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Correlation of E- Cadherin and Cyclin D1 expression with histomorphological features in Oral Squamous Cell Carcinoma: A cross- sectional study

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is the most common oral malignancy, representing up to 80–90% of all malignant neoplasms of the oral cavity. E-Cadherin as a tumour suppressor gene sets a threshold for Wnt/β-catenin signalling. When expression of E- Cadherin is lost, potentiation of Wnt signalling pathway occurs leading to loss of cell–cell adhesion. Cyclin D1 plays a major role in cell cycle transition from G1 to S phase by contributing to inactivation of the retinoblastoma gene product, and overexpression of CCND1 has been reported in 35–40% cases of OSCC.

The aim of study was to correlate the E- cadherin and Cyclin D1 expression with various histomorphological features in oral squamous cell carcinoma.

Objectives: To evaluate and correlate the expression of E-Cadherin and Cyclin D1 immunohistochemical markers expression with histomorphological features in Oral Squamous cell carcinoma.

Methodology: A retrospective study was carried out on 40 diagnosed cases of Oral Squamous Cell Carcinoma comprising of 14 cases of well differentiated OSCC, 16 cases of moderately differentiated OSCC and 10 cases of poorly differentiated OSCC.

Results: There was downregulation of E-Cadherin and overexpression of Cyclin D1 in increasing grades of OSCC and the difference was statistically significant. E-Cadherin was localised to membranous and shifted to cytoplasm as the grade worsened. Cyclin D1 was localised to nuclei of cells and the expression was seen more at the peripheral portions of tumour islands depicting the proliferative activity of tumour front. Lymphovascular invasion was also statistically significant with E- Cadherin IHC expression.

Conclusion: The study revealed a good prognostic role of both E-Cadherin and Cyclin D1 in OSCC. The markers can be used for prognostic as well as therapeutic purposes.

Keywords: Cyclin-D1; E-Cadherin; Ihc; Oral Squamous Cell Carcinoma.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common oral malignancy, representing up to 80–90% of all malignant neoplasms of the oral cavity. It is defined as 'A malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and/or the presence of intercellular bridges'.[1] Globally, oral cancer ranks sixth among all types of cancer.[2] Oral squamous cell carcinoma results from the multistep accumulation of heterogeneous

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genetic changes.[3] Important risk factors for OSCC include the use of tobacco or betel quid chewing, alcohol consumption, human papillomavirus and poor nutrition.[4] The current clinical gold standard for predicting the cancer progression risk for oral potentially malignant disorder requires biopsy and microscopic evaluation of H and E stained tissue to determine the presence and grade of dysplasia. Despite ubiquitous use, dysplasia is an imperfect risk marker because at its core, carcinogenesis is driven by the accumulation of somatic mutations and epigenetic changes.[3] Therefore much effort has been devoted to the discovery of molecular biomarkers to assess the progression of the lesion. Many molecular markers are associated with the occurrence, progression and prognosis of carcinoma. Markers of increased proliferation in oral potentially malignant disorders and oral cancer have been identified and explored for more than a decade.[5]

Various histomorphological features of OSCC like size, grading, perineural invasion, lymphovascular invasion, worst pattern of invasion, depth of invasion, T stage and N stage were studied.

E-Cadherin is a 120 kDa calcium-dependent transmembrane glycoprotein encoded by the CDH1 gene located on chromosome 16q21, and it is expressed in most epithelial cells.[6] In normal cells, E-Cadherin exerts its tumour-suppressing role mainly by sequestering β-Catenin from its binding to LEF (Lymphoid enhancer factor)/TCF (T cell factor). E-Cadherin function can be altered at genetic and epigenetic levels.[7]

Cyclin D1, a 45 kDa protein encoded by cyclin D1 gene (CCND1) located on chromosome 11q13, is a part of the molecular system that regulates the cell cycle G1 to S transition. Overexpression of cyclin D1 leads to shortening of G1 phase and less dependency on growth

factors resulting in abnormal cell proliferation which in turn might favour the occurrence of additional genetic lesions.[8]

With this background, this study was undertaken to evaluate the histomorphological features and prognostic role of E-Cadherin and Cyclin D1 in OSCC.

2. Materials and methods

The study was cross-sectional carried out in Department of Pathology, Rohilkhand Medical College and Hospital, Bareilly (U.P) for the duaration of one year. All histopathological confirmed cases of OSCC were included in this study.

3. Methodology

This study was conducted at tertiary care center after taking approval from the Institutional Ethics Committee(IEC) and informed consent from the patient. The specimens were fixed in 10% buffered formalin and subjected to gross and microscopic examination of H & E slides, and a tissue microarray was prepared and subjected for evaluation. Further IHC was applied as per standard protocol. Observation were made regarding staining percentage and intensity.

3.1. Immunohistochemical Analysis:[9]

The slides were prepared and examined under light microscope x200 magnification, for positive or negative immunostaining. Two observers individually noted the intensity of staining percentage of staining of E-Cadherin and Cyclin D1 in each field and were scored as:

Intensity of staining Score 0 = No Staining Score 1 = Mild Staining

Score 2 = Moderate Staining Score 3 = Intense Staining

3.2. Percentage of staining

- Score 0 = No staining of cells in any microscopic field
- Score 1+ = Less han 10% of tissue-stained positive
- Score 2+ =10–50% of tissue-stained positive
- Score 3+ =50–80% of tissue-stained positive
- Score 4+ = More than 80% of tissue stained positive

3.3. Final IHC scoring

Immunoreactive score (IRS) was obtained by the product of percentage score (0–4) and intensity score (0–3). A final score was assessed as

Score 0–1 = Negative Score 2–3 = Mild Score 4–8 = Moderate

Score 9–12 = Strongly Positive

Data was analysed using the Fisher's Exact Test or Chi-Square Test depending on the sample size and expected frequencies and a *P* value of less than 0.05 was considered statistically significant.

4. Results

In this study of 40 cases, maximum number of cases had tumor size between 2 to 4cm (62.5%). The grading system in our study showed 40% MDKSCC,25% PDKSCC and 35% WDKSCC. PNI was present in 25% of cases and LVI was present in 5% cases. Regarding the tumor invasion pattern ,65% showed strands of tumor cells in a single cell filing pattern(WPOI 4), 20% had invasive islands of more than 15 cells(WPOI 3). and 15% had a widely dispersed pattern (WPOI 5). Depth of invasion revealed 25% with0-5mm, 30% with 5.1- 10mm and 45% with more than 10mmm DOI. The study of 40 participants showed that 32.5% had early stage tumors (T1: 5%, T2: 27.5%) and 67.5% had advanced stage tumors (T3: 15%, T4a: 52.5%). Regarding nodal involvement 47.5% of participants had no nodal metastasis (N0), while 52.5% had nodal metastasis. Notably, tumor grading and lymphovascular invasion(LVI) exhibited significant associations with E-Cadherin final IRS ($P < 0.001$ and $P = 0.04$ respectively). With Cyclin D1 final IRS, tumor grading showed significant association ($P < 0.001$). While other histomorphological features did not show any significant correlation with both E-Cadherin and Cyclin D1 IHC.

Table 1 and 2 showing Ecadherin and Cyclin D1 correlation with various histomorphological features in OSCC

Table 1 E-cadherin membrane expression final IRS correlation with histomorphological features among OSCC cases

		E-CADHERIN MEMBRANE EXPRESSION (IRS)				**p-value**
		Negative	**Mild**	**Moderate**	**Strong Positive**	
		n (%)	**n (%)**	**n (%)**	**n (%)**	
SIZE	<2 cm	0(0.0)	0(0.0)	1(50)	1(50)	0.22
	2-4 cm	3(12.5)	6(25.0)	9(36)	7(28)	
	>4 cm	0(0.0)	1(7.7)	6(46.2)	6(46.2)	
GRADING	MDKSCC	0(0)	0(0)	16(100)	0(0)	**<0.001**
	PDKSCC	3(30)	7(70)	0(0)	0(0)	
	WDKSCC	0(0)	0(0)	0(0)	14(100)	
PNI	ABSENT	2(6.7)	5(16.7)	13(43.3)	10(33.3)	0.89
	PRESENT	1(10)	2(20)	3(30)	4(40)	
LVI	ABSENT	2(5.3)	6(15.8)	16(42.1)	14(36.8)	**0.04**
	PRESENT	1(50)	1(50)	0(0)	0(0)	
WPOI	1	0(0)	0(0)	0(0)	0(0)	0.36
	2	0(0)	0(0)	0(0)	0(0)	
	3	0(0)	3(37.5)	2(25)	3(37.5)	
	4	3(11.5)	2(7.7)	12(46.2)	9(34.6)	
	5	0(0)	2(33.3)	2(33.3)	2(33.3)	
	0 - 5 mm	0(0)	3(30)	3(30)	4(40)	

DOI	5.1 - 10 mm	2(16.7)	3(25)	4(33.3)	3(25)	0.39
	>10 mm	1(5.6)	1(5.6)	9(50)	7(38.9)	
T STAGE	ADVANCED (T3, T4)	1(3.7)	4(14.8)	13(48.1)	9(33.3)	0.33
	EARLY (T1, T2)	2(15.4)	3(23.1)	3(23.1)	5(38.5)	
N STAGE	ABSENT	1(5.3)	4(21.1)	6(31.6)	8(42.1)	0.64
	PRESENT	2(9.5)	3(14.3)	10(47.6)	6(28.6)	

Used Fisher Exact Test **

Table 2 CYCLIN - D1 nuclear expression (final IRS) correlation with histomorphological features among OSCC cases

		CYCLIN D1 NUCLEAR EXPRESSION (IRS				**p-value**
		Negative	**Mild**	**Moderate**	**Strong Positive**	
		n (%)	**n (%)**	**n (%)**	**n (%)**	
SIZE	< 2 cm	0(0.0)	1(50)	1(50)	0(0.0)	0.23
	2-4 cm	2(8.0)	5(20.0)	9(36)	9(36)	
	>4 cm	0(0.0)	6(46.2)	6(46.2)	1(7.7)	
GRADING	MDKSCC	0(0)	0(0)	16(100)	0(0)	**<0.001**
	PDKSCC	0(0)	0(0)	0(0)	10(100)	
	WDKSCC	2(14.3)	12(85.7)	0(0)	0(0)	
PNI	ABSENT	2(6.7)	8(26.7)	13(43.3)	7(23.3)	0.66
	PRESENT	0(0)	4(40)	3(30)	3(30)	
LVI	ABSENT	2(5.3)	12(31.6)	16(42.1)	8(21.1)	0.09
	PRESENT	0(0)	0(0)	0(0)	2(100)	
WPOI	1	0(0)	0(0)	0(0)	0(0)	0.79
	2	0(0)	0(0)	0(0)	0(0)	
	3	1(12.5)	2(25)	2(25)	3(37.5)	
	4	1(3.8)	8(30.8)	12(46.2)	5(19.2)	
	5	0(0)	2(33.3)	2(33.3)	2(33.3)	
DOI	0 - 5 mm	1(10)	3(30)	3(30)	3(30)	0.55
	5.1 - 10 mm	0(0)	3(25)	4(33.3)	5(41.7)	
	>10 mm	1(5.6)	6(33.3)	9(50)	2(11.1)	
T STAGE	ADVANCED (T3, T4)	1(3.7)	8(29.6)	13(48.1)	5(18.5)	0.38
	EARLY (T1, T2)	1(7.7)	4(30.8)	3(23.1)	5(38.5)	
N STAGE	ABSENT	1(5.3)	7(36.8)	6(31.6)	5(26.3)	0.74
	PRESENT	1(4.8)	5(23.8)	10(47.6)	5(23.8)	

Used Fisher Exact Test *

5. Discussion

The development of oral squamous cell cancer is a multistep process involving the accumulation of multiple genetic alterations modulated by genetic pre-disposition and environmental influences such as tobacco and alcohol use, chronic inflammation and viral infections.[3] All of these factors can lead to a wide range of genetic and molecular alterations that can be detected using a range of molecular studies. The alterations mostly affect two large groups of genes: oncogenes and tumor suppressor genes, which can be either inactivated or overexpressed through mutations, loss of heterozygosity, deletions or epigenetic modifications such as methylation.[10] Many molecular markers are associated with the occurrence, progression, and prognosis of carcinoma.

In normal oral mucosa, there was strong membranous expression of E-cadherin. The staining intensity was moderate to intense and more than 80% of tissue was positively stained. There was loss of staining of E-Cadherin with an increase in the grade of carcinomas. WDSCC showed greater expression of E-Cadherin than MDSCC while PDSCC showed the least expression and the difference was highly significant (P = < 0.001). Figure: 1a,1b,2a,2b,3a,3b.

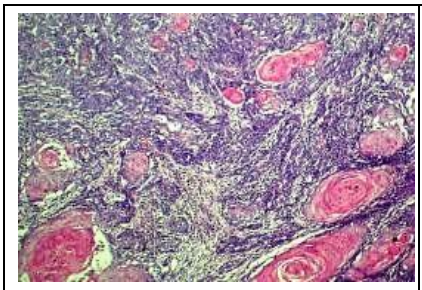	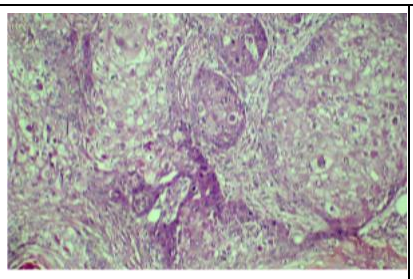	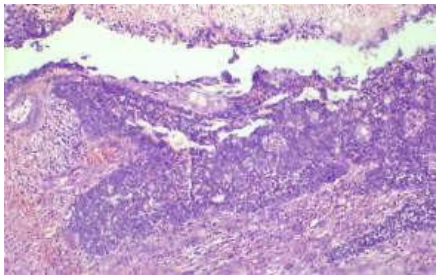
Figure 1a H&E(100X)	**Figure 2a** H&E(100X)	**Figure 3c** H&E(100X)
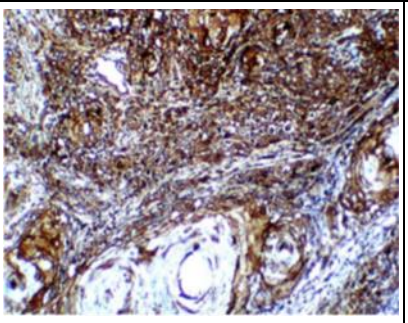	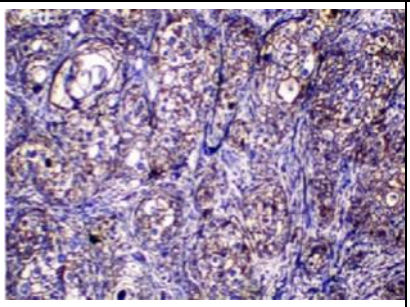	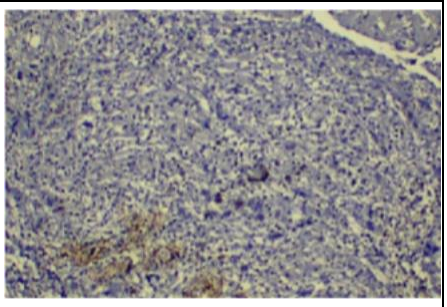
Figure 1b E-CADERIN IHC at (100X)	**Figure 2b** E-CADERIN IHC at (100X)	**Figure 3b** E-CADERIN IHC at (100X)
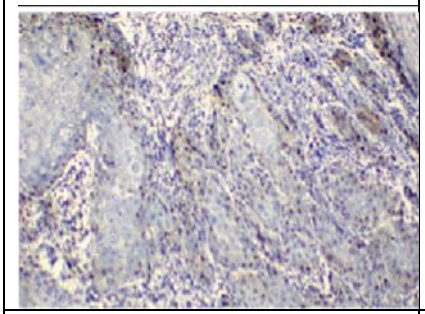	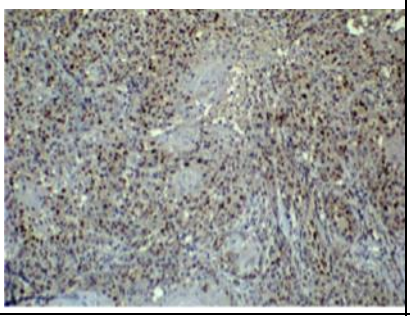	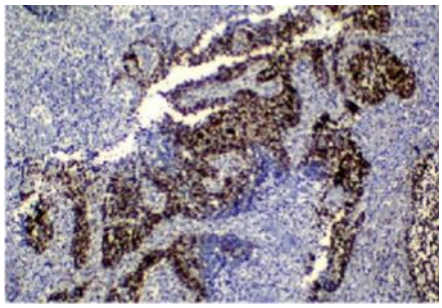
Figure1c Cyclin D1 IHC at(100X)	**Figure 2c** Cyclin D1 IHC at (100X)	**Figure 3c** Cyclin D1 IHC at (100X)
Figure 1 OSCC Well Differentiated	**Figure 2** Moderately Differentiated OSCC	**Figure 3** OSCC Poorly Differentiated

WDSCC showed weak staining of cyclin D1. In MDSCC, showed moderate staining. In our study, intense staining was observed in PDSCC. Figure: 1a,1c,2a,2c,3a,3c .The difference between the mean scores of intensity of staining of cyclin D1 between the study groups was found to be statistically significant. (p = < 0.001).

MDKSCC tumors showed 100% moderate IRS, PDKSCC tumors predominantly exhibited mild IRS (70%) and WDKSCC tumors demonstrated 100% strong positive IRS. These findings align with Al-Ravi et al.[11] who reported that higher E-Cadherin IRS scores are associated with well-differentiated tumors, while lower scores correlate with poorly differentiated and more aggressive tumors.

Notably, tumor grading exhibited a significant association with Cyclin D1 IRS (P < 0.001), with MDKSCC tumors predominantly showing moderate IRS (100%) and PDKSCC tumors exhibiting strong positive IRS (100%), while WDKSCC tumors largely showed mild IRS (85.7%) with a few negative cases which was concordant with Shergill K et al.[12] who similarly found that strong positive Cyclin D1 IRS is prevalent in aggressive tumors with nodal metastasis, highlighting its prognostic value.

Based on tumor differentiation, our study had 40% cases of moderately differentiated squamous cell carcinoma (MDKSCC), 35% well-differentiated (WDKSCC), and 25% poorly differentiated (PDKSCC). This distribution aligns with previous studies, which often report a higher prevalence of MDKSCC due to its intermediate aggressiveness and capacity for invasion. Al-Rawi et al.[11] observed a similar grading distribution in their OSCC cohort, emphasizing that MDKSCC is the most common grade encountered in clinical settings. Yogesh et al.[13] also reported a predominance of higher-grade tumors, linking poorer differentiation with increased invasiveness and metastatic potential. Monteiro et al.[14] higher-grade tumors, reinforcing its role in promoting cell cycle progression and tumor proliferation. The significant representation of WDKSCC in our study is consistent with Shergill K et al.[12] who noted that well-differentiated tumors, while less aggressive, still pose substantial clinical challenges due to their ability to mimic normal tissue structures, complicating diagnosis and treatment. These findings highlight the importance of comprehensive tumor grading and molecular profiling in prognostication and personalized treatment planning. Future research should explore the molecular mechanisms underlying tumor differentiation and assess the therapeutic potential of targeting these pathways to mitigate OSCC aggressiveness and improve patient outcomes.

6. Conclusion

Our study reports that alteration of E-Cadherin and cyclin D1 is frequent in OSCC. Expression of E-Cadherin and cyclin D1 was significantly altered in different grades of OSCC. This indicates and supports the previous studies that overexpression of cyclin D1 and downregulation of E-Cadherin may be an early event in oral cancer development.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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