

## RELATIONSHIP BETWEEN THICKNESS OF FIBROSIS AND EPITHELIAL DYSPLASIA IN ORAL SUBMUCOUS FIBROSIS

P.R. Jayasooriya\*, K.A.N. Jayasinghe and W.M. Tilakaratne

*Department of Oral Pathology, Faculty of Dental Sciences, University of Peradeniya, Peradeniya*

### Introduction

Oral submucous fibrosis (OSMF) is a chronic debilitating disease of oral mucosa that is commonly found in patients of South East Asian origin. Arecoline component of the areca nut, which is used in the betel chewing, plays a major role in the pathogenesis of the disease, but other factors such as nutritional deficiencies, immunity of the person and genetic predisposition may also contribute in the disease process (Tilakaratne et al., 2006).

OSMF is characterized by fibrosis of the sub epithelial connective tissue, with normal, atrophic or dysplastic changes of the overlying epithelium. However, if a relationship between fibrosis and epithelial changes, particularly dysplasia exists, identification of such a relationship would be immensely beneficial to the management of the patients.

However, most of the research done on OSMF deals mainly with the isolated changes that occur in the connective tissue or the epithelium (Chiang et al 2000, Hazarey et al 2007). But the outcome of the disease depends on the occurrence of pre-malignant and malignant changes in the epithelium may be, influenced by connective tissue changes such as fibrosis and vascular changes.

The aim of the study was to assess the relationship between the thickness of

fibrosis and presence of epithelial dysplasia in OSMF.

### Materials and Method

Hematoxylin and eosin (H&E) stained sections of 107 cases of OSMF, diagnosed during a 4 year period from 2000-2004, were selected from the archives of the Department of Oral Pathology, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka for the study. Site wise, 78 and 17 biopsies were from the buccal mucosa and tongue respectively.

Each section was examined individually and the highest thickness of fibrosis from the basal layer of the epithelium up to the end of the fibrous layer was measured using a standard 24 mm linear graticule. Evaluation of presence or absence of epithelial dysplasia was done on all 107 samples using WHO criteria of histological typing of cancer and pre cancer of oral mucosa (Barnes et al 2005).

Finally, the relationship between presence/ absence of epithelial dysplasia and thickness of fibrous layer was statistically analyzed using Student's *t-test*. In addition, the relationship between the age, sex and site of the lesion with dysplasia status and thickness of fibrosis was also evaluated using Chi square test.

## Results

According to the results, 57% (n=61) of OSMF lesions showed a non-dysplastic overlying epithelium while 43% (n=46) showed varying degrees of epithelial dysplasia. With reference to dysplastic grading, 93.4% (n=43) showed mild epithelial dysplasia and only 6.7% (n=3) of the lesions were moderately dysplastic while none of the lesions showed severe epithelial dysplasia.

The mean thickness of fibrosis of non-dysplastic lesions was  $0.91 \pm \text{SD}0.41\text{mm}$  and ranged from 0.25mm to 1.9mm. The mean thickness of fibrosis of dysplastic lesions was  $1.17 \pm \text{SD}0.52\text{mm}$  and ranged from 0.48 to 3 mm. Accordingly, the results revealed a significant increase in the incidence of epithelial dysplasia as the thickness of fibrosis increased ( $P < 0.004$ ).

In addition, the lesions which showed moderate epithelial dysplasia had significantly thick fibrous layers ( $2.3 \pm \text{SD}0.68\text{mm}$ ) compared to lesions which showed mild epithelial dysplasia ( $1.09 \pm \text{SD}0.39\text{mm}$ ) ( $P < 0.000$ ).

The statistical analysis using Chi-Square test did not reveal a significant relationship between the age, sex or site of the lesion and thickness of fibrosis or dysplasia status ( $P > 0.05$ ).

## Discussion

A statistically significant relationship between the thickness of the fibrous layer and the presence/absence of epithelial dysplasia was observed in the present study. Incidence of

epithelial dysplasia was found to increase with the increase of the thickness of fibrosis, highlighting the fact that the advancement of fibrosis increases the risk of occurrence of epithelial dysplasia. Thus, it can be predicted that prevention of advancement of the fibrotic process by any measures may reduce the risk of occurrence of epithelial dysplasia and ultimately the development of oral squamous cell carcinoma in OSMF patients.

According to our previous work on OSMF, hypoxia causes atrophy and ulceration of the epithelium by inducing apoptosis (Tilakaratne et al 2008). In addition over-expression of HIF-1 $\alpha$  (Hypoxia Induced Factor 1 $\alpha$ ) is seen in OSMF, which indicates changes in cell proliferation, maturation and metabolic adaptation, increasing the possibility of malignant transformation (Tilakaratne et al., 2008). The correlation of thickness of fibrosis to dysplasia status in the present study provides more evidence to support our previous hypothesis of hypoxia and malignant transformation of OSMF.

The treatment modalities of OSMF include drug therapy, surgical treatment and physiotherapy. The final aim of these treatment modalities are to reduce fibrosis, and according to the results of the present study by reducing fibrosis, incidence of epithelial dysplasia, and hence development of oral squamous cell carcinoma in OSMF patients may be prevented. However, further studies are necessary to understand the exact mechanism of fibrosis leading to hypoxic environment predisposing OSMF



patients to develop squamous cell carcinoma.

### Conclusion

Incidence of epithelial dysplasia was found to increase with the increase of the thickness of fibrosis, highlighting the fact that the advancement of fibrosis increases the risk of occurrence of epithelial dysplasia in OSMF.

### References

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