Mini Symposium: Head and Neck

p53 immunoprofiling of potentially malignant oral disorders: A case series analysis

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Abstract

CONTEXT: p53 tumor suppressor gene which is a frequent target for mutations in a high percentage of oral cancer is regarded as an early event in carcinogenesis. **AIM:** The role of p53 was assessed in potentially malignant oral disorders (PMOD) to ascertain its prognostic significance. **SETTINGS AND DESIGN:** Retrospective case series analysis was carried out on 30 paraffin-embedded tissue blocks of confirmed oral leukoplakia with dysplasia. **MATERIALS AND METHODS:** 10 cases of each of mild, moderate, and severe dysplasia were immunohistochemically analyzed for p53 expression. The intensity of staining, intracellular localization, and basal and/or suprabasal distribution were assessed. **STATISTICS:** The intensity of p53 staining and its distribution were analyzed by the Chi-square test. The intracellular localization of p53 in different grades of dysplasia was subjected to one way ANOVA. $P<0.05$ was considered significant. **RESULTS:** 21/30 cases of epithelial dysplasia were positive for p53 immunopositivity. Intensity of p53 expression was strong in 12 cases and weak in 9 cases ($P<0.05$). p53 positivity was confined to basal cells in mild dysplasia, while severe dysplasia showed both basal and suprabasal staining ($P<0.05$). Nuclear and cytoplasmic staining between and within the groups were F=9.027 and F=6.465 respectively with high significance noted between mild dysplasia and severe dysplasia. **CONCLUSIONS:** Increased p53 expressivity and greater cellular localization with increase in the severity of dysplasia indicated a direct association between the degree of epithelial dysplasia and p53 accretion, which occurs as an early event in oral carcinogenesis.

Key words: Epithelial dysplasia, Immunohistochemistry, leukoplakia, oral cancer, p53, potentially malignant oral disorders

Introduction

Oral cancers may be preceded by clinically evident potentially malignant oral disorders (PMOD) among which leukoplakia is the most common[1,2] with malignant transformation rate ranging from 0.6% to 18%.[3] This may be directly related to the severity of dysplasia as it ranges from 5% for leukoplakia with mild dysplasia to 43% for leukoplakia with severe dysplasia.[4] Thus, the transformation rate of leukoplakia to oral cancer is based on the microscopic assessment of dysplasia and the degree to which it occurs.[5-7] However, such an assessment is arbitrary, weighed down by great inter and intra-examiner variability.[8,9] Neoplastic process in PMOD has been assessed by DNA aneuploidy, loss of heterozygosity, mutations, and aberrant expression of genes.[10] Although, the tools for assessing these markers have shown promise in determining the risk of cancer, their use has been hampered by technical difficulties, making their wide-scale application challenging. In addition, some markers have proved to be of limited predictive value, thus necessitating validation of proven markers for risk assessment.

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One such marker is the p53 tumor suppressor gene which is a frequent target for mutations in a high percentage of tumors and is regarded as an early event in carcinogenesis. It is involved in cell cycle control, apoptosis, and the preservation of genomic stability.[11] The mutant form of p53 protein is

stable, has an extended half life, and can be detected by immunohistochemistry. This mutant form has been expressed in a high percentage of tumors including breast, lung, and colon cancers.[12] In our study, we aim to assess the role of p53 expression by immunohistochemistry in oral leukoplakia with different histological grades of epithelial dysplasia. We hypothesized that p53 immunostaining is important in ascertaining the prognostic significance of PMOD in particular oral leukoplakia with increasing degree of dysplasia.

Materials and Methods

Tissue samples

A purposive sampling of 30 formalin fixed paraffin embedded tissue blocks of oral leukoplakia with histological confirmation of epithelial dysplasia was retrieved from the department´s archives. These cases were further segregated into 10 cases of each of mild, moderate, and severe dysplasia, by routine H and E staining applying criteria put forth by Lumerman *et al.* 1995.[13] Identical tissue sections from each of the 30 cases were immunohistochemically analyzed for p53 expression using monoclonal antibody. Tissue sections of breast cancer and oral squamous cell carcinoma, which show strongly positive expression for p53, were used as positive controls. 10 normal oral mucosal tissue sections obtained from buccal mucosa were used for comparison with dysplastic epithelium.

Immunostaining protocol

5 μm sections were placed over 3-aminopropyl triethoxy silane (APES)-coated slides (Sigma Aldrich Chemical Co., St. Louis, MO, USA) and dewaxed through three changes of xylene and hydrated through descending grades of alcohol. Sections were dipped in freshly prepared 3% H_2O_2 in methanol for 20 min to block endogenous peroxidase activity. For antigen retrieval, sections were immersed in preheated 0.01 mM sodium citrate buffer and boiled for 12 min in a 5 L stainless steel pressure cooker. Following non-specific antigen blocking, the sections were incubated with the prediluted primary antibody (clone DO7; Dako Glostrup, Denmark) at 37°C for 60 min in a humid chamber. The sections were then incubated with the biotinylated secondary antibody (Fc conjugated Goat-antimouse IgG, Sigma Aldrich Chemical Co., St. Louis, MO, USA) diluted 1:200, at room temperature for 30 min. The sections were incubated with a streptavidin-peroxidase conjugate (Sigma Aldrich Chemical Co., St. Louis, MO, USA) diluted at a concentration of 1:200 for 30 min. Between each step, the sections were washed thoroughly for 5 min in two changes of PBS with 0.1% Tween 20. For visualization, the sections were incubated with DAB (Diaminobenzidine tetrahydrochloride, Dako cytomation, Denmark) at a concentration of 1:50 for 5 min. The sections were then counterstained using Mayer's haematoxylin for 45 seconds and washed gently in running tap water for 2 min.

Immunohistochemical evaluation

The presence of brown precipitate in the nucleus, cytoplasm, or both in the epithelial cells indicated p53-positive expression. Assessment of p53 expression was performed using a light microscope at x40 and x100 magnifications. In each of the positive tissue sections, the number of p53-positive cells, the intensity of p53 expression, pattern of staining in terms of its intracellular localization was assessed as well as its basal and supra basal distribution.

Each of the histological grades of dysplasia were evaluated for intensity of p53 expression and graded as negative (–), when there was no nuclear staining in any cell; weak (+), when the nuclear staining was in less than 25% cells and strong (++), when the nuclear staining was in more than 50%) cells.[10] The distribution of p53-positive cells in epithelium were assessed as basal or both basal and suprabasal.[14] The intracellular localization of p53 with reference to its nuclear or cytoplasmic staining was evaluated. For assessing the intracellular localization of p53 staining, 100 randomly selected cells were studied under a 100× objective. To eliminate subjective bias, two observers independently evaluated the values and its mean was subjected to further statistical analysis.

Statistical evaluation

Statistical analysis was performed using SPSS 13.0 software. The grading carried out by two independent observers was statistically analyzed using the Mann-Whitney U-test to check for inter observer variability. For analysis of p53 immunostaining, two observers independently evaluated the intensity and pattern of distribution and the mean values were subjected for further statistical analysis. The intensity of staining and p53 distribution in the epithelium was compared using the chi square "χ^2" test and the likelihood ratio. $P<0.05$ was considered significant. The reliability of the data was checked using inter class correlation coefficient. For comparing the different histological grades of epithelial dysplasia with the nuclear and cytoplasmic staining, the mean obtained was subjected to one way ANOVA test followed by post hoc test between different groups. The $P<0.05$ were considered significant.

Results

The present study included a total of 30 cases of oral leukoplakia for which immunohistochemical analysis of p53 expression was performed. Table 1 provides a detailed clinical, histological, and p53 immunoprofile. Immunohistochemical localization of p53 in dysplastic epithelium was found in the nucleus or in cytoplasm or both. Reliability of the data was checked by inter-class correlation coefficient, which was 0.99 for nuclear staining and 0.985 for cytoplasmic staining. In the normal oral mucosa p53 expression was observed in only a few cells of the basal layer [Figure 1a], while the suprabasal spinous cell layers were devoid of p53 antigen expression. In the present study, the control sections of breast carcinoma [Figure 1b] and oral squamous cell carcinoma [Figure 1c] showed strong p53 expression (++).

It was observed that 21 out of 30 cases (70%) were positive for p53 immunostaining [Table 2]. Among the cases which showed negative staining [Figure 1d], four

Table 1: Profiling of p53 expression in cases with different grades of dysplasia

Age	Sex	Habit	Per day	Years	Site	Variant	Grade	Expression*	Distribution
31	M	Cigarette	02 packs	08	Cheek	Homogenous	Mild	-	-
58	M	Bidi	10 number	18	Tongue	Homogenous	Mild	+	Basal
54	M	Bidi	25 number	16	Cheek	Homogenous	Mild	-	-
31	M	Tobacco	15 number	10	Cheek	Homogenous	Mild	-	-
64	M	Tobacco	04 pouches	20	Tongue	Homogenous	Mild	+	Basal
56	M	Cigarette	02 packs	21	Cheek	Homogenous	Mild	-	-
55	F	Tobacco	09 pouches	30	Lip	Homogenous	Mild	+	Basal
75	F	Tobacco	12 pouches	40	Cheek	Homogenous	Mild	+	Basal
46	M	Cigarette	01 pack	10	Cheek	Homogenous	Mild	+	Basal
48	M	Cigarette	01 pack	13	Tongue	Homogenous	Mild	+	Basal
70	F	Tobacco	10 pouches	30	Cheek	Speckled	Moderate	++	Supra basal
45	M	Tobacco	10 number	18	Cheek	Homogenous	Moderate	-	-
60	M	Cigarette	07 number	24	Tongue	Speckled	Moderate	++	Basal
57	F	Cigarette	20 number	20	Tongue	Homogenous	Moderate	+	Basal
75	M	Tobacco	9 pouches	32	Lip	Homogenous	Moderate	+	Basal
57	M	Tobacco	12 pouches	25	Tongue	Speckled	Moderate	++	Supra basal
80	M	Bidi	30 number	38	Cheek	Speckled	Moderate	++	Supra basal
55	M	Cigarette	02 packs	22	Cheek	Homogenous	Moderate	-	-
65	F	Tobacco	04 pouches	25	Tongue	Homogenous	Moderate	++	Supra basal
48	M	Tobacco	11 packs	14	Tongue	Homogenous	Moderate	-	-
47	F	Tobacco	05 packs	20	Cheek	Homogenous	Moderate	++	Supra basal
75	M	Bidi	25 number	32	Cheek	Speckled	Severe	++	Supra basal
50	M	Bidi	30 number	18	Cheek	Speckled	Severe	++	Supra basal
70	F	Tobacco	04 pouches	24	Lip	Homogenous	Severe	++	Supra basal
75	M	Bidi	25 number	25	Cheek	Speckled	Severe	-	-
64	F	Bidi	20 number	30	Cheek	Speckled	Severe	++	Supra basal
79	M	Tobacco	05 pouches	33	Tongue	Speckled	Severe	++	Supra basal
67	M	Tobacco	4 pouches	20	Cheek	Homogenous	Severe	+	Basal
52	F	Pan	05 packs	18	Tongue	Speckled	Severe	-	-
45	M	Pan	05 packs	14	Cheek	Homogenous	Severe	++	Supra basal

Table 2: Expression of p53 in different grades of epithelial dysplasia

Intensity score grading of dysplasia	Negative (–)	Weak (+)	Strong (++)	Total no. of cases
Mild dysplasia	4	6	0	10
Moderate dysplasia	3	2	5	10
Severe dysplasia	2	1	7	10
Total	9	9	12	30

were histologically diagnosed mild epithelial dysplasia, three were the moderate dysplasia, and two were severe dysplasia. On the other hand, p53 immunopositivity was observed in six cases of mild dysplasia, seven of moderate dysplasia and eight of severe dysplasia.

Out of the positive cases, p53 staining was weak in 9 cases [Figure 1e] and showed strong intensity in 12 cases [Figure 1f]. The weak p53 staining was high for mild dysplasia as it was observed in all the six cases, while only two out of seven of moderate dysplasia and one out of eight with severe dysplasia showed weak staining [Figure 2]. In cases which showed strong p53 staining seven were severe dysplasia and five were moderate dysplasia. None of the tissue sections that were histologically diagnosed as mild dysplasia showed strong staining for p53. The chi-square test for intensity of different grades of dysplasia gave the likelihood ratio of 15.244, with $P<0.05$.

The assessment of p53 distribution in dysplastic epithelium revealed that p53 positivity was confined primarily to the basal cells in mild dysplasia, while three out of seven cases of moderate dysplasia showed basal distribution and remaining four cases showed both basal and suprabasal distribution. The basal as well as suprabasal staining was noted in seven out of eight cases of severe dysplasia and the only other case of severe dysplasia showed basal distribution. The exact *P* value obtained by the chi-square "χ^2" test was 10.619, with highly significant *P* value ($P=0.004$) [Figure 3].

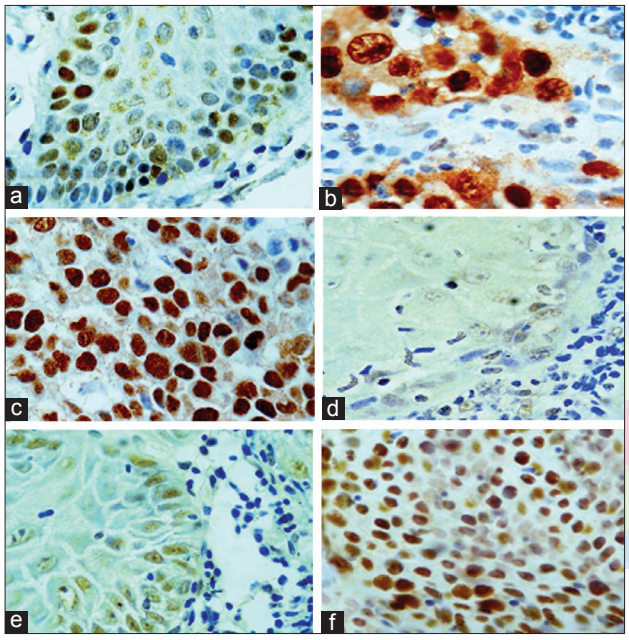

Figure 1: Photomicrograph showing p53 expression (a) in normal oral mucosa - ×100; (b) breast carcinoma - ×100; (c) oral squamous cell carcinoma - ×100; (d) negative staining (–) in dysplasia - ×100; (e) mild dysplasia - ×100; (f) severe dysplasia - ×100

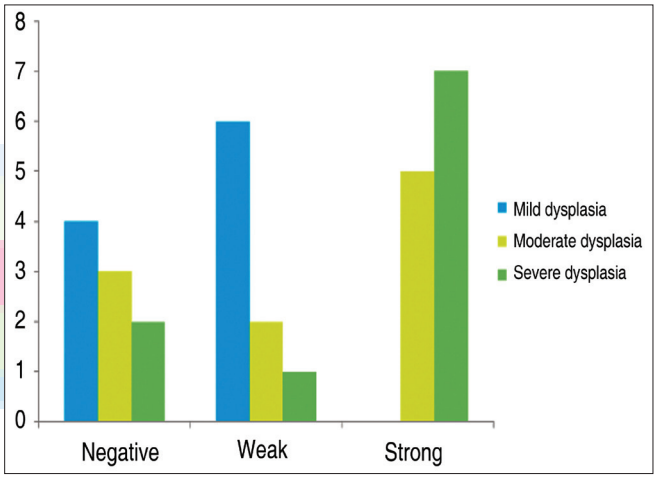

Figure 2: Bar diagram depicting intensity of p53 expression in different grades of dysplasia; Chi square "χ2" test - 11.833; Exact mid *P* value = .019

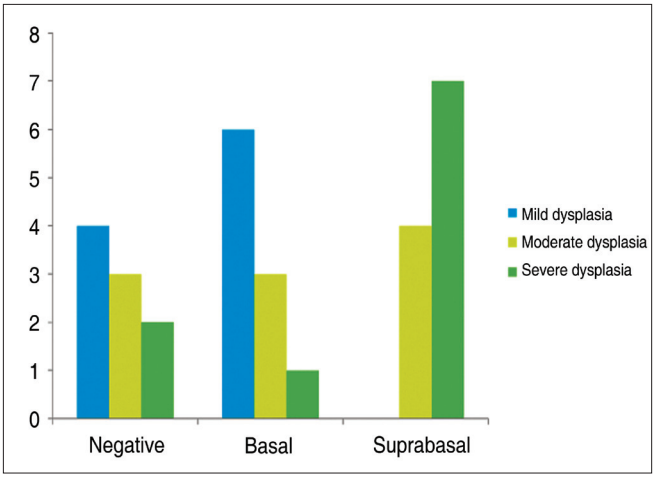

Figure 3: Bar diagram depicting the distribution of p53 in the basal and suprabasal half of dysplastic epithelium; Chi Square "χ2" test -10.619; Exact *P* value = 0.004

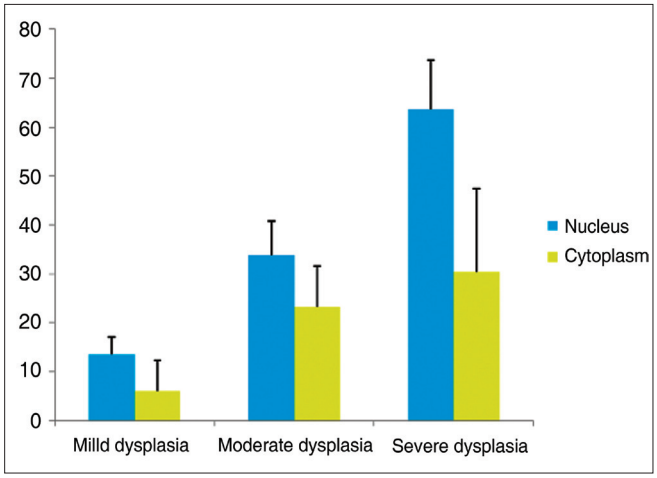

Figure 4: Bar diagram showing the mean of intra cellular localization of p53-positive cells in different histological grades of dysplasia; F = 47.72; *P*<0.001 (Between the groups) and F = 28.409 *P* <0.001 (Within the group)

Immunohistochemical staining of p53 positive dysplastic cells for intra-cellular localization with reference to its nuclear or cytoplasmic staining was evaluated. In six positive cases of mild dysplasia, the mean number of cells showing nuclear staining was 13.5 ± 6.33, while cytoplasmic staining was seen in 6 ± 3.55 cells. Out of seven positive cases of moderate dysplasia, the mean number of cells with nuclear staining was 33.7 ± 7.13 and those with cytoplasmic staining were 23.2 ± 8.40. Likewise, in eight positive cases of severe dysplasia, the mean number of cells with nuclear staining was 63.6 ± 16.93 and with cytoplasmic staining were 30.4 ± 10.11. It was found that the mean of nuclear and cytoplasmic staining between and within the groups were found to be $F = 47.72$; $P<0.001$ and $F = 28.409$ $P<0.001$ respectively [Figure 4]. From these tests, it was evident that there was a very high significance noted between mild dysplasia and severe dysplasia cases.

Discussion

p53, a tumor suppressor protein, acts as a "molecular brake" to critically regulate the cell cycle. This DNA-binding protein has also been involved in DNA repair and synthesis, cell proliferation, cell differentiation, programmed cell death, and in the maintenance of genomic stability. As p53 protein has been reported to be expressed at high levels in malignant lesions[14,15] assessment of its levels in premalignant lesions is significant.[16,17] Since majority of OSCCs have the occurrence of leukoplakia in its close vicinity and tobacco being a common risk factor in this multistep and multifocal process,[18] the analysis of p53 levels in tobacco-associated potentially malignant disorder of the oral cavity through its various histological grades was regarded to be crucial.

In a normal cell, the p53 protein is kept at a low concentration by rapid degradation. In addition, p53 exists in a latent, inactive form.[19] Several stressful situations including genotoxic DNA damage, hypoxia, and deprivation of growth factors and loss of cell to cell contact can induce the formation of functional p53. Activation of p53 occurs by increasing the p53 protein concentration by enhanced translation or by the transformation of p53 protein from a latent to an active conformation or by the translocation of p53 protein from cytoplasm to the nucleus.[20]

Our observation, revealing highly significant differences in p53 immunolocalization and staining intensity in severe dysplasia cases more than in mild dysplasia is in agreement with other studies carried out by Girod *et al*.,[21] Iwasa M *et al*.[22] and Kovesi *et al*.[23] These findings suggest a strong correlation between p53 expression and degree of dysplasia, thus confirming that p53 may be involved in proliferative events as well as in neoplastic transformation.[24]

Comparison of p53 staining intensity in positive cases revealed that p53 expression was weak in mild dysplasia compared to moderate and severe dysplasia which showed stronger staining intensity. Similar observations have been made by Langdon *et al*.,[10] where the intensity was greater with increase in cellular atypia, particularly due to tobacco associated habits. This may be directly related to the activity of p53 which may be increased during the early stages of tumor progression.[25] The p53 molecule can be further modulated during the advancement of lesion, because of a functional interaction between the p53 molecule and other cellular proteins. The weak intensity observed in two cases of moderate and one case of severe dysplasia can be explained due to the role of other oncogenes like H ras, C-fos, jun family, c-myc, and trophic factors that participate in growth regulation and when inappropriately expressed, generate growth signals that may override the cellular control of p53.[26]

Distribution of p53 immunoexpression confined to the basal layer in cases of mild dysplasia, as opposed to moderate and severe dysplasias expressed in both the basal and suprabasal staining with increased frequency is in agreement with studies by Kerdpon *et al*.,[24] Cruz *et al*.,[27] and Nylander *et al*.[28] Expression of p53 in suprabasal cells in moderate and severe dysplasia states indicated that the superficial cells of the epithelium were mitotically active resulting in an abnormally proliferative state. This is in contrast to normal mucosa, where it is only the basal cells of the epithelium, which proliferate, differentiate, and mature to form keratinized squames. It has also been pointed out that an increase in p53-positive cells in suprabasal layers of the epithelium in oral premalignant lesions of leukoplakia suggests an imminent potential for aggressive behavior.[28]

Our observations made with respect to correlation between grading and intracellular localization of p53 suggest that moderate and severely dysplastic leukoplakias have greater potential for malignant transformation than that of mild dysplasia or no dysplasia. These changes could be attributable to the regulation of p53 which is either through enhanced nuclear import or decreased nuclear export or retention.[29] Binding of p53 with MDM2 is essential for p53 degradation in the cytoplasm by ubiquitination. However, abnormal sequestration of wild-type p53 in cytoplasm, which is known to occur in many human malignancies, may be due to its loss of function as a transcription factor to bring about cell cycle arrest.

Mutations in p53 gene also results in the protein accumulation within the nucleus[30] and studies suggest that tumorigenesis could result from a defect in the regulation of wild-type p53 nuclear import.[14,15] Since the presence of detectable p53 does not necessarily reflect the effect of mutations, no definitive conclusions could be drawn about mutations resulting in cellular proliferation based on immunohistochemistry results alone. However, the mutant form of p53 proteins are known to be more stable, have an extended half life and thus accumulate in higher concentrations as is observed in carcinoma of breast and colon.[29]

Conclusions

Our observations contribute to previous findings that p53 immunoexpression could be used as a specific marker for lesions that are at high risk of malignant transformation. p53 as a prognostic marker may stand as a useful supplement of histopathological assessment in the prognosis of potentially malignant oral lesions. However, further studies with larger sample size using a panel of related molecules are necessary to establish the full potential of p53 as a prognostic marker in potentially malignant oral lesions.

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