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E-Cadherin is a diagnostic biomarker in the progression of oral epithelial dysplasia to squamous cell carcinoma

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ABSTRACT

Background: Oral squamous cell carcinoma is a common cancer of head and neck region with poor prognosis and may sometimes show a premalignant stage. Cell-cell adhesion molecules play an important role in the process of malignant transformation. E-cadherin, a cell-to-cell adhesion molecule, plays a crucial role in maintaining cell polarity and adhesion of epithelial cells.

Aims: To assess the expression of E-cadherin in various grades of oral epithelial dysplasia and oral squamous cells carcinoma and compare it to unremarkable oral mucosa.

Materials and methods: The study comprised a total sample size of 80 with 10 cases of unremarkable oral mucosa which is the control group, 40 cases of oral epithelial dysplasia and 30 cases of oral squamous cell carcinoma. One section was stained with haematoxylin and eosin to confirm the histopathological diagnosis and other section was stained immunohistochemically with E-cadherin.

Results: The study found that E-cadherin expression was strongly positive in unremarkable mucosal epithelium, reduced in oral epithelial dysplasia, and gradually decreased as it progressed to oral squamous cell carcinoma. These findings were found to be statistically significant.

Conclusion: The study found a correlation between E-cadherin expression loss and oral squamous cell carcinoma progression, suggesting that E-cadherin can serve as a diagnostic biomarker for malignant transformation of oral epithelial dysplasia and predict disease prognosis in oral squamous cell carcinoma.

1. Introduction

Oral squamous cell carcinoma (OSCC), the sixth most common cancer globally, accounts for 90 % of oral cancer cases and has high mortality and morbidity rates.[1,2] The World Health Organization (WHO) classifies OSCC into well-differentiated, moderately differentiated, and poorly differentiated types based on tumour differentiation.[3] Early or microinvasive SCC is characterized by an irregular infiltrative border and a relatively thin tumour confined to the papillary lamina propria as defined by the depth of the rete pegs.[4] This stage is described as a predominantly intraepithelial lesion with superficial stromal or lamina propria invasion.[5]

OSCC often progresses from a premalignant stage, which can persist for many years.[2] This stage, known as oral epithelial dysplasia (OED), involves a spectrum of architectural and cytological changes in the epithelium.[6] The WHO also grades dysplasia as mild, moderate, or severe based on these changes.[7] Carcinoma in situ (Ca-in-situ) is a histopathological diagnosis characterized by dysplastic epithelium involving the entire epithelial thickness and was included in the WHO classification in 2005.[7]

Malignant transformation in OSCC involves the loss of epithelial phenotype and reduced differentiation, facilitated by the epithelial to mesenchymal transition (EMT), which remodels the epithelial cell cytoskeleton.[8] EMT is characterized by reduced intercellular adhesion, loss of epithelial cell polarity, and increased motility, and is observed in both OED and its progression to OSCC.[8] Cell-cell adhesion molecules such as E cadherins play a crucial role in this process, and partial or total loss of its expression have been observed in a lot of human carcinomas.

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E-cadherin, a 120 kDa transmembrane glycoprotein, is a key cell-to-cell adhesion molecule that mediates epithelial cell adhesion and maintains cell polarity.[2,8–10] It also has a role in signalling processes and transcriptional regulatory events in the maintenance of basement membrane complex. E-cadherin loss is linked to the progression of OED, predicting metastases, recurrence, and disease prognosis in OSCC.[8] While some studies suggest that E-cadherin is a good prognostic indicator in oral cancer progression, others are contradictory.[2,8–12] Thus, E-cadherin expression maybe used as a biomarker along with other clinical and histopathological parameters to guide the treatment plan and may serve as a focus of targeted therapy in the future.

This study aims to assess the role of E-cadherin as a biomarker in the progression of OED to OSCC. Specifically, we evaluate E-cadherin expression and intensity of staining in unremarkable oral mucosa (UOM), various grades of OED, and different stages of OSCC.

2. Materials and methods

This was a secondary data analysis involving histopathologically diagnosed cases of various grades of oral dysplasia and squamous cell carcinoma from the from the archives of the Department of Oral & Maxillofacial Pathology and Microbiology, Amrita School of Dentistry, Kochi. Ethical clearance was obtained from the Institutional Review Board (IRB-XXXX-2020-155 dated 20-03-2020). Sample size was calculated based on the proportion of 2+ expression of E-cadherin in mild form of oral epithelial dysplasia and well differentiated squamous cell carcinoma obtained from similar study of Yuwanati MB et al.[2.] With an estimated risk difference of 0.75, power 80 % and α-error 5 %, the minimum sample size was estimated to be 6 per group. Our study includes 10 samples per group.

Thus, a total of 80 cases which included 40 cases of histopathologically diagnosed OEDs (10 cases each of mild dysplasia, moderate dysplasia, severe dysplasia and ca in situ), 30 cases of histopathologically diagnosed OSCC (10 cases each of early invasive, well differentiated and moderately differentiated SCC) and 10 cases of UOM which was the control group were included in the study. The inclusion criteria were the histopathology confirmed cases of OEDs, and OSCC. Recurrent cases of oral cancer, repeat biopsies of oral epithelial dysplasia and oral squamous cell carcinoma in the same patients and patients who already underwent treatment for oral carcinomas were excluded from the study. The haematoxylin & eosin (H&E) slides were screened to confirm the previous histopathological diagnosis and then immunohistochemical staining with E-cadherin was done to evaluate the expression & intensity of E-cadherin in UOM, OED and OSCC.

Four micrometre thick sections were then obtained on 3 aminopropyl triethoxysilane (APTES) coated slides from each of the selected cases for immunohistochemical staining. The slides were deparaffinized by passing them through three changes of xylene for 5 min each. They were passed in descending grades of ethanol and finally rehydrated in water. The slides were then transferred to citrate buffer and autoclaved for antigen retrieval at 15 lbs pressure for 15 min. After allowing to cool, they were washed in phosphate buffer solution for 5 min. The slides were then treated with protein block reagent (3 % hydrogen peroxide) for 10 min. Immunohistochemical staining was then performed using primary antibody – rabbit monoclonal E-cadherin (PathnSitu Biotechnologies) as per the manufacturer's instructions. The slides were then mounted in DPX and observed under light microscope. The membranous expression of E-cadherin in epithelial cells were seen as brownish granules.

After immunostaining, E-cadherin expression and intensity was evaluated by counting hundred cells in three random high-power fields of the epithelium, from stratum basale to stratum superficiale in OED cases and from invasive islands in OSCC cases. To minimize potential errors in recounting the same cells, areas were selected at random which were not adjacent to each other.

The staining intensity of E-cadherin was scored as absent, light moderate & intense while the membranous expression was scored as 0,1+, 2+ & 3+ as per the study of Gupta et al.[10] All samples were evaluated separately by 2 independent observers under light microscopy in high power field (400X) by blinding the sample characteristics and kappa value was calculated.

The obtained data was tabulated and analysed using SPSS software version 20 for windows. The number of stained cells in each group was expressed as frequencies and percentage. Chi -square test was applied to compare the results with respect to grades of percentages (1+, 2+ & 3+) among the various groups (UOM, OED and OSCC). The p value of less than 0.05 was taken as statistically significant.

3. Results

It was observed that the expression of E-cadherin was strongly positive in UOM(n = 10) while a reduced expression was noticed in OEDs (n = 40) and OSCCs (n = 30). Each slide was examined by two observers (DK and VS) to avoid subjectivity. The inter-rater agreement (kappa) scores were calculated and substantial agreement (60–80 %) was found for all groups.

Both the observers found a strong membranous homogenous staining of E-cadherin in the cells of the basal, parabasal, and spinous layers except in the layer above spinous layer of UOM (Fig. 1A & B).

3.1. Oral epithelial dysplasia

All the 10 cases of mild dysplasia in our study showed 3+ expression score of E-cadherin (Fig. 1C & D). Strong staining intensity was noticed in 8 cases and moderate intensity was noticed in 2 cases of mild dysplasia while among the 10 cases of moderate dysplasia, only 7 cases showed 3+ expression score, while 3 cases showed 2+ expression score of E-cadherin. Only 2 cases of moderate dysplasia showed strong staining intensity, while 7 cases showed moderate staining intensity and only 1 case with light staining intensity. A strong expression in parabasal and lower two-third of spinous layer in moderate epithelial dysplasia and a slight reduction in expression in basal layer and upper one third of spinous layer was seen (Fig. 1E & F). Among the 10 cases of severe dysplasia, only 4 cases showed 3+ expression score and 6 cases showed 2+ expression score of E-cadherin (Fig. 1G & H). 7 cases of severe dysplasia showed moderate staining intensity, 2 cases showed light staining intensity and only one case showed strong staining intensity. Of the 10 cases of ca-in-situ, 2 cases showed a 3+ expression score, 6 cases showed 2+ expression score and 2 cases showed 1+expression score of E-cadherin (Fig. 2A & B). 7 cases out of 10 cases of ca-in-situ showed moderate staining intensity, 2 cases showed light staining intensity and only 1 case showed strong staining intensity of E-cadherin. Its expression was higher in mild form of dysplasia and gradually showed a statistically significant reduction in expression when the severity of the grades increased (p value = 0.04).

The staining intensity and expression of E-cadherin is given in Table 1. The intensity of E-cadherin staining was significantly higher in mild dysplasia, which gradually decreased as the severity increased to ca in situ (Fig. 1D, F, 1H & 2B) (p value = 0.01).

Association of UOM and OEDs with regard to both expression pattern and intensity (Table 2) were statistically significant (p-value = 0.040 and p value < 0.001).

3.2. Oral squamous cell carcinoma

Among the 10 cases of early invasive SCC, 7 cases showed 2+ score, 2 cases showed 1+ score and 1 case showed 1+ score of E-cadherin expression. We also found that, 7 cases of early invasive SCC showed light staining intensity and 3 cases with moderate staining intensity (Fig. 2C & D). In case of well differentiated SCC, 7 out of 10 cases showed 2+ score, 2 cases showed 3+ score and only 1 case showed 1+ score of E-cadherin expression. 8 cases of well differentiated SCC in our

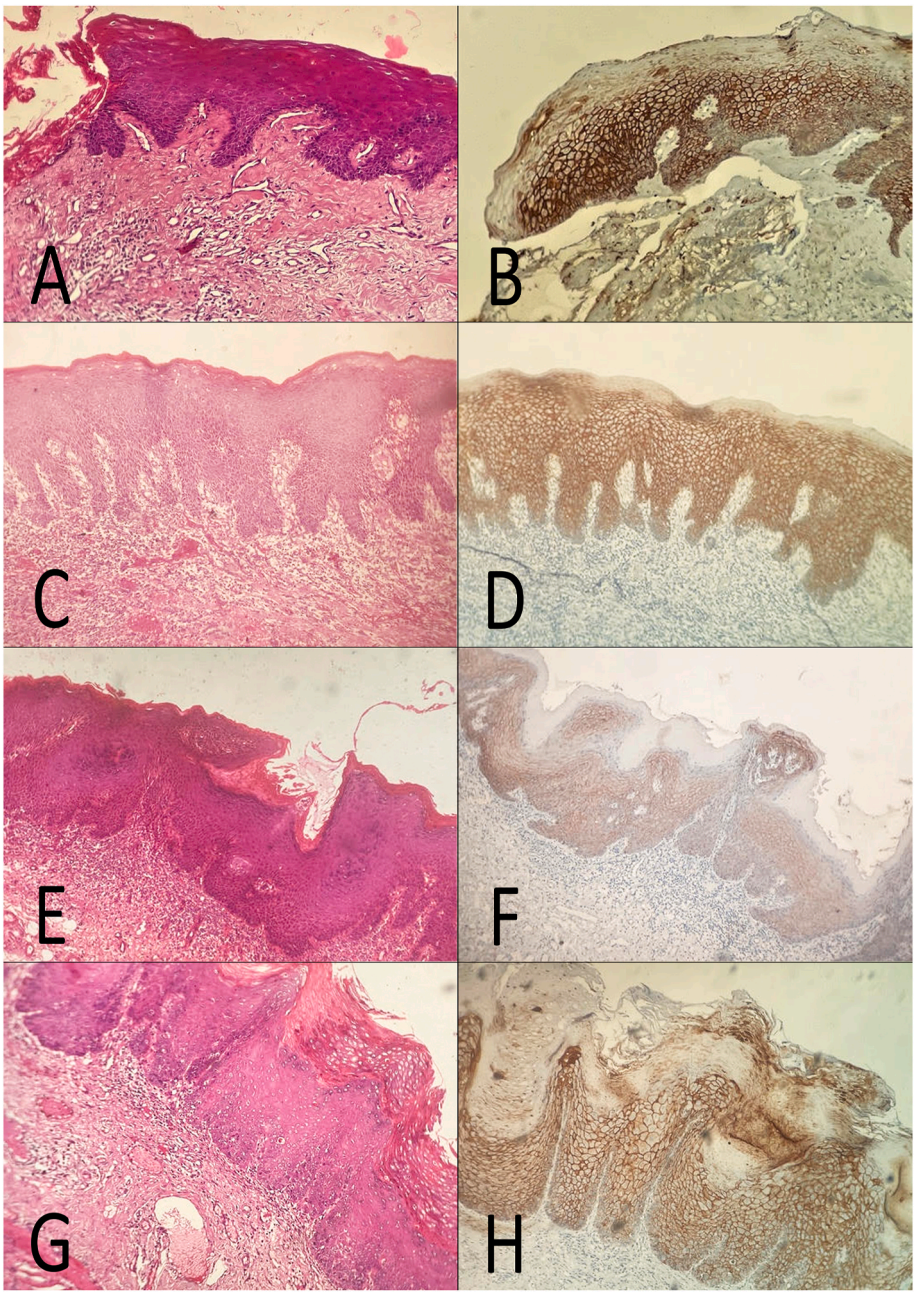

Fig. 1. Comparison of expression and intensity of E-cadherin in unremarkable oral mucosa and various grades of epithelial dysplasia **A & B**. Unremarkable oral mucosa, H&E & E-cadherin (10x); **C & D**. Mild epithelial dysplasia, H&E & E-cadherin (10x); **E & F** Moderate epithelial dysplasia, H&E & E-cadherin(10x); **G & H** Severe epithelial dysplasia, H&E & E-cadherin (10x). (H&E – Haematoxylin & Eosin).

study showed moderate staining intensity, 1 case showed strong staining intensity and one case showed light staining intensity (Fig. 2E & F). Among the 10 cases of moderately differentiated SCC, 4 cases showed 1+ score of E-cadherin expression, 3 cases showed 2+ score of E-cadherin expression and 3 cases showed null expression of E-cadherin. 7 cases of moderately differentiated SCC showed light staining intensity, 2 cases showed moderate staining intensity and only one case showed null staining intensity (Fig. 2G & H). The number of cells that expressed E-cadherin was more in early invasive SCC and gradually showed a reduction in expression when the severity increased. The intensity of E-cadherin staining was higher in early invasive SCC and well differentiated SCC and it gradually decreased as it progressed to moderately differentiated SCC (Fig. 2D, F & 2H). This difference was also statistically significant (p value = 0.035) (Table 3).

Association of UOM and OSCCs with regard to both expression pattern and intensity (Table 4) were also statistically significant (p value < 0.001 and < 0.001 respectively).

4. Discussion

Oral squamous cell carcinoma (OSCC) is associated with a high mortality rate.[2,13] Despite advances in therapeutic interventions, the incidence and mortality of OSCC continue to rise.[14] OSCC often develops from a premalignant stage known as oral epithelial dysplasia (OED).[6] Carcinogenesis involves genetic changes that disrupt normal cellular regulatory networks. Various molecular methods have been explored for early diagnosis and facilitate appropriate treatment. One such molecule is E-cadherin, which plays a significant role in cell-to-cell adhesion and its expression is often reduced during the progression from OED to OSCC.[2] It was suggested that, in addition to conventional dysplasia

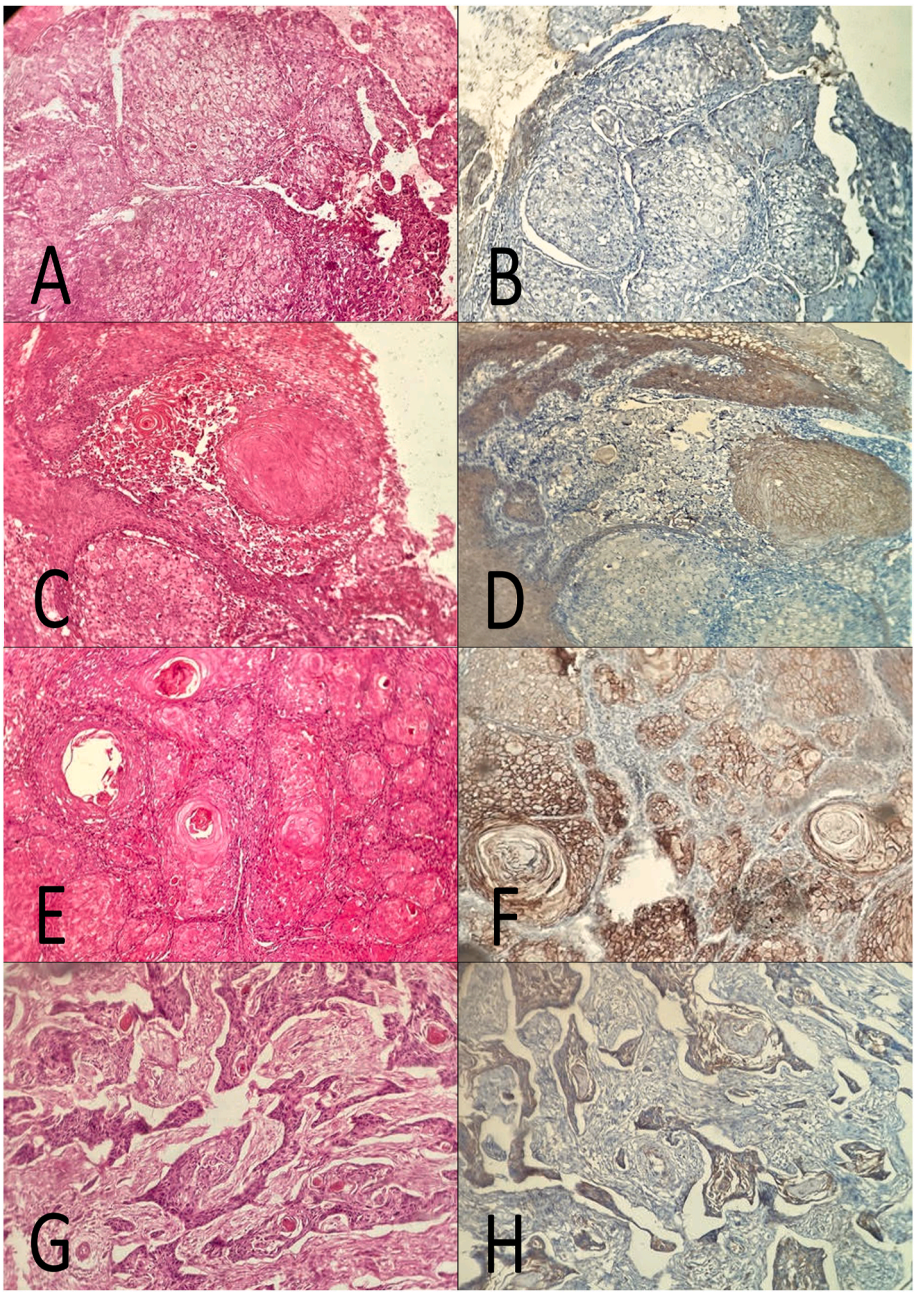

Fig. 2. Comparison of expression and intensity of E-cadherin in Ca-in-situ and various grades of oral squamous cell carcinoma. **A & B** Ca-in-situ, H&E & E-cadherin (10x); **C & D** Early invasive SCC, H&E & E-cadherin (10x); **E & F** Well differentiated SCC, H&E & E-cadherin (10x); **G & H** Moderately differentiated SCC H&E & E-cadherin (10x). (H&E – Haematoxylin & Eosin).

grading, features like loss of cohesion should be given additional weightage.[11] It was also noted that as dysplastic cells acquire invasive properties, there is a phenotypic change accompanied by the loss of E-cadherin expression, indicating that even a single transformed cell can become invasive. Loss of cell-to-cell adhesion, linked to E-cadherin dysfunction, is observed as normal epithelium progresses to dysplasia.

E-cadherin was strongly expressed in the epithelium of UOM, particularly in the basal, parabasal, and lower one-third of the spinous layer in our study. The uppermost part of the spinous layer and the layer above it showed lesser E-cadherin expression, likely due to the normal desquamation process. Similar findings have been reported in literature.[3,8,10,11,15–17] However, Sridevi et al. documented the absence of E-cadherin expression on the basal surface of the basal layers of UOM epithelium.[12] The strong staining intensity and expression of E-cadherin in UOM underscores the key role of E-cadherin in maintaining the integrity and structure of epithelial tissue.

The severity of dysplasia significantly influences the likelihood of malignant transformation, with studies showing that pre-cancerous lesions with oral epithelial dysplasia are more likely to develop into OSCC.[8,17,18] The study revealed a decrease in E-cadherin expression with the severity of dysplasia. Mild and moderate dysplasia showed higher expression and intensity of E-cadherin compared to severe dysplasia and carcinoma in situ. These findings are consistent with several other studies.[2,8,10,15–17,19] However, the study by Sridevi et al. did not find a significant association between the degree of dysplasia and E-cadherin downregulation.[12]

In our study, the expression pattern and staining intensity of mild epithelial dysplasia were similar to that of UOM, showing strong membranous expression in the basal, parabasal, and lower two-thirds of the spinous layer. This observation aligns with findings from other

Table 1
Comparison of expression and intensity of E-Cadherin between different types of dysplasia.

		Group				p value
		Mild (n,%)	Moderate (n,%)	Severe (n,%)	Ca in situ (n,%)	
Expression	Absent	0	0	0	0	0.040*
		0.0 %	0.0 %	0.0 %	0.0 %	
	1+	0	0	0	2	
		0.0 %	0.0 %	0.0 %	20.0 %	
	2+	0	0	6	6	
		0.0 %	0.0 %	60.0 %	60.0 %	
	3+	10	2	4	2	
		100.0 %	20.0 %	40.0 %	20.0 %	
Intensity	Absent	0	0	0	0	0.010*
		0.0 %	0.0 %	0.0 %	0.0 %	
	Light	0	1	2	2	
		0.0 %	10.0 %	20.0 %	20.0 %	
	Moderate	2	7	7	7	
		20.0 %	70.0 %	70.0 %	70.0 %	
	Intense	8	2	1	1	
		80.0 %	20.0 %	10.0 %	10.0 %	

Table 2
Comparison of expression and intensity of E-Cadherin between patients with UOM and dysplasia.

		Group		p value
		Unremarkable (n,%)	Dysplasia (n,%)	
Expression	1+	0	2	0.040*
		0.0 %	6.6 %	
	2+	0	5	
		0.0 %	16.7 %	
	3+	10	23	
		100.0 %	76.7 %	
Intensity	Light	0	5	<0.001*
		0.0 %	12.5 %	
	Moderate	0	23	
		0.0 %	57.5 %	
	Intense	10	12	
		100.0 %	30.0 %	

Table 3
Comparison of expression and intensity of E-Cadherin between different types of OSCC.

		Group			p value
		EISCC (n, %)	WDSCC (n, %)	MDSCC (n, %)	
Expression	Absent	0	0	3	0.065
		0.0 %	0.0 %	30.0 %	
	1+	2	1	4	
		20.0 %	10.0 %	40.0 %	
	2+	7	7	3	
		70.0 %	70.0 %	30.0 %	
	3+	1	2	0	
		10.0 %	20.0 %	0.0 %	
Intensity	Absent	0	0	1	0.035*
		0.0 %	0.0 %	10.0 %	
	Light	7	1	7	
		70.0 %	10.0 %	70.0 %	
	Moderate	3	8	2	
		30.0 %	80.0 %	20.0 %	
	Intense	0	1	0	
		0.0 %	10.0 %	0.0 %	

EISCC: Early invasive squamous cell carcinoma, WDSCC: Well differentiated squamous cell carcinoma, MDSCC: moderately differentiated squamous cell carcinoma.

studies.[2,10,11] In moderate dysplasia, there was a mild reduction in expression and intensity of E-cadherin on comparing to the mild dysplasia which was in agreement with other studies.[2,8,10,11] We found a strong expression in parabasal and lower two-third of spinous layer in

Table 4
Comparison of expression and intensity of E-Cadherin between patients with UOM and OSCC.

		Group		p value
		Unremarkable (n,%)	OSCC (n,%)	
Expression	0	0	3	<0.001*
		0.0 %	10.0 %	
	1+	0	7	
		0.0 %	23.3 %	
	2+	0	17	
		0.0 %	56.7 %	
	3+	10	3	
		100.0 %	10 %	
Intensity	Absent	0	1	<0.001*
		0.0 %	3.3 %	
	Light	0	15	
		0.0 %	50.0 %	
	Moderate	0	13	
		0.0 %	43.4 %	
	Intense	10	1	
		100.0 %	3.3 %	

moderate epithelial dysplasia and a slight reduction in expression in basal layer and upper one third of spinous layer. A similar finding was noticed in other studies also.[2,10] Our study showed a gradual reduction in E-cadherin expression in severe form of dysplasia which in agreement with other studies.[2,8,11] Further, when it progresses to ca-in-situ, a slight reduction in expression of E-cadherin was found when comparing with severe dysplasia. The study found no significant difference in E-cadherin staining intensity between severe dysplasia and ca in situ, but a statistically significant loss of expression and intensity of E-cadherin occurred during the progression of UOM to OED, which is consistent with other studies in literature.[2,8,10–12,15–17,19] The three tier classification of oral epithelial dysplasia is often unreliable and has often higher inter-observer variability, though it is often used to predict the progression of the disease process. EMT is an important mechanism which is essential in malignant transformation leading to development of invasive property and this process has been reported in not only carcinomas but also in epithelial dysplasia. The loss of cellular adhesion is one of the key features of EMT. Hence, E-cadherin expression in oral dysplasia can be considered as an indicator of EMT and can, thus be taken as a reliable predictor of malignant transformation.

Many studies have indicated that epithelial to mesenchymal transition (EMT) may predict the progression of OSCC.[8,20,21] The expression of mesenchymal genes during carcinogenesis is often associated with increased cell motility and the loss of epithelial phenotype, including decreased cell-to-cell adhesion and loss of cell polarity.[8] In our study, the

expression and intensity of E-cadherin were found to be reduced in cases of OSCC compared to OED. Additionally, E-cadherin expression and intensity decreased with the progression of OSCC. Higher expression and intensity were observed in early invasive SCC and well-differentiated SCC compared to moderately differentiated SCC. These findings are consistent with several other studies.[10,17,22–24] However, studies by Sridevi et al., Shinohara et al., and Freitas et al. did not find a significant association between tumour differentiation and E-cadherin expression.[12,25,26]

This reduction in expression and staining intensity indicates increased loss of cellular adhesion as the tumour progresses. Bagutti et al. documented that the least differentiated tumours showed reduced E-cadherin expression during later stages, with these tumour cells acquiring an invasive phenotype.[27] Yuwanati et al. also demonstrated reduced E-cadherin expression in OSCC, noting a decrease in expression with increased pleomorphism.[2] In our study, there was no reduction in expression and staining intensity of E-cadherin in early invasive SCC as it progresses to well differentiated SCC. The loss of expression and intensity of E-cadherin in OSCC when compared to UOM in our study was found to be statistically significant, and this is consistent with other studies.[10,17,22,24,25] Some studies have reported that E-cadherin expression in well-differentiated SCC is often as strong as in normal stratified squamous epithelium, whereas in poorly differentiated SCC, E-cadherin expression is almost lost or restricted to the cytoplasm, and in moderately differentiated SCC, its expression is heterogeneous.[17] Our study found a significant reduction in E-cadherin expression and staining intensity in moderately differentiated SCC compared to well-differentiated SCC, consistent with the findings of Gupta et al.[10] Thus, our results indicate that the loss of E-cadherin expression is associated with the histological grade of differentiation in OSCC.

The loss of E-cadherin from the surface of epithelial cells result in loss of cellular adhesion and is one of the important characteristics of EMT which helps the cells to acquire mesenchymal phenotype which is required for invasion and metastasis. Hence, the loss of E-cadherin signifies the loss of epithelial characteristics and acquisition of mesenchymal properties of the malignant cell in squamous cell carcinoma. This loss during carcinogenesis can be attributed to genetic or epigenetic mechanisms, with moderately and poorly differentiated SCC with nodal involvement showing reduced membranous and high cytoplasmic expression.[8] Gupta et al. stated that the loss of E-cadherin-mediated cell adhesion in tumour progression correlates with the loss of epithelial cell morphology and the acquisition of metastatic potential.[10] They also noted a loss of E-cadherin expression in the basal cell layers as the severity progresses.

Key strengths of this study included the assessment of both expression and intensity of E-cadherin, a key indicator of oral cancer invasiveness, in both in-situ and early invasive carcinoma samples, a rare area not extensively studied in literature. However, the inclusion of poorly differentiated squamous cell carcinoma cases and those with metastatic lymph nodes was limited due to insufficient sample availability. However, further studies with larger sample sizes are necessary to further substantiate these findings. This additional research could aid in early detection and improved treatment planning for OPMD and OSCC, ultimately reducing morbidity and mortality significantly.

5. Conclusion

In our study, we observed significant variations in E-cadherin expression and intensity with increasing grades of OED and tumour differentiation in OSCC compared to UOM. A greater reduction in E-cadherin expression was associated with increasing severity of SCC. This indicates a strong relationship between reduced expression of E-cadherin, decreased cellular differentiation and increased invasiveness. Therefore, E-cadherin can be considered a potential biomarker for predicting the severity of oral potentially malignant disorders and their progression to oral squamous cell carcinoma.

Patient consent

Not applicable as it is an invitro study.

Ethics statement

This research was approved by the Institutional Ethics Committee of XXXX (IRB-XXXX-2020-155 dated 20-03-2020). The authors do not have any financial or other competing interests to declare.

Data availability statement

All relevant data extracted from included studies are available in the paper. Any additional data will be available on reasonable request from the authors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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