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Original Research Article

Association of E-cadherin with epidermal growth factor receptor in squamous cell carcinoma of oral cavity

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ABSTRACT

Background: Oral cancer is the sixth most common cancer worldwide. Despite new modalities of treatment there has been no significant improvement in mortality and morbidity. E-cadherin responsible for cell-cell adhesion in epithelial tissues. It plays role in establishment and maintenance of polarity and structural integrity. Low expression helps in process of carcinogenesis. Epidermal growth factor receptor (EGFR) overexpression is found in majority of oral squamous cell carcinoma and association have been made between increased expression levels and an aggressive phenotype.
Aim of study: To study the association of E-cadherin with epidermal growth factor receptor in different grades of oral squamous cell carcinoma.
Materials and Methods : After taking informed consent from patients 75 cases of OSCC were included in the study and subjected to immunohistochemistry of E-cadherin and EGFR.
Results: It was concluded from the study that with decrease in differentiation of OSCC expression of E-cadherin decrease while expression of EGFR increases. On correlating both were found to be inversely proportional to each other.
Conclusions: During EMT there is loss of cell adhesion molecules. In our study with decrease differentiation there is loss of E-cadherin. E-Cadherin expression was inversely correlated to EGFR expression.

1. Introduction

Among malignant epithelial neoplasms of the oral cavity, oral squamous cell carcinoma is the most prevalent. Sixth most frequent cancer overall, oral cancer accounts for more than 90% of all malignancies of oral cavity with male to female ratio of 1.5:1.[1] 2-4% of all cancer cases worldwide are contributed by oral cancer.In spite of newer therapeutic modalities available for treatment of oral squamous cell carcinoma there has been no downfall in morbidity and mortality.[2] During cancer progression, cancer cells at the invasive front frequently convert epithelial cell phenotypes to mesenchymal cell-like phenotype called as epithelial mesenchymal transition (EMT). Metastatic, migratory and invasive properties of cancer cells are influenced by EMT. Cadherin switch is considered as hallmark of EMT is reduction of E-Cadherin and gain of N-Cadherin.[3] E-cadherin is a transmembrane glycoprotein encoded by the CDH1/E-cadherin gene located on chromosome 16q22.1, keep a check on cell cycle and is considered as tumor suppressor gene. Loss of its expression in oral squamous cell carcinoma is associated with metastasis, recurrence and poor prognosis.[4] Growth factors are essential for development, growth and homeostasis. Epidermal growth factor receptor (EGFR) overexpression is found in majority of oral squamous cell carcinoma and association have been

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made between increased expression levels and an aggressive phenotype, poor prognosis and resistance to anticancer therapy.[5]

2. Materials and Methods

This study was conducted on 75 biopsy samples. Firstly, all the samples were stained by hematoxylin and eosin and examined. They were classified into well, moderate and poorly differentiated oral squamous cell carcinoma. Subsequently, immunohistochemical analysis by using rabbit polyclonal antibodies was performed on the serial sections. Immuno-histochemistry for E-cadherin and EGFR was performed on paraffin embedded tissue sections using the kits, Thermo Scientific E-cadherin and Thermo scientific EGFR respectively. E-cadherin clone used was EP700Y with normal buccal mucosa as positive control while EP38Y was the clone used for EGFR with placenta as positive control. Immunoreactivity of E-cadherin was scored from 1-12 which was obtained by multiplying intensity score and proportion score. Intensity score was calculated as: 0- absence of staining, 1+ weak staining, 2 + moderate staining, 3+ strong staining. Proportion was calculated as: 1: <10% of cells were positive, 2: 10-50% of cells were positive, 3: 50-80% cells were positive, 4: >80% cells were positive. Final score obtained was graded as: 0 - negative immunoreactivity, 1-4- low immunoreactivity score and >4 - high immunoreactivity score. Immunoreactivity of EGFR was also scored as 1-12 with score 1- 0, no expression, score 2- 1-3, low expression, score 3- 4-7, intermediate expression, score 4- 8-12, high expression. This was also obtained by multiplying intensity score with proportion score. Intensity was graded as: 0 Non staining, 1 Weak staining, 2 Intermediate staining, 3 Intense staining. Proportion score was calculated as: 0 None of the cells stained, 1- <10% cells stained, 2- 10-50% cells stained, 3- 50-80% cells stained, 4- >80% cells stained. Study was undertaken after taking permission from institutional ethics committee.

3. Observations

Out of 75 cases 30 cases were of well differentiated, 30 cases were of moderately differentiated and 15 cases were of poorly differentiated oral squamous cell carcinoma. Immunostaining by E-cadherin and EGFR showed different immunoreactivity score in different grades of OSCC.

In the present study it was found that mean IHC score of E-cadherin was 10.37 ± 1.92 in cases of well differentiated OSCC, 3.03 ± 1.52 in cases of moderately differentiated OSCC and 2.13 ± 1.46 in cases of poorly differentiated OSCC. Thereby, implying that as the tumor progress towards poor differentiation, there was a decrease in mean IHC score from 10.37 to 2.13, which was found statistically significant (p<0.001).

Mean IHC score of EGFR in well differentiated OSCC was found to be 1.90 ± 1.16, in moderately differentiated it was 8.50 ± 2.21 while in poorly differentiated it was found to be 10.60 ± 1.80. Thus, it is inferred that with decrease in differentiation from well to poor mean IHC score of EGFR increases from 1.90 to 10.60, which was found statistically significant (p<0.001).

When correlation test was performed it was found that E-cadherin (IRS Score) was negatively correlated with EGFR (IRS Score). E-cadherin was found to be inversely proportional to EGFR with significant results (r = -0.829, p< 0.01).

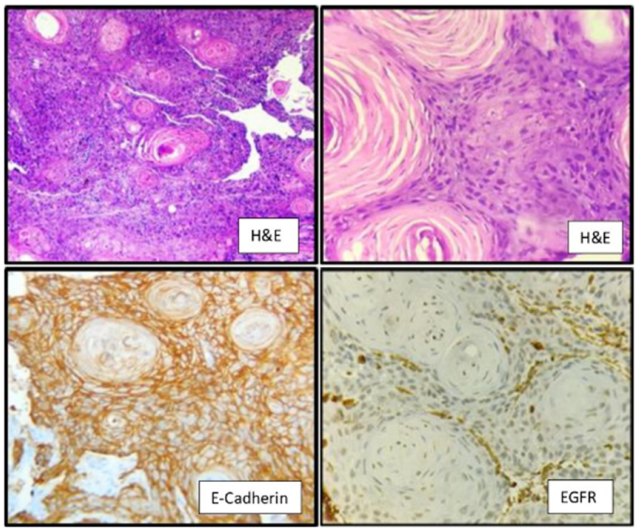

Fig. 1: Well differentiated squamous cell carcinoma showing bright expression of E-cadherin and decrease expression of EGFR

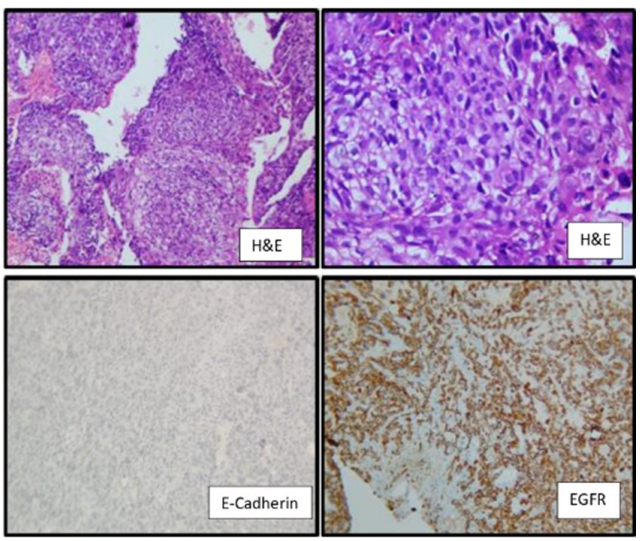

Fig. 2: Poorly Differentiated squamous cell carcinoma showing bright expression of EGFR and no expression of E-cadherin.

Table 1: E-cadherin expression in different grades of OSCC

E-Cadherin IRS	Grade of OSCC							
	Well		Moderately		Poorly		Total	
	Cases	(%)	Cases	(%)	Cases	(%)	Cases	(%)
Negative (0)	0	0.00	0	0.00	1	6.67	1	1.33
Low Expression (1-4)	0	0.00	27	90.00	13	86.67	40	53.33
High Expression (>4)	30	100.00	3	10.00	1	6.67	34	45.33
Total	30	100.00	30	100.00	15	100.00	75	100

Table 2: EGFR expression in different grades of OSCC

EGFR IRS	Grade of OSCC							
	Well		Moderately		Poorly		Total	
	Cases	(%)	Cases	(%)	Cases	(%)	Cases	(%)
No Expression (0)	1	3.33	0	0.00	0	0.00	1	1.33
Low Expression (1-3)	24	80.00	1	3.33	0	0.00	25	33.33
Intermediate Expression (4-7)	5	16.67	5	16.67	0	0.00	10	13.33
High Expression (8-12)	0	0.00	24	80.00	15	100.00	39	52.00
Total	30	100.00	30	100.00	15	100.00	75	100

4. Discussion

Oral squamous cell carcinoma accounts for major public health problem worldwide. 90-95% malignancies of oral cavity are squamous cell carcinomas and stands on 6^{th} position worldwide among all cancers. There are differences in clinicopathological and biological behaviour across different geographical regions mainly attributed to various known risk factors e.g., tobacco, alcohol, HPV infection etc. Global incidence and mortality are on rise and many new therapeutic and prognostic markers are under evaluation.[6]

Present study was conducted to evaluate the correlation of E-cadherin and EGFR and to correlate their expression with different grades of OSCC.

In our study E-cadherin was found to be inversely correlated with differentiation of OSCC.

In a study conducted by Kar and Sohini.,2021 35 cases of OSCC and 5 cases of normal buccal mucosa were subjected to E-cadherin staining. The staining patterns and localization of E-cadherin in normal mucosa were bright within the epithelium in a circumferentially membranous basolateral fashion. No cytoplasmic or nuclear staining was noted in all five cases, the basal and parabasal cells displayed the greatest intensity of staining, whereas the most external and differentiated layers were not stained. Furthermore, there was no stromal staining. The semi-quantitative evaluation of E-cadherin expression in cell membrane of normal mucosa was found to be 130.8, while in well differentiated squamous cell carcinoma (WDOSCC) it was 123.7, moderately differentiated squamous cell carcinoma (MDOSCC) it was 103.6 and in poorly differentiated squamous cell carcinoma (PDOSCC) 88.52. Thus, similar to our study they concluded E-cadherin expression is reduced with higher grades of OSCC and it can be used a prognostic marker of OSCC.[7] Zaid K.,2014 also evaluated the expression of E-cadherin and β-catenin in OSCC and concluded that expression of both decreases as the tumor differentiation decreases. Thus, both are related to tumor progression.[8] Similar results were also found in the studies of Rosado et al., Kushwaha et al. and Sharma et al.[9–11]

In our study it was found that as the tumor differentiation decreases expression of EGFR increases. Hanabata.,2011 in a similar study found that EGFR/SGLT1 expression was inversely correlated with tumor differentiation ($p = 0.004$) in oral squamous cell carcinoma and concluded that EGFR/SGLT1 coexpression may contribute to the growth and survival of OSCC.[12] Study conducted by Huang et al 2009., showed a positive correlation between EGFR and lymph node metastasis but they did not study the correlation with grade of differentiation.[13]

In our study correlation was performed between expression of E-cadherin and EGFR and both were found to be inversely correlated to each other ($r = -0.829$). In a similar study conducted by Zou et al.,2011 they concluded that EGFR activation promoted cell migration and invasion in HNSCC cell line SCC10A possibly by inducing an EMT-like cell phenotype change and MMP-9-mediated degradation of E-cadherin related to activation of ERK-1/2 and PI3K signalling pathways.[14]

5. Conclusions

1. During EMT there is loss of cell adhesion molecules. In our study with decrease differentiation there is loss of E-cadherin. E-Cadherin expression was inversely correlated to EGFR expression.
2. With regard to the histologic grades of oral squamous cell carcinoma, loss of E-cadherin expression and overexpression of EGFR are prognostic indicators,

indicating that the expression of these molecules changes as the tumour progresses to a reduced differentiation.

3. We can conclude from our study that immunoreactivity of E-cadherin and EGFR can be utilized to assess the prognosis, metastatic behavior, survival and management of patient.

6. Conflict of Interest

None.

7. Source of Funding

None.

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