EXPRESSION OF P53 TUMOUR SUPPRESSOR GENE IN ORAL LEUKOPLAKIA

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ABSTRACT

BACKGROUND

The presence and degree of dysplasia are often used to predict malignant transformation. Among these the p53 tumour suppressor gene, which deserves particular attention not only because of its central role in genomic stability and cell cycle regulation, but also in the case of oral mucosa in pre-invasive stages. Mutation of p53 gene is one of the most common events in oral carcinogenesis. This suggests that p53 gene mutation may be an early step in the malignant conversion of oral dysplastic lesions

The objectives of this study were- 1. To study p53 expression in relation to proliferative status in normal and dysplastic lesions of the oral mucosa 2. To determine whether a correlation exists between the accumulation of p53 and the degree of epithelial dysplasia present in oral leukoplakia.

MATERIALS AND METHODS

The study group comprised of 60 subjects in which 30 cases were of oral leukoplakia and 30 healthy individuals were in control group without white patch on oral mucosa. Study was done in Ambedkar Dental College, Patna.

RESULTS

Both the groups were evaluated for epithelial dysplasia histopathologically and accordingly labelled as mild, moderate and severe dysplasia as per Shafer criteria. In the control group 100% of the subjects depicted no dysplasia. Out of 30 subjects in the study group, 21 (70%) had mild, 7 (23.3%) had moderate and 2 (6.7%) subjects had severe dysplasia.

CONCLUSION

Expression of p53 was absent in subjects with no dysplasia, but overexpression of p53 was observed in dysplasia. p53 protein level was highly significant in moderate and severe dysplasias.

KEYWORDS

p53 protein, Leukoplakia.

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BACKGROUND

Oral leukoplakia is a precancerous or potentially malignant lesion, and thus in morphologically altered tissue, cancer is more likely to occur than in apparently normal tissue. In general, it is more or less accepted that approximately 5% of all leukoplakias will transform into cancer in an average period of 5 years. Tobacco smoking is an important risk factor for precancerous lesions of the mouth.[1] The presence and degree of dysplasia are often used to predict malignant transformation.[2] Relevant biomarkers hold more promise as early prognostic markers. Among these the p53 tumour suppressor gene product, which deserves particular attention not only because of its central role in genomic stability and cell cycle regulation, but also in the case of oral mucosa in pre-invasive stages.[2] Mutation of p53 gene is one of the most common events in oral carcinogenesis. This suggests that p53 gene mutation may be an early step in the malignant conversion of oral dysplastic lesions.[3] This is especially important because detection of p53 mutation could predict malignant transformation in dysplastic lesions and guide early prophylactic intervention.[4]

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Aims and Objectives

1) To study p53 expression in relation to proliferative status in normal and dysplastic lesions of the oral mucosa.
2) To determine whether the protein of the suppressor gene p53 accumulates in leukoplakia of the oral cavity in individuals who use tobacco.
3) To determine whether a correlation exists between the accumulation of p53 protein and the degree of epithelial dysplasia present in oral leukoplakia.

MATERIALS AND METHODS

Total number of subjects included in our study was 60, out of which 30 cases were in group A (Study group having

leukoplakia) and 30 cases not having any evidence of leukoplakia but fulfilling the inclusion criteria were labelled as group B (Control group).

Inclusion Criteria

- Subjects of age group 30-60 years were included.
- Only those leukoplakia cases using tobacco in any form were included in GROUP A. (Study group)
- Only those subjects not using tobacco and not having white patch on oral mucosa and came to the OPD for impacted tooth and/or gingival enlargement, were included in GROUP B (control group).

Punch biopsy was taken, and the tissue was divided into two parts.

First half was for histopathological examination and the second half was subjected for p53 estimation. The patients were given postoperative instructions, analgesic and antibiotics after biopsy. All cases were recalled to visit after one week.

In the present study p53 was graded in five categories in accordance with the grading system given by Khanna S. et al (2012)[3] which is as follows: -

1. Grade 0- Score indicates non immunoreactive to p53.
2. Grade 1- Score shows p53 immunoreactive in less than 5% of cells.
3. Grade 2- score immunoreactive 5-9% of cells.
4. Grade 3- Indicates p53 immunoreactive in 10-49% of cells.
5. Grade 4- Suggests p53 immunoreactive in more than or equal to 50% of cells.

RESULTS

Based on the criteria of individuals histological features and expression of the cytological changes from the basal cell layer and upward epithelial dysplasia has been subdivided into

- Mild (Grade I)- Demonstrates proliferation of atypical or immature basal cells above the parabasal region but not extending the lower third of the epithelium.
- Moderate (Grade II)- Similar proliferation as in grade I into the middle third of the epithelium.
- Severe (Grade III)- Reserved for abnormal proliferation from the basal layer into the upper third of the epithelium.

A correlation between smoking and level of p53 was also found in our study where p53 level was found to be high in heavy smokers in comparison to mild to moderate smokers.

The statistical analysis was done by the statistical department.

Age Group (yrs.)	Study Group												Control Group	
	No. of Patients (30)		Clinical Diagnosis				Histopathological Diagnosis							
			Homogenous		Speckled		Mild		Moderate		Severe		(30)	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Total	28	2	17	1	12	0	20	1	6	1	2	0	26	4
30-40	13	0	8	0	5	0	11	0	1	0	1	0	12	0
41– 50	5	1	3	1	2	0	3	1	2	0	0	0	3	2
51 - 60	10	1	6	0	5	0	6	0	3	1	1	0	11	2

Table 1. Age and Sex Distribution of Cases According to Their Clinically and Histopathologically Diagnosed Types of Leukoplakia

Group	Histopathological	Frequency	Percent (%)
Control Group (30)	Epithelial Hyperplasia	24	80
	Hyperkeratosis	5	16.6
	Normal Epithelium	1	3.3
Study Group (30)	Mild Dysplasia	21	70
	Moderate Dysplasia	7	23.3
	Severe Dysplasia	2	6.7

Table 2. Frequency Distribution According to Histopathological Diagnosis

Degree of Dysplasia	P-53 (0)	P-53 LEVEL (1-5)	P-53 LEVEL (5-10)	P-53 LEVEL (10-14)	Chi Square Value	Spearman Correlation	Level of Significance
No Dysplasia (Group B)	30	0	0	0	60.000	1.000	0.000 Strong Correlation
MILD Dysplasia	0	21	0	0			
Moderate Dysplasia	0	0	7	0			
Severe Dysplasia	0	0	0	2			

Table 3. Correlation Between Degree of Dysplasia and Level of P-53

DISCUSSION

Oral Leucoplakias are heterogenous group of lesions unified by their predominantly white aspect and by their recognized, but variable, risk for malignant transformation The need to follow up patients with oral leukoplakia is generally accepted in view of the established premalignant character of some oral leukoplakia. The presence and degree of dysplasia are often used to predict malignant transformation. However, the assessment of dysplasia can be relatively subjective and the predictive values for malignant transformation are far from ideal.[2]

Relevant biomarkers hold more promise as early prognostic markers in pre-cancerous lesions and carcinomas. Among these the p53 tumour suppressor gene (Tp53) product, p53 deserves particular attention not only because of its central role in genomic stability and cell cycle regulation, but also its function is abrogated in most human cancers, and in case of oral mucosa, also in pre-invasive stages.[2]

Hence need was felt to elucidate the levels of p53 in normal, non-dysplastic, dysplastic and neo dysplastic lesions of the oral mucosa especially oral leukoplakia and to determine whether these markers have potential for an early indicator of malignancy[5]. Our study included the total sample size of 60 subjects divided into two equal groups i.e. 30 patients each in study and control groups respectively. The samples were obtained from Ambedkar dental college Patna. The total no of 30 subjects who were selected in control group were not smokers with apparently normal oral mucosa. In the study group 30 patients were selected having habit of smoking and clinically diagnosed all variants of leucoplakias were included in the study (Table 1).

In Group A (Study group), out of total 30 subjects on the basis of clinical impression a total of 18(60%) subjects were diagnosed with homogenous leukoplakia and the remaining 12(40%) subjects had speckled leukoplakia. Out of those 18 subjects with homogenous leukoplakia, 17 were males (8, 3 and 6 subjects in the predefined age group of 30-40 years, 41-50 years and 51-60 years respectively). Only one female in the age group of 41-50 years was diagnosed clinically with homogenous type of leukoplakia. All the 12 subjects with speckled type of leukoplakia were males (5 subjects each in the age group of 30-40 years, and 51-60 years, and only 2 cases were in 41-50 years age group. (Table 1) In control group (Group B) the total numbers of male patients were 28 (13 in the age group of 30-40 years, 5 subjects reported in the age group of 41-50 years and 10 in the age group 51-60 years). A total of 2 females were present in the control group (1 each in in both the predefined age group of 41-50 years, and 51-60 years respectively) (Table 1).

Both the groups were evaluated for signs of epithelial dysplasia histopathologically having, mild, moderate and severe dysplasia. Epithelial dysplasia was diagnosed according to the criteria and the definition proposed by Sheffer. A study done by Jasbir et al (1994)[6,7,8] also found that the frequency of p53 protein overexpression was high in premalignant and malignant oral lesions of patients who were heavy consumers of betel, arecanut and tobacco. (INt cancer 1994) these results were similar to the observation in our study where p53 level was higher in heavy smokers than moderate smokers. J. K Field et al (1991)[9] stated in their study that a correlation exists between the patients having smoking history and positive p53 staining. On immunohistochemistry p53 protein staining was seen in leukoplakia and none of the normal oral mucosal biopsies. These findings suggest that p53 gene mutation could be an important event in oral carcinogenesis.[10] Further in oral dysplastic lesions expression of p53 protein could indicate high risk for malignant conversion of the lesion.[11,12]

CONCLUSION

p53 expression showed statistically significant differences between hyperplastic lesions and severe dysplasia. p53 protein was highly significant in moderate and severe dysplasias in comparison to the control group and mild dysplasia. Increased expression of p53 suggest that they may be useful biomarkers of malignant transformation in oral precancerous lesions and conditions and may be useful in early detection and prevention of oral mucosa.

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