary samples were obtained by expectoration, in the absence of chewing movements, in dry plastic vials with the test subject sitting in a relaxed position. The collected saliva samples were centrifuged (2000 gm for 10 minutes). The supernatants were stored at –20°C until further analysis. Samples were collected at the same time of day (10 am-12 pm) and at least 2 hours after the last intake of food or drink.

Analysis of Saliva

p53 concentration was analyzed by ELISA technology using commercially available kits (DRG Instruments GmbH, Germany).

Statistical Analysis

Data were analyzed by ANOVA followed by the Student-Newman-Keuls post hoc test. Differences among means were considered statistically significant if $p < 0.05$. Data are expressed as mean (SEM).

RESULTS

The mean concentration of salivary p53 was significantly different between the groups [$F_{2,70} = 5.4$, $p < 0.05$] (Fig. 1). It was significantly higher in patients with plaque-like form OLP compared to both patients with erosive form OLP and the control group, with no significant difference between patients with erosive form OLP and the control group.

DISCUSSION

p53 is a well known tumor suppressor protein, is a nuclear protein that regulates cell cycle check points, and is responsible for maintaining the integrity of genome. Activation of p53 after DNA damage or oncogenic signaling is an important protective mechanism, which facilitates DNA repair and stimulates apoptosis of the condemned cells. Many studies have shown that alterations in the expression of p53 are essential for carcinogenesis, and can indicate an important step in the transformation from normal to neoplastic epithelium. It has been well documented from previous reports that deregulation of p53 is a valuable biomarker in predicting malignant transformation in premalignant oral lesions.[12,13]

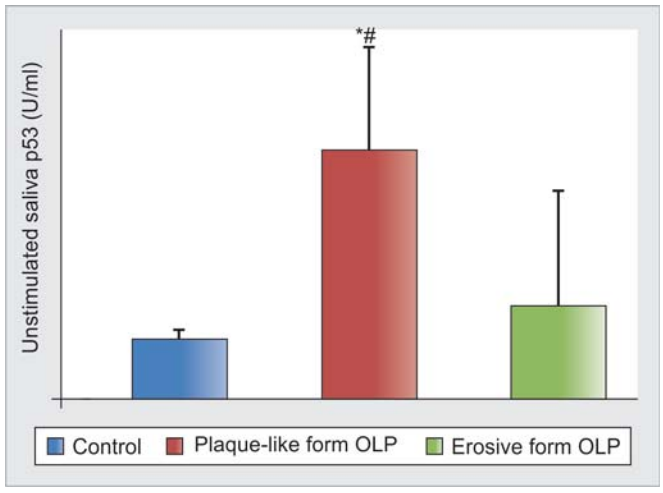

Fig. 1: Unstimulated whole saliva concentration of p53 in patients with erosive and plaque-like form of OLP, and control individuals. Data are expressed as mean (SEM).
*Different from control; #Different from patients with erosive OLP; $p < 0.05$

p53 protein expression was detectable in premalignant oral lesions. In general, there appears to be a positive correlation between heavy smoking and elevated p53 expression.[14] We excluded this confounding factor, and no member of the case or control groups in this study were smokers.

The role of p53 as prognostic indicator has been widely investigated in oral cancers and precancerous lesions. Many researchers have examined the role of p53 expression in OLP by immunohistochemistry, and the immunopositivity of p53 ranged from 18 to 100% in OLP. The mechanism of p53 over-expression in OLP is still unknown.[12]

The advantages of using saliva are that it is noninvasive, rapid, and painless to perform. These considerations show that this method is ideal for research related to head and neck lesions. Therefore in the present study, we assessed unstimulated salivary p53 via ELISA technique. Further studies using saliva samples of precancerous lesions, such as OLP are needed to determine the p53 mutations in OLP and all its different forms.[15,16]

Our results show that unstimulated salivary p53 values in reticular OLP patients were significantly higher than healthy subjects, and in erosive form. It was higher in erosive OLP patients than healthy people, but not significantly.

There are numerous reports on the potential for malignant transformation, especially in patients with erosive forms of the disease. Their reasons are that the mucosa in erosive OLP is more vulnerable to the effects of internal or external insults, such as inflammation, mechanical trauma,

or mutagens than normal or hypertrophic mucosa, resulting in higher frequencies of malignant transformation.[12]

Some authors have indicated that the frequency of malignant transformation ranges from 0.4% to more than 5%, with the highest rate noted in erythematous and erosive lesions. In the reported series, none of the carcinomas developed from reticular lesions.[17] On the other hand, multiple reports indicate that keratotic forms of OLP need particular care, both when they exist alone and when associated with atrophic—erosive ones in mixed form. They reported that all except 2 of 24 carcinomas arose in pre-existing keratotic OLP lesions. They therefore believe that classification of the clinical form of OLP is a very important step in order to program the follow-up, and necessarily requires removing all clinical factors that could modify clinical features of OLP.[18]

And finally, a few authors did not confirm recent evidence of higher disease activity, in terms of enhanced p53, in atrophic-erosive forms with respect to reticular OLP. The distribution of p53 in the present study highlights the wide distribution of values both in the group of patients with reticular lesions, and in those with erosive OLP. p53 expression, ranging from 10 to 45%, was found in patients with similar clinical presentation and *vice versa*.[19]

CONCLUSION

We conclude that plaque like form of OLP is important in view of the potential for malignancy and is not safety form.

CLINICAL SIGNIFICANCE

According to our finding, reticular form of OLP is important in view of the potential for malignancy and is not safety form. Since, the mechanism of p53 over-expression in OLP is still unknown, we believe all forms of OLP must be considered accurately, should be followed up with biannual examinations, and if possible, assessment of salivary p53 every year.

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