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Original Research

The New Norm for Tumor Suppressor Gene p53: Assessing the existing Grading System of Oral Epithelial Dysplasia

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ABSTRACT:
Background: Identification and management of potentially malignant oral epithelial dysplasia at highest risk of malignant transformation (MT) holds great promise for successful secondary prevention of oral squamous cell carcinoma (OSCC), potentially reducing oral cancer morbidity and mortality. However, to date, neither clinical nor histopathologic risk predictors have been identified that can reliably predict the transformation of OPMD's to malignancy. Therefore, the underlying molecular mechanisms facilitate the discovery of diagnostic, prognostic and predictive markers. **Aims and Objectives:** Immunohistochemical localization of p53 value in varying grades and system of Oral Epithelial Dysplasia and also to evaluate the need to study p53 expression in precisely grading and enhancing the current histopathological grade of Oral Potentially Malignant Disorders. **Materials and Methods:** 30 cases of oral epithelial dysplasia were included in the study and were subjected to H/E and immunohistochemical staining using antibody kits for P53. **Result:** The immunoexpression of p53 staining was seen in different cell layer and combines score was calculated. **Conclusion:** Improvement in the standard of the histopathology reporting of OED lesions could be achieved by consideration of several points. The future may rely on the application of molecular markers which identify lesion at the early levels of genetic changes.
Key Words: Epithelial Dysplasia, Oral Potentially Malignant Disorders, p53, Squamous Cell Carcinoma

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INTRODUCTION

Oral Epithelial Dysplasia (OED) is the diagnostic term used to describe the histopathological changes seen in a chronic progressive and premalignant disorder of the oral mucosa. Dysplasia is a Greek word that means abnormal atypical tissue proliferation. The term 'dysplasia' was introduced by Reagon (1958) in relation to the cells exfoliated from lesions of the uterine cervix.[1] The presence of dysplastic regions in the epithelium is thought to be linked to the development and progression of cancer. A precancerous lesion is a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart. A precancerous condition is a generalized state that is related to a higher risk of cancer.[2],[3] Due to the lack of a validated grading system, current histopathological grading of oral epithelial dysplastic lesions is ambiguous and a topic of debate since years. It is subjective and lacks inter and intra observer agreement and reproducibility. Many studies show wide variability in the diagnosis and grading of OED with results demonstrating only poor to moderate agreement on grading OED.[4],[5]An accepted gold standard is not available for assessing the validity and grading of OED which is thought to be better than pathologist's observation.[6] Early, accurate diagnosis and grading of oral epithelial dysplasia helps in prevention and reducing the malignant transformation rate of OED to OSCC. Since histopathological criteria lack objectivity, molecular markers aids in diagnosing precisely OED. Thus, it appears that regarding, reproducibility as well as in terms of prognosis, still a lot of progress

has to be made.[7] Progression of OED to oral cancer may be a result of an accumulation of genetic and epigenetic alterations, the epigenetic alterations referring to a multitude of aberrations, including chromosomal rearrangements, mutations, methylation, and others, which affect the expression and function of oncogenes and tumor suppressor genes. The clinical appearance and microscopic changes of OED are driven by specific molecular alterations that accumulate over time; eventually culminating in malignant transformation. As a result, there is a never-ending search for molecular markers that can identify the premalignant nature of a lesion not just with greater accuracy but also before the accompanying clinicopathologic changes appear.[8] p53 tumour suppressor gene (TP53) product deserves particular attention, not only because of its central role in genomic stability, accumulation in cells having genotoxic stress and cell cycle regulation but also because its function is abrogated in most human cancers arising in normal oral mucosa or in pre invasive stages. Inactivation of p53 leads to the inability of a cell with DNA damage to induce cell cycle arrest or DNA repair or the induction of apoptosis. Wild-type p53 may be inactivated by complex formation with mutant p53, viral or aberrant host-binding proteins. The mutant form of p53 protein is more stable than wild type, has an extended half life, and can be detected by immunohistochemistry.[9] 80% of oral squamous cell carcinomas carry p53 mutations, indicating that the oral mucosa is one of the more common targets for p53 mutation and suggesting that knock-out of p53 normal function is a common step in oral carcinogenesis. Wild-type p53 protein activates the transcription of genes involved in G1 arrest, particularly thep21/Waf-1/CIP-1 gene, allowing DNA repair before replication. In addition, p53 may trigger the apoptosis of cells with irreversible DNA damage. Both mechanisms provide a barrier to the propagation of mutated cells and consequently p53 has been designated as 'the guardian of the genome.[10] The proportion of positive cases with p53 over expression increased from normal and hyperplastic lesions, to dysplasia and oral squamous cell carcinoma, indicating an involvement of p53 in neoplastic transformation and proliferative events.[11],[12] The limitations of subjective variability and reproducibility in the histologic grading of OED has caused considerable distress for pathologists because of ambiguous diagnostic criteria and differences of opinion among pathologists, suggest either the necessity to improve histologic assessment or need to identify more reliable makers which helps in determining the early malignant transformation rate or prognostic implications of white lesions.[13],[14] Therefore alterations of this crucial gene are commonly studies because it is not only proceeded by other genetic alterations, but facilitate the accumulation of further genetic alterations needed for the multistep process of carcinoma development. Thus this study was designed with the aim of elucidating the new norms of grading OED by initiating IHC grading system as a new tool in existing histopathological gradings which is required for the benefit and prognostic point of view of the patient. Henceforth molecular analysis of P53 would result in uniformity in reporting and interpretation, resulting in correct detection and definition of grades of dysplasia which could improve the survival rate and prognosis of disease.

MATERIALS AND METHODS

PATIENTS AND TISSUES

Thirty formalin-fixed, paraffin-embedded tissue of OED were included in the study. For each case, a single 4 µm thick tissue sections were obtained and stained with Harris Haematoxylin and Eosin examined by light microcopy. Two certified oral pathologists and one postgraduate student belonging to the Department of Oral and Maxillofacial Pathology and Microbiology were included in the study for inter-observer examination. The final selected 30 cases of OED were coded and randomly arranged for all the examiners for examination. In first part of study inter-observer of the cases was done where the pathologists were not provided with any demographical information regarding the expected distribution of severity of the cases. The inter-observer variability of the cases was carried out based on three grading systems, Smith and Pindborg, Brothwell DJ et al. & WHO 2005 criteria by three observers. OED was subdivided into three prognostically significant categories as mild, moderate and severe. Further 30 cases were assessed and analyzed by Post Graduate for intra observer variability within 3 months of interval. In second part of study, 3micron thick sections of the same cases were obtained and subjected for immunohistochemical analysis using p53 antibody (Biogenex Indpvt ltd, Clone number BP53-12-1).

IMMUNOHISTOCHEMICAL PROCEDURE

Immunohistochemical analysis for p53was performed on 4µm paraffin sections were obtained using a rotary microtome. In brief, following dewaxing, washing and rehydration of the slides through xylene and graded alcohol concentrations, citrate buffer at pH 6.0–6.2 was used for antigen retrieval. Slides were subsequently treated with 3%hydrogen peroxide to block endogenous peroxidase. Following incubation with the primary antibodies, p53 (Biogenex) and the secondary conjugate antibody was applied and followed by chromogen DAB and counterstaining with Mayer's hematoxylin.

POSITIVE CONTROL

Squamous cell carcinoma tissues were selected as a positive control and immune-stained in the same manner as other study cases.

IMMUNOHISTOCHEMICAL ANALYSIS

All the immune-stained slides were viewed under the light microscope. Positive immune-histochemistry expression of p53 was defined by a nuclear staining pattern of epithelial cells. The distributions of p53-positive cells in epithelium of OED were assessed as basal, supra-basal and superficial. The intracellular localization of p53 with reference to its nuclear or cytoplasmic staining was evaluated. Quantitative and Qualitative analysis of p53 along with combine scoring was done as mentioned.

QUANTITATIVE ANALYSIS OF p53

Quantitatively immunoexpression of p53 was assessed in the basal, parabasal and in superficial cells layers of OED. 5 random fields were selected and quantitative analysis was done by counting total number of 1000 cells (200 cells/ HPF). Mean labeling index of p53 was calculated as below:

Mean Labeling Index = Total no of cells Positive×100
Total number of cells counted

QUALITATIVE ANALYSIS OF p53

The qualitative analysis was done by observing intensity of each case and compared it with positive control and score was given as:

a. 0 = Negative
b. 1+ = Mild Intensity
c. 2+ = Moderate intensity
d. 3+ = Intense intensity.

COMBINED SCORE OF IMMUNOEXPRESSION of p53

The combined score was determined by calculating the weighted Cut off values of p53 obtained from counting total no of positive cells for total 30 cases of OED. Weighted Cut off values for p53 was given as : 1= Less than 34.5, 2=34.81-48.8, 3=48.81-71, 4= More than 71. These values were combined with the values obtained by qualitative analysis. The score obtained determines the levels of immuno-staining of p53 which statistically ranged from 0 to 7.

a. 0= Negative immunoexpression
b. 1-3 = Level I (mild) immunoexpression of p53
c. 4-5 = Level II (intermediate) immunoexpression of p53
d. 6-7 = Level III (high) immunoexpression of p53

STATISTICAL ANALYSIS

Descriptive statistics including the mean values, standard deviations, and ranges (minimum and maximum) were calculated for each variable. The resulting data were analyzed using SPSS software. Data have been expressed as mean and standard deviation. Differences between the different variables were analyzed using ANOVA test and post hoc test followed by Bonferroni test. The significance, i.e., $P < 0.05$ was considered to be significant. Unweighted Cohens kappa is used to interjudge agreement for categorical variables for intra-observer agreement.

RESULTS

The results of our study showed that interobserver agreement between the three observers was found to be best in Brothwell DJ et al. (94%) followed by Smith & Pindborg (92%) and was minimum in WHO (20005)(90%). Similarly, the intraobserver agreement was seen maximum in Brothwell DJ et al. grading system (80%) with minimum standard error (.095), whereas WHO (2005) shows 60% agreement with standard error (1.22) and lest agreement in Smith & Pindborg system (55%) with standard error(1.22). Accordingly, after interexaminer variability analysis, there was a redistribution of 30 cases OED following three grading system. According to Smith and Pindborg grading system 14 cases of were Mild Dysplasia, 10 were Moderate Dysplasia and 6 were Severe Dysplasia. Similarly according to WHO (2005) grading system 8 cases of were Mild Dysplasia, 13 were Moderate dysplasia and 9 were Severe Dysplasia. Further in Brothwell DJ et al grading system 9 cases were Mild Dysplasia, 12 were Moderate Dysplasia and 9 were Severe Dysplasia. p53 immuno expression of 30 study cases of OED was evaluated out of which 29 were positive and 1 was negative. Quantitative analysis of all the cases were done which showed that in Smith and Pindborg grading system the mean labelling index of p53 is increasing from mild dysplasia(41±15), moderate(54±17) and severe(100±56). Similarly in WHO (2005) the mean labelling index of p53 is in mild dysplasia(41±14), moderate (45±18) and severe (88±48) and Brothwell DJ et al. the mean labelling index of p53 is in mild dysplasia (33±14), moderate (51±14) and severe(88±48) grading system were seen. These results were statistically significant. ($p \leq 0.05$). Qualitative analysis of p53 immuno-expression showed that according to all the three grading system, in cases of mild dysplasia, maximum cases showed mild to moderate intensity and none of the cases shows intense intensity. In cases of moderate dysplasia, all the cases were mild to moderate in intensity. Similarly in severe dysplasia, maximum cases were intense in intensity. Only one case is negative in p53 immuno-expression. Further layer wise analysis of p53 immunoexpression was done in varying grades of OED following 3 grading system. The results showedthat out of 30 cases of OED, the mean value of p53 positive cells is decreasing from basal layer to suprabasal layer and minimum in superficial layer in mild dysplasia. Similarly in moderate dysplasia the mean value of cells is decreasing from basal layer to suprabasal layer and minimum in superficial layer. Similar results were obtained for severe dysplasia. Mean value of p53 in basal, supra basal and in superficial cell layer is increasing from mild to moderate and was maximum in severe dysplasia. The results were

statistically significant (p≤0.05). Combined score of p53 immunoexpression showed the comparison of H and E cases of varying grades of OED with levels of immunostaining of p53 between three grading system.In Smith & Pindborg grading system, 14 cases of mild dysplasia, 6 cases showed level I immunostaining and 8 shows level II staining. Out of 10 cases of moderate dysplasia (H&E), 3 cases showed level II staining, 5 cases showed level I staining and 2 cases shows level III staining. Similarly 6 cases of severe dysplasia (H&E), on comparisons with combined score of immunoexpression of p53 analysis 5 cases showed level III immunostaining and 1 case showed negative staining. In WHO (2005) grading system,8 cases of mild dysplasia (H&E), 3 cases showed level I immunostaining and 5 shows level II staining. Out of 13 cases of moderate dysplasia (H&E), 5 cases showed level II staining, 7 cases showed level I staining and 1 case showed level III staining. Similarly 9 cases of severe dysplasia (H&E), 6 cases showed level III immunostaining and 1 case each showed level II, level I and negative staining. In Brothwell DJ et al. grading system on comparisons with combined score of immunoexpression of p53 analysis, out of 8 cases of mild dysplasia (H&E), 5 cases showed level I immunostaining and 4 cases shows level II staining. Out of 13 cases of moderate dysplasia (H&E), 6 cases showed level II staining, 5 cases showed level I staining and 1 case showed level III staining. Similarly 9 cases of severe dysplasia (H&E), 6 cases showed level III immunostaining and 1 case each showed level II, level I and negative staining. Results were statistically significant. (p≤ 0.05) [Table:2]

Table 2: Comparison of H&E staining (Smith &Pindborg, WHO (2005) and Brothwell DJ et al. grading system) with combined score of p53 immunoexpression in case of OED

	Distribution of cases(H&E)	**Distribution of cases according to levels of immunoexpression of p53Combined score**				
Grades (Smith and Pindborg)	**N**	**Negative (0)**	**Level I (1-3)**	**Level II (4-5)**	**Level III (6-7)**	**p value**
Mild	14	0	6	8	0	.005
Moderate	10	0	5	3	2	
Severe	6	1	0	0	5	
Total	30	1	11	11	7	
(WHO)	**No of cases**	**Negative (0)**	**Level I (1-3)**	**Level II (4-5)**	**Level III (6-7)**	**p value**
Mild	8	0	3	5	0	.03
Moderate	13	0	7	5	1	
Severe	9	1	1	1	6	
Total	30	1	11	11	7	
(Brothwell DJ et al)	**No of cases**	**Negative (0)**	**Level I (1-3)**	**Level II (4-5)**	**Level III (6-7)**	**p value**
Mild	8	0	5	4	0	.01
Moderate	13	0	5	6	1	
Severe	9	1	1	1	6	
Total	30	1	11	11	7	

FIG: 1 Hematoxylin and eosin stained section of Mild epithelial dysplasia (H and E stain, 40x magnification)

FIG: 2 Mild epithelial dysplasia showing Level II p53 immunostaining seen as strong positivity in basal and suprabasal cell layers (IHC, 40x magnification)

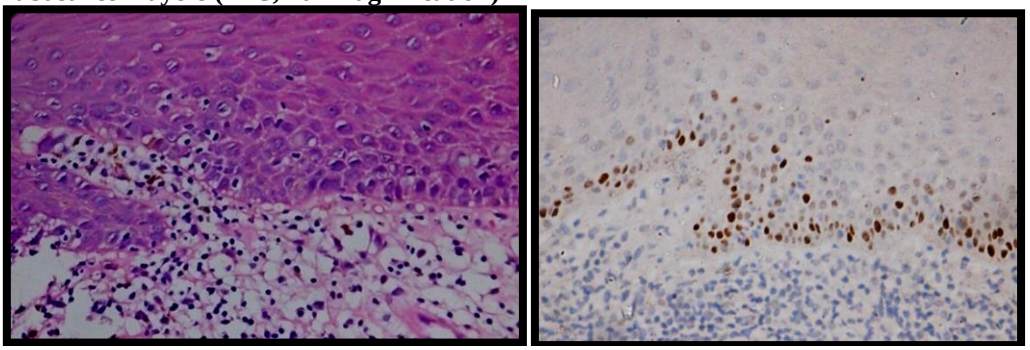


FIG: 3 Hematoxylin and eosin stained section of Moderate epithelial dysplasia (H and E stain, 40x magnification)
FIG: 4 Moderate epithelial dysplasia showing Level I p53 immunostaining seen in basal and parabasal cell layers (IHC, 40x magnification)

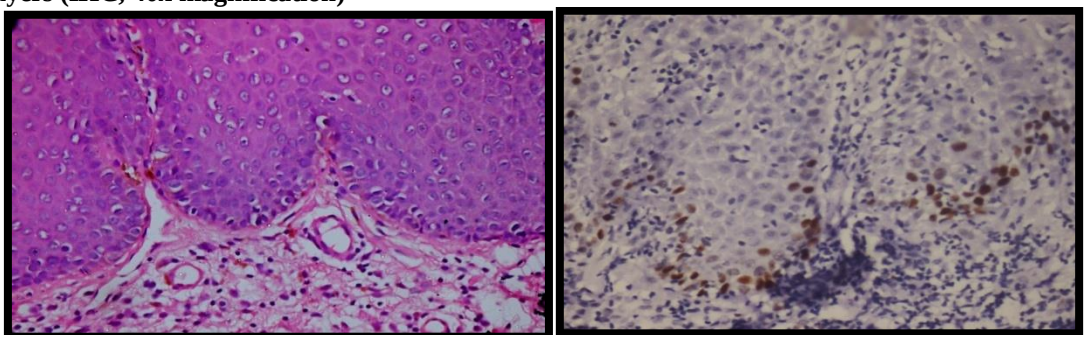
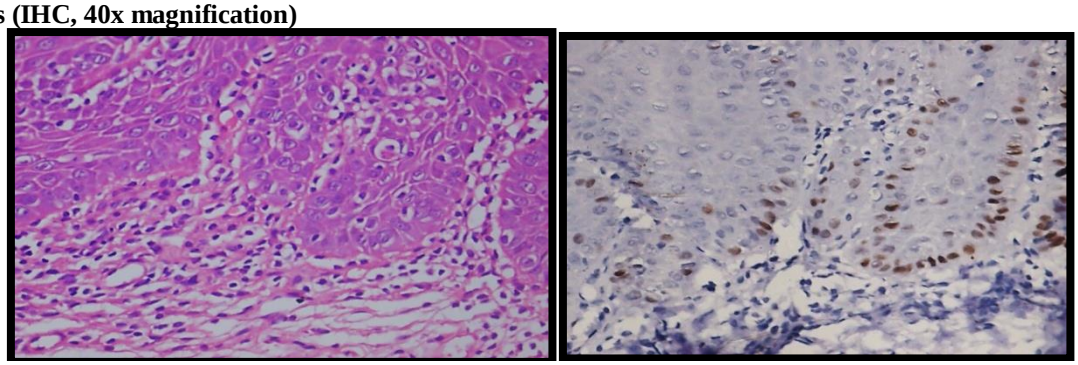


FIG: 5 Hematoxylin and eosin stained section of severe epithelial dysplasia (H and E stain, 40x magnification)
FIG: 6 Severe epithelial dysplasia showing Level I p53 immunostaining seen in basal and parabasal cell layers (IHC, 40x magnification)



DISCUSSION

Alterations of the head and neck (H&N) mucosa have been intimately involved in the advancement of our understanding of precancers or potentially malignant lesions.[15]Oral carcinomas frequently arise from a spectrum of abnormalities ranging from hyperplasia to intraepithelial neoplasia termed histopathologically oral epithelial dysplasia (OED). These lesions are graded into different categories and this grading process is based on the likelihood risk of malignant transformation.[4],[14] Assessment of dysplasia depends upon the microscopic diagnosis which is based on grading the changes considering combination of architectural and cytological features. Grading of dysplasia is subjective and lacks intra and inter observer reproducibility due to insufficiency of validated morphological criteria and the biological nature of dysplasia.[13],[16] P53, a tumour suppressor protein, controls the cell cycle by acting as a "molecular brake." This DNA binding protein is also involved in DNA repair and synthesis, cell proliferation, differentiation, programmed cell death, and genomic stability maintenance. The presence of p53 protein in premalignant lesions is important because it has been shown to be expressed at high levels in malignant lesions. The p53 protein is rapidly degraded in a normal cell, keeping its concentration low. Furthermore, there is a dormant, inactive version of p53. Enhanced translation, the change of p53 protein from a latent to an active conformation, or the translocation of p53 protein from the cytoplasm to the nucleus are all examples of stressful circumstances that can lead to the creation of functional p53.[10],[11],[17] P53 is found only in the proliferative basal cell layer of normal oral epithelium. Overexpression of inactivated or mutant versions of p53 in oral epithelial dysplasia has been linked to an increased risk of early-stage OSCC transformation.[18], [19] The molecular study of precursor lesions may disclose some of the alterations that dictate the development of cancer, independently of recognizable morphological alterations. Mutations of p53, a gene that is located on chromosome 17p, have been detected in 15–19 per cent of oral premalignant lesions, including lesions with mild dysplasia, and in tumor-distant epithelia of head and neck cancer patients. These findings support the idea that p53 mutation is an early event in oral epithelial dysplasia which can lead to oral carcinogenesis.[10] Thus this study was conducted to determine the expression of P53 in varying histopathological grades of OED and combining molecular analysis with routine histopathology which can boost a potential of existing grading system for the determination of prognosis of OPMD. In the present study, after interobserver variability analysis was done, all 30 cases of OED were redistributed as mild, moderate and severe dysplasia following three grading system

as Smith & Pindborg system et al, WHO (2005) and Brothwell DJ et al. On quantitative analysis of p53 immunoexpression in varying histopathological grades of Dysplasia, out of total 30 cases of OED 29 cases were immunopositive and only one case was immunonegative. **Prives C (1999)** explained the reason of immunopositivity of P53 in cases of dysplasia is because its existence in a latent, inactive form which could be due to DNA damage, hypoxia, and deprivation of growth factors and loss of cell to cell contact can induce the formation of functional p53. Functional 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.[11],[20] **Regezi et al. (1996)** could not find a clear correlation between grade of dysplasia and the percentage of p53-positive cells in oral premalignant lesions. In contrast to this, Wood et al. found a significant correlation between p53 expression and grade of dysplasia in 42 oral leukoplakias analyzed by IHC which shows significantly higher number of p53-positive cells in lesions showing moderate or severe dysplasia than in lesions showing mild dysplasia. The discrepancies found among studies may be due to subjectivity in the assessment of dysplasia, differences in the populations studied, or sampling differences.[21] Our results showed statistically significant increase in Mean labeling index of p53 from mild to moderate dysplasia and was maximum in severe dysplasia according to all three grading system. Our results is in accordance with the study done by **Cruz et al. (1998)** and **Nylender et al. (2003)**where they have demonstrated that p53 increased in moderate to severe dysplasia which may be due to increase in number of mitotically active cells in increasing grades of dysplasia which result in abnormal proliferative state. Similar study done by **Girod et al. (1998)**, **IwasaM et al. (2001)** and **Kovesi et al. (2003)** found that p53 may be involved in proliferative events as well as neoplastic transformation suggesting that there is a strong correlation between p53 expression and degree of dysplasia. According to **Reddy et al. (2012)**increased p53 immunolocatization in moderate and severe grades were attributed to greater potential for malignant transformation, where these changes can be due to regulation of p53, either through enhanced nuclear import or decreased nuclear export orientation.[11],[22],[23],[24],[25],[26] Qualitatively, p53 immunoexpression was seen more intense in severe dysplasia in comparison to moderate and mild dysplasia. A possible reason for this immunoexpression was suggested by **Langdon et al. (1992)** intensity of p53 was greater with increase in cellular atypia as well as also increase in early stages of tumor progression. **Reddy VM et al. (2017)**had commented on the reasons of weak intensity in few cases of severe and moderate dysplasia which may be 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.[Table:1][10],[11],[27]

Table 1: Qualitative and quantitative layerwise analysis of p53 immunoexpression in varying grades of OED in 3 grading system

			Qualitative Analysis					Quantitative Analysis		
Grading System	**Grades**	**N**	**0**	**+**	**++**	**+++**	**P value**	**Basal (Mean ±SD)**	**Suprabasal (Mean ±SD)**	**Superficial (Mean ±SD)**
Smith and Pindborg	Mild OED	14		8	6		0.00	30±10	10±6	.2±.9
	Moderate OED	10		5	5			35±9	14±6	4±6
	Severe OED	6	1		1	4		57±32	29±18	13±8
p value								0.01	0.01	0.00
WHO(2005)	Mild OED	8		4	4		0.019	31±8	9±7	.0±.0
	Moderate OED	13		8	5			30±11	11±5	2±4
	Severe OED	9	1	1	3	4		52±27	24±16	11±8
p value								0.17	0.08	0.00
Brothwell DJ et al.	Mild OED	9		6	3		0.016	26±10	7±4	.0±.0
	Moderate OED	12		6	6			34±8	14±5	2±4
	Severe OED	9	1	1	3	4		52±27	24±16	11±8
p value								.01	0.003	0.00

Further in our study, we found one negative case of p53 expression, which is similar to the results found by **Cruz et al. (1998)** suggesting that absence of p53 do not include malignant transformation, there may

be other factors (HPV, EBV, mdm2) and p53 mutation as well which can lead to dysfunction of p53 resulting in undetectable p53 protein. Another reason given by **Rowley et al. (1998)** tumor with non-sense or frame shift mutation or gross deletion may not express p53 protein by IHC. The reasons of layer wise analysis of p53 in cases of OED is in accordance to the **Kerdpon et al. (1997)** where he found positive staining in basal and parabasal cells of mild and moderate dysplasia as well as in atypical cells in more superficial layer in severe dysplasia implying a positive relation of p53over expression and degree of cellular atypia in severe dysplasia as compared to mild dysplasia. However, suprabasal p53 immunoexpression may be a useful tool for malignant transformation risk assessment of potentially malignant disorders independent of dysplasia grade. According to **Cruz IB et al. (1998)**, basal and parabasal layer constitutes to the proliferative compartment and therefore exposure to genotoxic stress will lead to p53 accumulation in these layers. Whereas in superficial cells p53 do not accumulate, as these cells have lost their capacity to divide. In contrast p53 expression in suprabasal cells was only detected in premalignant cases, likely reflecting the presence of mutant protein which may be due to its decreased turnover, will persist for a longer time. Similar study was done by **Reddy et al. (2017)** where he pointed out that increase in p53 positive cells in suprabasal layer of epithelium suggesting imminent potential of determining the aggressive behavior of the lesion.[Table:1][11],[12],[28],[29] Results of combined score analysis of our study determines the level of immunostaining of p53 in histologically confirmed cases of mild, moderate and severe dysplasia. Our analysis was supported by **Rowley et al. (1998)** where he said that p53 molecules help in determining the early event changes occurring prior to gross histologic alteration and also assessment of p53 helps in identifying the cells which are in proliferative pool and mutant protein which accumulates in the epithelium due to decreased turnover rate. He also said that the detection of p53 mutations in premalignant lesions has led to various predictions regarding the timing of genetic events involving oral epithelium. Histopathological grading along with add on immunohistochemical analysis can strengthen our existing grading system by giving more accurate diagnosis and determining the prognosis and prediction of the treatment. This hypothesis of our study is supported by **Pandya et al. (2018)** where they explained Tp53 expression is an important marker in predicting the biological behavior of a premalignant lesion which cannot be done at histological level. Since it has a key role in initial stages of oncogenesis, its variability in expression may help in predicting the transformation of premalignancy to a frank carcinoma. Thus combined with routine histopathology studies, molecular markers could have a great potential for the grading OPMD. [Table:2][27],[30] Therefore with the outcome of the results of study it is suggested that p53 combined score analysis is an important parameter which should be included along with histopathology on routine basis while grading OED as it delivers the most convenient results for patients of OPMDs. Thus molecular analysis of p53 forms the new norms of grading OED by initiating IHC grading system as a working model of OED grading and challenging the initial concept of H/E grading

CONCLUSION

Oral epithelial dysplasia grading is not an exact science, and pathologists do their utmost to achieve the best possible outcome. Several factors could be taken into account to improve the standard of histopathological reporting of OED lesions. The use of molecular markers to detect lesions at the earliest stages of genetic alterations may be the way of the future. As a result of the findings of this investigation, p53 immunoexpression could be employed as a particular marker for lesions with a high risk of malignant transformation. In the prognosis of possibly malignant oral lesions, P53 as a prognostic marker could be a beneficial adjunct to histological examination. Ultimately the goal is to use molecular tools to assist in earlier identification of high risk lesions and to lead to more accurate histopathological diagnosis.

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