ORIGINAL ARTICLE

Expression of proliferative marker Ki-67 in epithelial dysplasia and squamous cell carcinoma of oral cavity

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Abstract

Background: The proliferative index helps to evaluate the growth rate and aggressiveness of the malignant tumor. Ki-67 is one of the proliferating markers that help to predict the patient's survival in Oral Epithelial Dysplasia (OED) and Oral Squamous Cell Carcinoma (OSCC). Hence, the present study evaluated the expression of Ki-67 in OSCC and OED. *Aim and Objectives:* To evaluate the expression of Ki-67 in OED and OSCC and to correlate the Ki-67 expression with various grades of OED and OSCC. *Material and Methods:* A prospective observational study was done on clinically suspected oral epithelial dysplasia and malignancy cases received in the histopathology section. For each case, two sections of 4 µm were prepared. One was stained by hematoxylin and eosin stain, and another section was used for immunohistochemical staining of Ki-67. *Results:* Out of 64 cases evaluated for Ki-67 expression, 19 cases were OED, and 45 were OSCC. In OED, 15 cases were mild, and three were severe. In severe OED, Ki-67 expression was seen in all three lining epithelium layers: basal, parabasal, and spinous. In mild OED, Ki-67 expression was noted only in the basal layer. Out of 45 cases of OSCC, 31 cases were moderately differentiated, and one was poorly differentiated OSCC. Ki-67 expression was highest in poorly differentiated OSCC and lowest in well-differentiated OSCC. *Conclusion:* Ki-67 expression was high in poorly differentiated carcinoma compared to well-differentiated squamous cell carcinoma, and in severe OED Ki-67 was noted in all layers of lining epithelium. These findings suggest that Ki-67 expression correlates with the grading of OED and OSCC. Thus, it can be considered a proliferating marker that predicts the malignant transformation in OED and the aggressiveness of tumor.

Keywords: Epithelial dysplasia, Ki-67, Squamous cell carcinoma

Introduction

Oral malignancy is one of the most common malignancies reported in India. Squamous Cell Carcinoma (SCC) is the commonest oral malignancy type accounting for 95% of all malignant tumors detected in the oral cavity [1-3].

Conventional diagnostic modalities such as imaging and routine histopathology examination are insufficient to predict the behavior of malignant tumors in the oral cavity. Treatment strategies for oral malignancy are based on lymph node involvement, tumor size, and distant metastases. However, in some cases, these criteria do not justify the prognosis. Hence, molecular marker studies are done to assess the aggressiveness of malignant tumors [2].

One of the commonest, Immunohistochemistry (IHC) markers for cell proliferation studies is Ki-67 [1, 4]. Ki-67 study was done on various malignancies such as carcinoma breast, carcinoma of the cervix and large intestine, and it was concluded in these studies that Ki-67 could be considered as one of the markers for predicting the behavior of

the tumor. Ki-67 protein can be considered a potential therapeutic target by applying strategies that inactivate Ki-67 protein and may reduce further tumour proliferation [1-2].

Very few studies have evaluated Ki-67 expression in Oral Epithelial Dysplasia (OED) and Oral SCC (OSCC) to predict the aggressiveness of the tumor. Proliferative index activity in OSCC may help to evaluate the cancer growth rate and aggressiveness of the tumor on which the outcome and the choice of treatment depend [1-2]. Hence, the present study evaluated the expression of Ki-67 in OED and OSCC and the association of Ki-67 expression in various grades of OED and OSCC.

Material and Methods

The study was done on specimens of clinically suspected cases of epithelial dysplasia and malignancy of the oral cavity received in the histopathology section of the Department of Pathology from 1st December 2020 to 31st July 2022. The study design was descriptive and cross-sectional study. The current study was approved by the Institutional Review Board and Institutional Ethics Committee (IEC No. 09/2021 Date- 22/01/2021). Informed consent was obtained from all the participants.

All the specimens which were clinically suspected as malignant lesions of the oral cavity received in the histopathology section were processed as per the standard format of tissue processing, and paraffin blocks were prepared. For each case, two sections of 4 μm were prepared. One section was stained by routine Haematoxylin and Eosin (H&E) stain, and another was used for IHC staining for Ki-67. Cases diagnosed with epithelial dysplasia and malignancy on histopathology were included in the study. Biopsy specimens in which tissue was inadequate for further processing for immunohistochemistry were excluded.

Immunohistochemistry (IHC) staining was done as mentioned below:

Sections were cut at 4 μm thickness & placed on pre-coated slides. Sections with pre-coated slides were incubated at 60° C for 1 hour in an incubator. Deparaffinization was done by keeping the slides in an incubator at 60° C for 30 minutes. Sections were kept in citrate buffer in the microwave for antigen retrieval. Three percent of hydrogen peroxide was added to the slide and kept for 10 min. The sections were washed in 0.05mM solution of Tris-buffered Saline (TBS) at a pH of 7.4. For primary antibodies, the antibodies used were diluted monoclonal antibodies, especially against Ki-67. Incubation of these sections was done at 37° C for 1 hour. Washing was done in 0.05 mM solution of TBS. Conjugation of the secondary antibody was done with peroxidase- labelled dextran polymers. The sections were incubated with this antibody at room temperature for 30 minutes. Rinsing was done with TBS. Sections were treated then with 0.5 mg/ml of 3, 3' diaminobenzidine solution that contained hydrogen peroxide of 0.001%. Counterstaining was done with Mayer's haematoxylin for 3 min. Sections were dehydrated in ethanol, cleared in xylene, and then the mounting of slides was done. The known case of breast carcinoma was taken as a positive control, and adipose tissue was taken as a negative control.

IHC slides were scanned under 400x magnification for the Ki-67 expression. In cases of OED, the expression of Ki-67 was studied according to the Ki-67 positivity seen in the epithelial layers. When Ki-67 expression was noted just above the

basement membrane, it was mentioned as Ki-67 positivity in the basal layer. When Ki-67 expression was noted within the two layers above the basement membrane, it was mentioned as Ki-67 positivity in the basal and parabasal layers. When Ki-67 expression was noted in one more upper layer above the parabasal layer, it was mentioned as Ki-67 positivity in the basal, parabasal, and spinous layers [5]. In cases of OSCC, the Ki-67 Labelling Index (LI) was done as per the study done by Chandrakanta *et al.* [6].

Regardless of the staining intensity, all the Ki-67 stained nuclei were counted as positive. All sections with invasive tumour areas and areas having a higher density of Ki-67 labelled tumour-positive cells were selected by screening the IHC sections at 100x magnification. The number of tumour cells showing Ki-67 positivity in nuclei were calculated and expressed as the percentage of Ki-67 positivity. Ki-67 LI was calculated as the number of Ki-67-positive cells multiplied by 100, divided by the total number of neoplastic epithelial cells observed [6]. The analysis of Ki-67 expression was done as per the study done by Gonzales-Moles *et al.* [7]. as follows:

- Score 1 (+) [1-25% of tumour cells stained by Ki-67],
- Score 2 (++) [26% to 50% of tumour cells stained by Ki-67],
- Score 3 (+++) [51-75% of tumour cells stained by Ki-67] and
- Score 4 (++++) [76% to 100% of tumour cells stained by Ki-67]

As per the study done by Takkem *et al.* [1], the anticipated mean ± SD of Ki-67 among OED was 36.83 ± 19.56. Based on this finding, the formula used for the calculation of sample size was,

$$n = \frac{z^2 SD^2}{d^2}$$

Where Z^2 = Statistic at α level of significance

d^2 = Absolute error

SD^2 = Common standard deviation

The required minimum sample size was 62, with a 95% level of confidence and precision 5. The total sample size in the present study was 64. Statistical analysis was done using a Statistical Package for the Social Sciences (Version 20). The statistically significant difference between OED and OSCC was found using the Chi-Square test/Kruskal Wallis test. Value of p less than 0.05 was considered statistically significant.

Results

In the present study, total of 64 cases of clinically suspected cases of epithelial dysplasia and squamous cell carcinoma of the oral cavity were studied for Ki-67 expression and its correlation with histopathological grading. Out of 64 cases, 60 cases were biopsies, and in 4 cases, resection specimens were received. Out of 64 cases, 45 cases were histopathologically diagnosed as OSCC, and 19 cases were diagnosed as OED. Their demographic profile, which includes gender, age and site of the lesion, was elicited and is presented in Table 1. The youngest age in the present study was 18 years old, which was a biopsy of an oral lesion. This case was diagnosed as mild OED on histopathology. In OSCC, the youngest age of the patient was 28 years, and the eldest case was 75 years, which was diagnosed as Moderately Differentiated (MD) OSCC. Male preponderance was noted in the present study, amounting to 76.5%. Buccal mucosa was the most common site of involvement, followed by the tongue.

Out of 19 cases of OED, a maximum number of cases were diagnosed as mild dysplasia, followed by severe dysplasia (Table 2). In these cases, mild dysplasia was secondary to inflammation. Only one case of moderate dysplasia was noted in the present study in the age group of 31 to 40.

Out of 45 cases of OSCC, the maximum number of cases were diagnosed as MDOSCC, amounting to 69%, followed by Well-differentiated OSCC (WDOSCC), amounting to 29% cases (Table 3).

Table 1: Demographic details of study cases (N=64)

Characteristics		OED (N=19)	Percentage (%)	OSCC (N=45)	Percentage (%)
Gender	Female	06	31.6	09	20.0
	Male	13	68.4	36	80.0
Age (years)	10-20	01	5.3	00	00
	21-30	02	10.5	02	4.4
	31-40	02	10.5	04	8.9
	41-50	07	36.8	11	24.4
	51-60	04	21.1	13	28.9
	61-70	01	5.3	09	20.0
	71-80	02	10.5	06	13.3
Site of the lesion	Buccal mucosa	05	26.3	21	46.7
	Tongue	09	47.4	14	31.1
	Lip	02	10.5	01	2.2
	Cheek	03	15.8	01	2.2
	GB sulcus	00	00	05	11.1
	Retromolartrigone	00	00	01	2.2
	Hard palate	00	00	01	2.2
	Posterior cricoid	00	00	01	2.2

Table 2: Correlation of histological grading of dysplasia and Ki-67expression in OED

Histological Grading	Ki-67 Expression (N=19)						Chi Square	*p*
	Basal layer		Basal and parabasal layer		Basal, parabasal, and spinous layer			
	N	%	N	%	N	%		
Mild dysplasia (N=15)	12	80	3	20	0	0	16.213	**0.003***
Moderate dysplasia (N=1)	0	0	1	100	0	0		
Severe dysplasia (N=3)	0	0	1	33.3	2	66.7		
Total	**12**	**63.1**	**5**	**26.4**	**2**	**10.5**		

Table 3: Correlation of histological grading of OSCC and Ki-67score in OSCC

Histological Grading	Ki-67 Expression (N=45)								Chi Square	*p*
	Score 1 (1-25%)		Score 2 (26-50%)		Score 3 (51-75%)		Score 4 (76-100%)			
	N	%	N	%	N	%	N	%		
WD OSCC (N=13)	0	0	6	46	6	46	1	8	68.382	**0.001***
MD OSCC (N=31)	3	9	4	13	20	6	4	13		
PD OSCC (N=1)	0	0	0	0	0	0	1	100		
Total	**3**	**6.7**	**10**	**22.2**	**26**	**58**	**6**	**13.1**		

In mild OED, Ki-67 positivity was noted in the basal layer in a maximum number of cases. All cases of moderate dysplasia and 1 case of severe dysplasia showed Ki-67 positivity in the basal and parabasal layer, and 2 cases of severe dysplasia showed Ki-67 positivity in the basal, parabasal, and spinous layer (Figures 1-6).

Statistical analysis of the correlation of histopathological grading and Ki-67 expression in cases of OED (Table 2) showed a p-value of 0.003, suggesting a statistically significant correlation between histopathological grading of dysplasia and Ki-67 expression.

The highest Ki-67 expression was noted in Poorly Differentiated (PD) OSCC, and the lowest Ki-67 expression was noted in WD OSCC (Figures 7-16). In WD OSCC, a score of 4 was noted in 8% of cases. In MD OSCC, score four was noted in 13% of cases. In PD OSCC, score four was noted in 100% of cases. Statistical analysis of the correlation of histopathological grading and Ki-67 expression in cases of OSCC showed a p-value of 0.001, suggesting a statistically significant correlation between histopathological grading and Ki-67 expression (Table 3).

When the analysis was done for the correlation between sex and Ki-67 expression in OED, Ki-67 expression in the basal layer was higher in females as compared to males. However, the difference was not statistically significant. In OSCC, the Ki-67 expression score was slightly higher in males than in females. However, the difference was not statistically significant. When the analysis was done for the correlation between age and Ki-67 expression in OED, the maximum number of cases showing Ki-67 positivity was found in the age group of 41-50 years. However, the difference was not statistically significant. When the analysis was done for a correlation between age and Ki-67 expression in OSCC, the maximum number of cases was found in the age group 51-60 years. However, the difference was not statistically significant.

In 45 cases of OSCC, a correlation between the Ki-67 positivity LI and various OSCC grades was done which is presented in Table 4. Statistical analysis of the Ki-67 positivity labeling index in various grades of OSCC showed a statistically significant correlation between Ki-67 positivity LI and various grades of OSCC with a p-value of 0.034.

Table 4: Ki-67 Labelling Index (LI) In Various Grades OF OSCC (N=45)

Squamous Cell Carcinoma	Mean ± SD Ki-67 LI	Kruskal Wallis Value	*p*
WD OSCC	54.00 ± 10.01	6.7	**0.034***
MD OSCC	59.00 ± 15.00		
PD OSCC	80.00 ± 00.00		

**- significant at p<0.05*

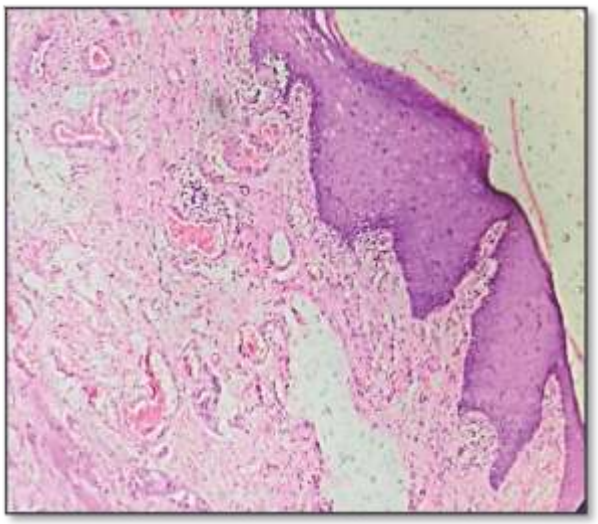

Figure 1: Photomicrograph showing mild dysplasia (H&E 40×)

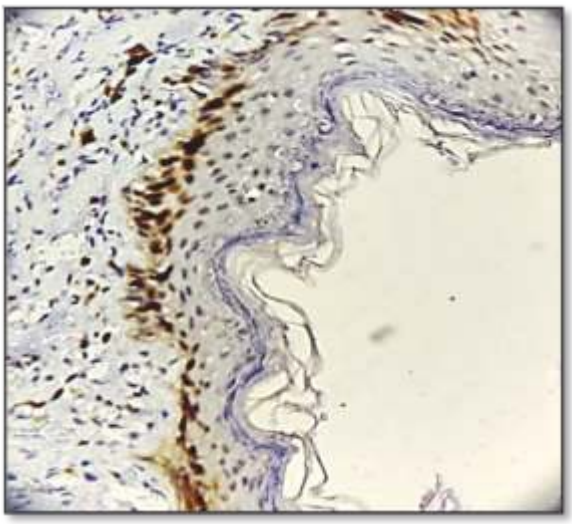

Figure 2: Photomicrograph showing Ki-67 expression in basal layer(IHC 40×)

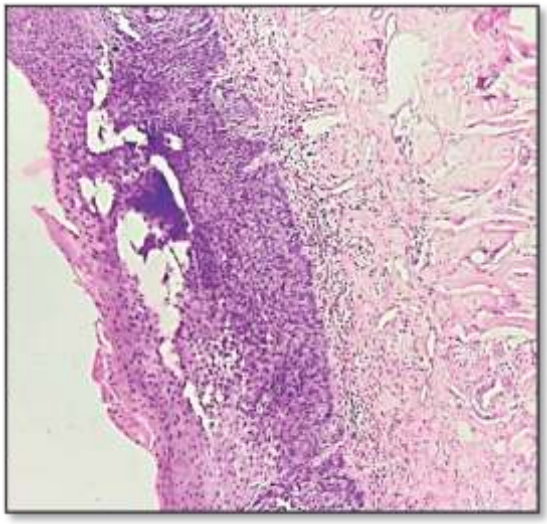

Figure 3: Photomicrograph showing moderate dysplasia (H&E 100×)

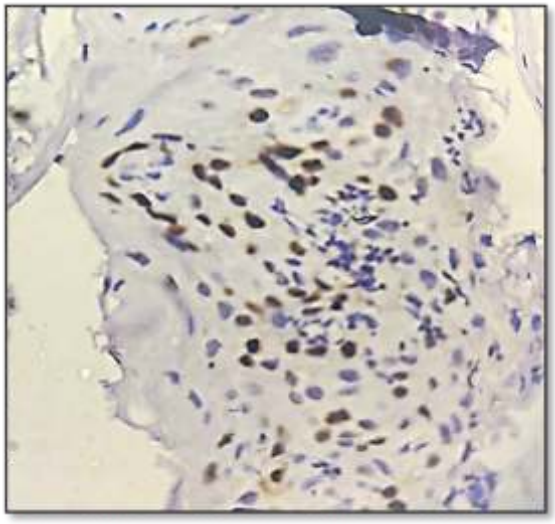

Figure 4: Photomicrograph showing Ki-67 expression in basal & parabasal layer (IHC 400×)

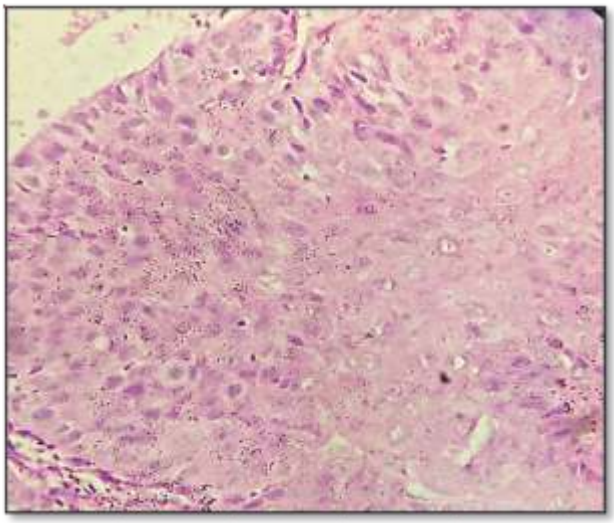

Figure 5: Photomicrograph showing severe dysplasia (H&E 400×)

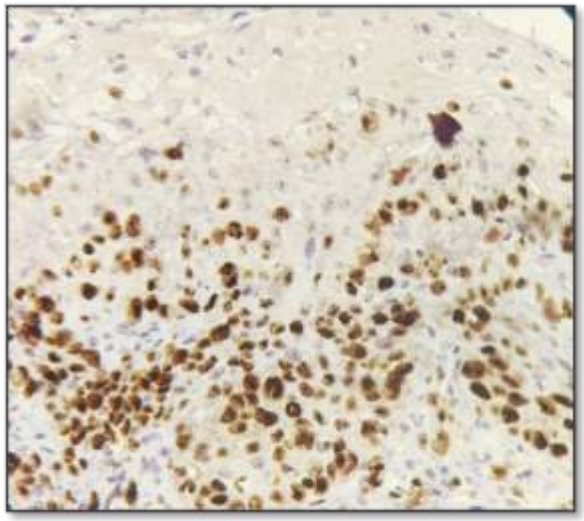

Figure 6: Photomicrograph showing Ki-67 expression in basal, parabasal and suprabasal layer (IHC 400×)

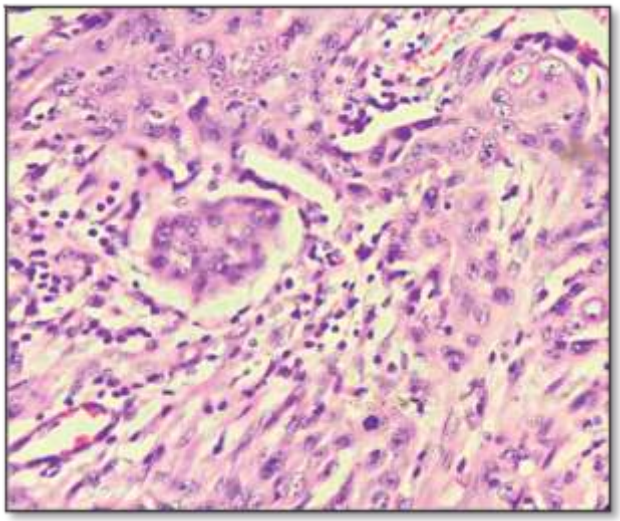

Figure 7: Photomicrograph showing tumor giant cells in WD OSCC (H&E 400×)

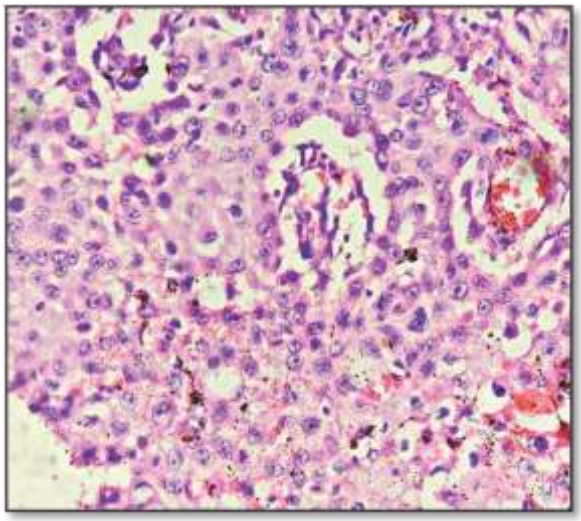

Figure 8: Photomicrograph showing WD OSCC (H&E 400×)

Figure 9: Photomicrograph showing Ki-67 expression in WD OSCC (IHC 100×)

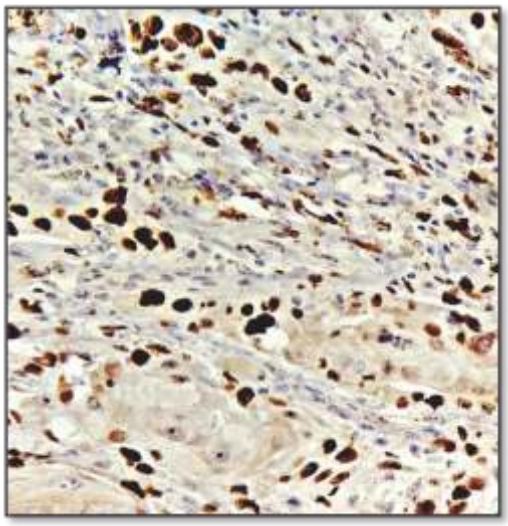

Figure 10: Photomicrograph showing 45% Ki-67 LI as 50% in WD OSCC (IHC 400×)

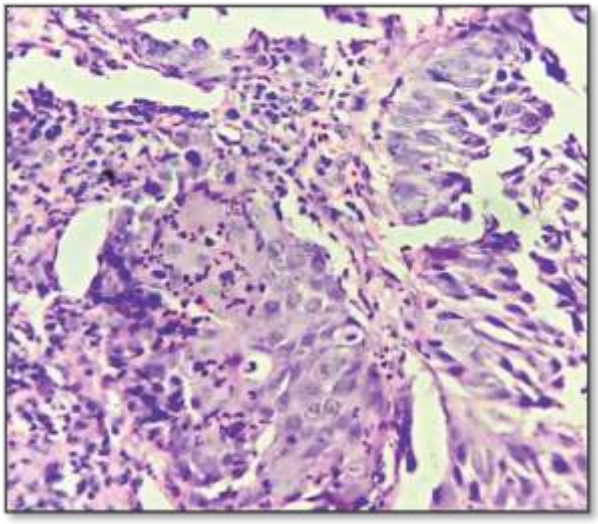

Figure 11: Photomicrograph showing MD OSCC (H&E 400×)

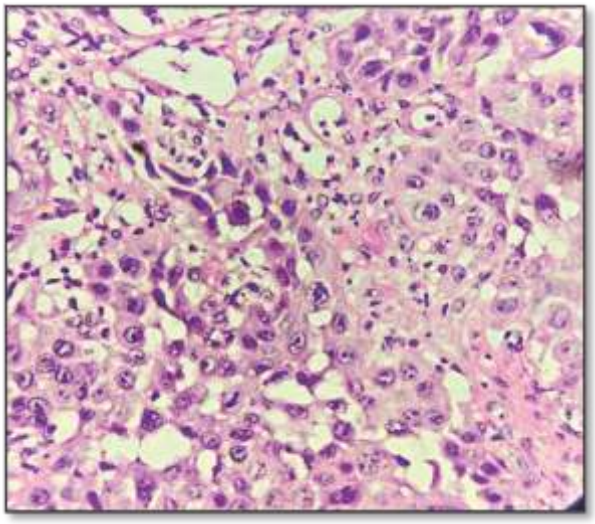

Figure 12: Photomicrograph showing MD OSCC with atypical mitotic figure (H&E 400×)

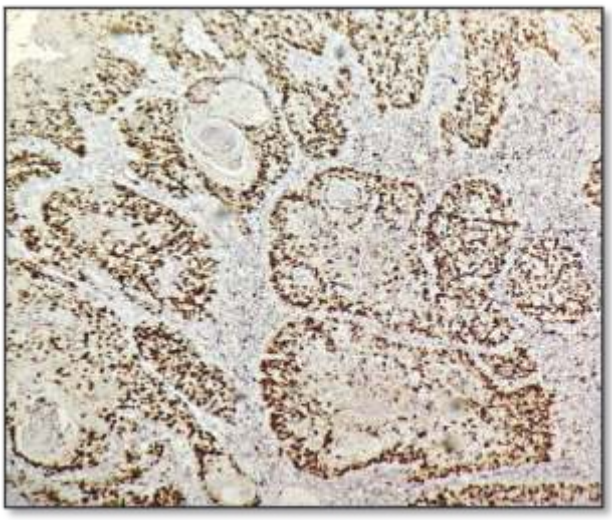

Figure 13: Photomicrograph showing Ki-67 expression in MD OSCC (IHC 100×)

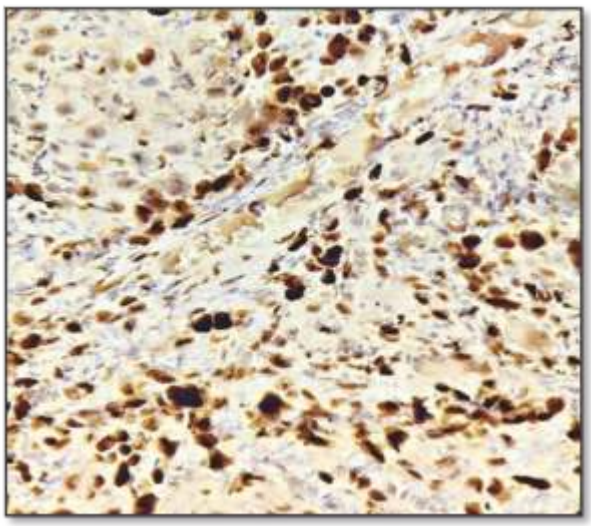

Figure 14: Photomicrograph showing 60% Ki-67 LI in MD OSCC (IHC 400×)

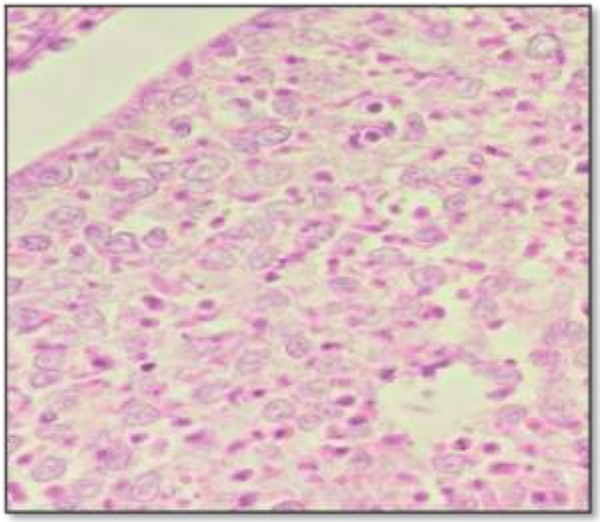

Figure 15: Photomicrograph showing PD OSCC (H&E 400×)

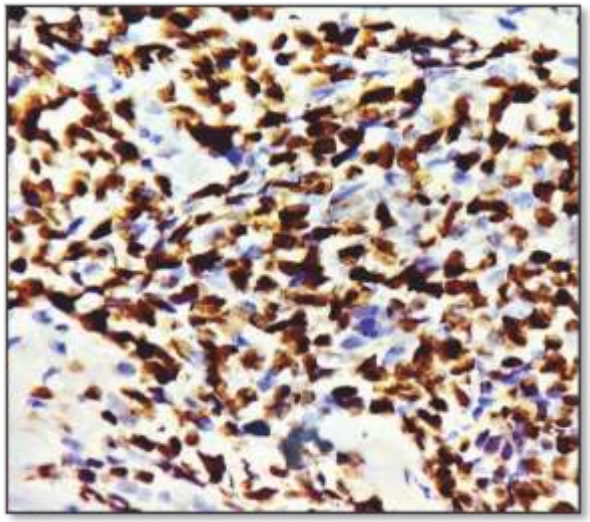

Figure 16: Photomicrograph showing 80% Ki-67 LI in PD OSCC (IHC 400×)

Discussion

Oral epithelial dysplasia on histology is characterized by cellular atypia, loss of cell differentiation and loss of orderly arrangement in stratified squamous lining epithelium [4]. Multiple genetic mutations leading to chromosomal damage and loss of cellular proliferation control may be responsible for normal tissues to progress to dysplasia and squamous cell carcinoma [8-9]. Ki-67 positivity is one of the most common immunohistochemical marker used to study cell proliferation [1]. In this study, Ki-67 expression was evaluated in 19 cases of OED and 45 cases of OSCC diagnosed on histopathology.

The most common age of presentation for OSCC in various studies was between 41 to 60 years of age [7, 10, 11]. Similar findings were noted in the present study. Oral Squamous Cell Carcinoma (OSCC) may affect any site in the oral cavity, but the tongue and the floor of the mouth were the commonest sites observed in various studies [6, 12-13]. Similar findings were observed in the present study.

Ki-67 is considered as one of the best predictors of survival and recurrence [14-15]. This study examined the expression of immunohistochemistry marker Ki-67by IHC staining in OED and OSCC. Diffuse basal Ki-67 positivity, with or without parabasal expression of Ki-67, was considered as a sign of uncontrolled proliferation and an important hallmark of malignancy in OED [16]. In a study done by Gonzales *et al.* [7], it was reported that increased proliferation of cells in the parabasal layers of pre-malignant oral epithelium is more likely to be linked with loss of heterozygosity in 9p, 3p, and 17p.40. This may increase the risk of developing multiple tumours. A collection of highly proliferating parabasal cells may create more subclones with a higher invasion capacity. Hence, an increase in the proliferation rate of cell clones transforming into malignancies appears necessary for a precancerous field to generate a tumour [7, 17].

In the present study, in all cases of moderate dysplasia, Ki-67 expression was seen in the basal and parabasal layers. In 66.7% of cases of severe dysplasia, Ki-67 expression was noted in the basal, parabasal, and spinous layers of the epithelium, suggesting increased proliferation of the cells in parabasal layers of the epithelium. The present study observed that Ki-67 expression was increased with the severity of dysplasia. It suggests a higher malignant transformation rate in severe dysplasia. Our study findings of Ki-67 expression correlate with other studies [5, 18]. However, the number of moderate and severe dysplasia cases in the present study is less; hence a more significant number of cases with multicentric study may help to conclude the findings.

In various studies of OSCC, it was observed that the percentage of Ki-67 expression in PD OSCC was highest, and that of WD OSCC was the lowest indicating that Ki-67 expression increases with decreasing tissue differentiation [6, 10]. Similar findings were noted in the present study.

In a study done by Chandrakanta *et al.* [6] and Gonzales *et al.* [7], the evaluation of Ki-67 expression was done as per the LI. Ki-67 LI was calculated as the percentage of the cells in a tissue stained for this marker [6,7]. Ki-67 LI was highest in PD OSCC compared to WD OSCC and MD OSCC [6-7]. Similar findings were noted in the present study (Table 5).

Table 5: Comparison of Ki-67 LI with other authors' studies

Grade of OSCC	Chandrakanta *et al.* [6]	Gonzales *et al.* [7]	Present study
WD OSCC	28.52 ± 21.25%	46.1 ± 26.1%,	54 ± 10.01%
MD OSCC	42.85 ± 18.2%	57.8 ± 28.6%	59 ± 15%
PD OSCC	68.57 ± 17.6%	69.6 ± 21.8	80 %

In the present study in 3 cases of OSCC, additional findings were seen after the Ki-67 IHC study. One case was diagnosed as suspicious for malignancy on the H&E section, whereas after the Ki-67 immunohistochemistry study, it was diagnosed as severe dysplasia with SCC showing minimal invasion. It showed high Ki-67 expression in the basal and the supra-basal layers of the epithelium and mild focus of invasion with Ki-67 positive tumour cells in the sub-epithelium. Two cases were diagnosed as MD OSCC on the histopathology slide, and after the Ki-67 IHC study, a focus of severe dysplasia with minimal invasion was noted. In the focus of severe dysplasia, Ki-67 positivity was noted in basal, parabasal, and spinous layers of the epithelium with a focus of minimal invasion in the sub-epithelial tissue suggesting that severe dysplastic lesion might have undergone malignant transformation.

Conclusion

Ki-67 can be used as a prognostic and predictive marker for determining the severity of OED and histological grading of OSCC. Ki-67 can be used as a predictor or proliferative marker to assess epithelial dysplasia and OSCC. Also, Ki-67 may be used as a prognostic tool in detecting malignant transformation in epithelial dysplasia. Hence, a multicentric study with a more significant sample size can further aid in diagnosing oral pre-malignant and malignant lesions at an early stage, which can further help in the early treatment and better patient survival.

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