Comparative expression of adhesion protein N-cadherin in oral lichen planus versus other precancerous and cancerous oral conditions

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Abstract: Oral Lichen planus (OLP) is a common chronic mucocutaneous disorder with an immune mediated pathogenesis. It is a complex and poorly understood clinical condition with periods of remissions and exacerbations. The risk of malignant transformation of OLP is still a controversial topic. The current study aimed to investigate the role of N-cadherin in OLP by comparing its expression with premalignant oral diseases, oral squamous cell carcinomas and normal oral epithelium. 17 cases of premalignant conditions (oral submucous fibrosis, proliferative verrucous leukoplakia and leukoplakia with dysplasia), 15 cases of erosive ulcerative OLP, 15 cases of OSCC (5 cases from each histologic grade) and 5 cases of normal oral mucosa all were analyzed immunohistochemically for N-cadherin expression. N-cadherin was positively expressed in 47 cases (90.4%) and negative in 5 cases (9.6%). All the studied OSCCs and premalignant lesions demonstrated positive expression. A high statistically significant difference in N-cadherin expression among the studied different OSCC histological grades ($P=0.000$), OLP and OSCCs ($p=0.008$), OSCCs and normal oral mucosa ($p=0.000$), premalignant lesions and normal oral mucosa ($p=0.002$). Furthermore, no statistically significant difference between OSCCs and premalignant lesions ($p=0.107$). Conclusion: N-cadherin can differentiate between behavior of OLP, premalignant lesions and OSCCs.

Keywords: Lichen planus, premalignant lesions, N-cadherin, oral squamous cell carcinoma.

1- Introduction

Oral lichen planus (OLP) is a common disease affecting oral cavity which has a characteristic bilateral symmetric distribution of fine white lines known as Wickham's striae. Wickham's striae are usual character of the disease even in atrophic or erosive histological subtypes. There are various lesions that resemble OLP clinically and histologically known as oral lichenoid lesions (OLLs) (Shirasuna,2014). The risk of malignant transformation of OLP is still a topic of ongoing debates. Some authors have suggested that only OLLs, but not OLP, are of premalignant nature. Others contradict that finding as many cases of OSCC developed in patients diagnosed with OLP without preceding dysplastic epithelium. Additionally, multifocal dysplasia and OSCC subsequently occurred in some patients had OLP, suggesting the possible field cancerization in OLP (Shirasuna,2014, Shearston,et.al.2019, Pariyawathe,et.al.2019).

Cadherins are a family of transmembrane glycoproteins that mediate cell to cell adhesion. Intercellular cadherin together with

their associated intracellular catenins assumes the key role in growth, cell polarity, stem and cell motility, cell differentiation, morphogenesis of tissues, organogenesis and carcinogenesis (Labelle, et.al.2008, Micalizzi DS, Farabaugh SM, and Ford HL,2010). E- cadherin (epithelial cadherin) is the key component of adhesion junctions in epithelial cells which serves as a suppressor of tumor growth and invasion. Perturbation of its function contributes to an invasive phenotype in many tumors (Wheelock,et.al.,2008, Hazan,et.al.,2020). N- cadherin (nerve-derived cadherin) is expressed in neural tissues and fibroblasts. N-cadherin mediates a less stable and a more dynamic form of cell to cell adhesion (Wheelock,et.al.,2008, Takeichi,2011, Hazan,et.al.,2020). Invasion is mediated by N- cadherin through stimulation of interaction among tumor cells with the surrounding microenvironment and synergism with the fibroblast growth factor receptor (FGFr) to induce tumor invasion(Nagi,et.al.,2005). Previous studies have demonstrated a functional relationship of E-cadherin to N-cadherin in a phenomenon called (EN-switch) that positively contributes to tumor cell migration, invasion, and metastasis (Hazan,et.al.,2020, Islam,et.al.1996).

Accordingly, the present study aimed to investigate N-cadherin expression in OLP and comparing that expression with other premalignant oral conditions, OSCCs and normal oral mucosa.

2. Materials and methods:

2.1. Samples and data retrieval

The present retrospective study was carried out on selected 52 cases that categorized as follow; 17 cases of premalignant conditions (oral submucous fibrosis, proliferative verrucous leukoplakia and leukoplakia with dysplasia), 15 cases of erosive ulcerative OLP without obvious signs of epithelial dysplasia, 15 cases of OSCC (5 cases from each histologic grade) and 5 cases of normal oral mucosa that gained from surgical removal of operculum. The OLP cases followed the clinical and histopathological diagnostic criteria (Eisenberg,2000, Van der Meij, and Van der Waal, 2003, Augusto,et.al.,2009). Cases with risk factors of oral cancer or history of medication use and OLP cases that showed signs of epithelial dysplasia were excluded from the beginning of the study. Ethical approval of the current study was obtained from the Ethical Committee for Research of Faculty of Dentistry, Mansoura University. The examined samples and clinicopathological data were retrieved from the archive of Oral Pathology Department, Faculty of Dentistry, Mansoura University.

2.1. Immuno-histochemical staining

Paraffin blocks were cut at 4 um thickness and placed on coated slides. The sections subjected to xylene deparaffinization then rehydration using alcohol in descending grades then water. Buffer solution of 0.01 M citric acid (pH 6.0) was used to retrieve antigen by heating for 10 minutes in the microwave. Five minutes incubation of the sections in (3% H₂O₂) followed by washing with distilled water. Rabbit monoclonal antihuman antibody (clone; EPR 5111, 1:50, dilution, Abcam, 1 Kendall Square, Suite B2304, Cambridge, MA 02139-1517, USA) was used against N-cadherin. N-Cadherin positivity was Assessed by staining sections of colon cancer (the positive control for the antibody, figure 1 A). Negative control slides obtained by replacement of the primary antibodies by plain phosphate buffer saline. Immuno-detection was executed using Power- stain TM1.0 poly HRP DAB kit for mouse+ rabbit (Cat No 52-0017, Genemed Biotechnologies, Inc., 458 Carlton Ct., South San Francisco, CA 94080, USA). Immune staining was performed following manufacturer's instructions. Immunoreaction was visualized by adding DAB. Counterstaining of slides was performed with the Mayer hematoxylin.

Figure 1: Photomicrographs show high N-cadherin immunohistochemical expression in (A) colonic carcinoma the positive control (X 250), (B) grade III OSCC (X 250), (C) oral moderate severity dysplastic epithelium (X250) and OLP (X250).

2.1. Immunostaining evaluation

Assessment of N-Cadherin tissue reaction was made semi quantitatively by counting the number of positive tumor cells under $\times 400$ power magnifications from five random fields and the results were expressed as percentage of immunoreactive cells from total number of tumor cells. The images were obtained by using a microscope attached to a camera with software. Evaluation of N-cadherin immunostaining was performed using the method described by Afrem et.al.2014 (Afrem,et.al. 2014). N- cadherin immunoreactivity graded from (0) to (+3) as follow; (0) denoted absent reaction, (+1) positivity in less than 10% tumor cells, (+2) reactivity in 10–75% of tumor cells and (+3) reactivity in more than 75% of tumor cells. N-cadherin expression intensity also evaluated using scores from (1) that denoted weak reaction, score (2) denoted moderate reaction and score (3) for strong reaction. By multiplying the intensity scores with N-cadherin grading scores, the final scores were given. N-cadherin final staining scores that were lesser or equal to 4 and more or equal to 6 were regarded as tumors with low and high expression respectively.

2.2. Statistical analysis

The available data was analyzed using SPSS program version 22 (Inc., Chicago, IL, USA). The association between the different clinicopathological parameters and N-cadherin expression were tested using Chi square (χ^2) test. One-way ANOVA and LSD post Hoc tests were used to compare N cadherin expression in the studied four groups. A *P*-value that was lesser or equal to 0.05 was considered statistically significant.

3. Results:

The study included 52 cases of 19 females (36.5%) and 33 males (63.5%). All the selected cases were from oral cavity. The clinicopathological data of the studied cases is illustrated in **table (1)**.

N-cadherin was positively expressed in 47 cases (90.4%) and negative in 5 cases (9.6%). All the studied OSCCs and premalignant lesions demonstrated positive N- cadherin expression. Two cases of OLP (3.8%) and 3 cases of normal oral mucosa (5.8%) demonstrated negative N- cadherin expression. High N-cadherin expression observed in 9 cases of OSCC (60%), 5 cases of premalignant lesions (29.4%) and 3 OLP cases (20%; **figure 1 B:D**). Low N-cadherin expression observed in 6 cases of OSCC (40%), 12 cases of premalignant lesions (70.6%), 10 cases of OLP (66.7%) and 2 cases of normal oral mucosa (40%, **table 2, figure 2 A:D**). One way ANOVA test revealed a high statistically significant difference in N-cadherin expression among the studied different histologic entities ($P=0.000$). L.S.D post Hoc test illustrated that the statistically significant differences in N-cadherin expression present between these groups; OLP and OSCCs ($p=0.008$), OSCCs and normal oral mucosa ($p=0.000$), premalignant lesions and normal oral mucosa ($p=0.002$), OLP and normal oral mucosa ($p=0.018$). No statistically significant difference in N- cadherin expression was present neither between OSCCs and premalignant lesions ($p=0.107$) nor between premalignant lesions and OLP ($P=0.228$, **table 3**).

Regarding, N-cadherin expression in different histologic grades of OSCC. None of the studied cases had negative expression. Low expression demonstrated in 4 cases of well differentiated OSCC, 2 cases of moderately differentiated OSCC and none of poorly differentiated OSCCs. High expression was observed in only one case of well differentiated OSCC, 3 cases of moderately differentiated OSCC and all cases of poorly differentiated OSCC (**chart 1, table 4, figure 3**). There were a statistically significant difference in N-cadherin expression among the different histologic grades of OSCC ($P=0.029$). LSD post Hoc test revealed a high statistically significant difference in N-cadherin expression between well and poorly differentiated OSCCs ($p=0.009$, **table 5**).

Figure 2: Photomicrographs show low N-cadherin immunohistochemical expression in (A) OSCC (X400), (B) oral submucous fibrosis (X 250), (C) OLP (X250), (D) normal oral mucosa (x 250).

Figure 3: Photomicrographs show high N-cadherin expression in (A) grade I OSCC, (B) grade II OSCC and (C) grade III OSCC (x250).

Table (1): comparisons between clinicopathological variables of the studied cases.

Clinicopathologic variables	frequency	percentage
Age group		
< 40 years	17	32.7
≥ 40 years	35	67.3
Gender		
Males	33	63.5
females	19	36.5
OSCC	15	28.8
Grade I Grade	5	9.6
II Grade III	5	9.6
	5	9.6
	5	9.6
Premalignant lesions	17	32.7
Oral submucous fibrosis Proliferative	5	9.6
verrucal leukoplakia Leukoplakia with	6	11.5
dysplasia	6	11.5
Oral lichen planus	15	28.8
Normal oral mucosa	5	9.6
N cadherin expression		
Negative expression Low	5	9.6
expression	30	57.7
High expression	17	32.7
Total	52	100

Table 2: Expression of N-cadherin in the studied histologic groups.

	histologic category				Total
	OSCC	premalig- nant lesions	OLP	normal oral epitheli- um	
Negative Count	0	0	2	3	5
% within histologi- c category	0.0%	0.0%	13.3%	60.0%	9.6%
Low Count	6	12	10	2	30
% within histologi- c Category	40.0%	70.6%	66.7%	40.0%	57.7%
high Count	9	5	3	0	17
% within histologi- c category	60.0%	29.4%	20.0%	0.0%	32.7%

Table 3: difference in N-cadherin expression among different histologic groups

Histologic Category	histologic category	Std. Error	Sig.
OSCC	pre malignant lesions	.18621	.107
	OLP	.19194	.008
	normal oral epithelium	.27144	.000
pre malignant lesions	OSCC	.18621	.107
	OLP	.18621	.228
	normal oral epithelium	.26742	.002
OLP	OSCC	.19194	.008
	pre malignant lesions	.18621	.228
	normal oral epithelium	.27144	.018

normal oral	OSCC	.27144	.000
epithelium	pre-malignant lesions	.26742	.002
	OLP	.27144	.018

LSD post Hoc test *. The mean difference is significant at the 0.05 level.

Chart 1: N-cadherin expression in the three histologic grades of OSCC.

Table 4: N-cadherin expression in the three histologic grades of OSCC.

OSCC histologic grade		N cadherin OSCC		Total
		low expression	high expression	
well differentiated	Count	4	1	5
	% within N cadherin OSCC	66.7%	11.1%	33.3%
moderate differentiated	Count	2	3	5
	% within N cadherin OSCC	33.3%	33.3%	33.3%
poorly differentiated	Count	0	5	5
	% within N cadherin OSCC	0.0%	55.6%	33.3%
Total	% within N cadherin OSCC % of Total	40.0%	60.0%	100.0%

Table 5: difference in N-cadherin expression among different histologic grades of OSCC.

OSCC histologic Grade	OSCC histologic grade	Mean Difference	Std. Error	Sig.
well differentiated	moderate differentiated	-.40000-	.25820	.147
	poorly differentiated	-.80000-*	.25820	.009
moderate differentiated	well differentiated	.40000	.25820	.147
	poorly differentiated	-.40000-	.25820	.147
poorly differentiated	well differentiated	.80000*	.25820	.009
	moderate differentiated	.40000	.25820	.147

LSD post Hoc test

*. The mean difference is significant at the 0.05 level.

4. Discussion:

The purpose of the present study was to assess the expression of N-cadherin in OLP, and to compare that expression with other oral premalignant conditions, OSCCs and normal oral mucosa. Many studies reported OSCC developed from preexisting OLP. Establishment of biomarkers that are able to detect the potential malignant behavior of OLP, as well as in other lesions that considered to be potentially malignant was an objective of many research works (Barnard,et.al.1993, Eisen,2002, Laeijendecker,et.al.2005, Gangeshetty, and Kumar,2015, Hamalainen,et.al.,2019).

In the current study, N-cadherin positive expression was observed in all OSCC and premalignant cases. Regarding cases diagnosed with OLP, N-cadherin showed high expression in 20% of these cases, while other 66.7% had low expression. Our findings concerning N-cadherin expression in OSCCs were coincident with a study by DOMENICO et al. (2011) who concluded that N-Cadherin correlated significantly with poor histological differentiation (Di Domenico, et.al.,2011). Furthermore, they have observed a statistically significant trend for stage and a correlation with worst patients` outcomes in terms survival reduction, liability to loco-regional invasion and metastasis (Di Domenico, et.al.,2011). Hashimoto, et.al. (2007) noted that reduced E-cadherin and aberrant N-cadherin expressions are intimately joined together in oral cancer. The switching from E to N cadherin plays an important role in cancer development and metastasis (Hashimoto,et.al.2007).

The findings of OLP were in agreement with many studies which concluded that reduced E-cadherin expression was associated with increasing the severity of epithelial dysplasia, OLP and invasive squamous cell carcinoma development

(Neppelberg ,et.al.2007, Ebrahimi,et.al.2008, zeidler et.al.2014,Sridevi,et.al.2015, Hamalainen,et.al.2019). These findings on E-cadherin reinforce our results on N-cadherin. Loss of E-cadherin means perturbation of cell to cell adhesion that is the first step to have tumour cells with enhanced migratory and invasive capability (Hazan,et.al.2004). Thus, the acquisition of N-cadherin phenotype is extremely important to have motile and migratory tumor cells that progress and metastasize away from the primary tumor site.

In our study, the higher histologic grades of OSCCs (poorly differentiated SCC) revealed higher N- cadherin expression when compared to the lower grades (well and moderately differentiated SCC). Premalignant lesions and OLP also revealed positive N-cadherin immunoreactivity when compared with normal oral mucosa.

Many studies have shown that OLP has the potential to develop OSCC (Barnard,et.al.1993, Eisen,2002, Laeijendecker,et.al.2005, Gangeshetty, and Kumar,2015, Hamalainen,et.al.,2019). However, till now there is no enough data to prove the correlation between OLP and the occurrence of cancer. The molecular mechanisms involved in oral carcinogenesis up till now aren't well understood, nor has the complete genetic profile of cancer cells been characterized. Since an abnormal, unregulated, cellular adhesion mechanism is a peculiar feature in neoplastic diseases, cellular interactions represent a crucial point in cancer development and progression. Loss of epithelial morphology and acquisition of mesenchymal characteristics termed as EMT are typical for carcinoma cells during tumor progression and correlate with local invasiveness and metastatic potential of the tumor. As in OSCC, EMT make changes in tumor cells to become less differentiated from its original cells, so accordingly the tumor was graded histopathologically into well, moderate and poorly differentiated squamous cell carcinoma. The loss of differentiation from the original cells means gaining the mesenchymal phenotype that better indicated by mesenchymal marker such as N-cadherin (Harishchandra and Junaid,2019).

Clarification of the different mechanisms by which OLP becomes cancerous and the associated genes has drawn a widespread attention (Hashimoto,et.al.2007). Knowledge of that mechanisms is of great importance for early prevention, diagnosis and treatment of OLP lesions have malignant potential (Yong and Haobo,2015). Researchers reported that early EMT related changes were triggered prior to the presence of any morphologic dysplastic changes (Gangeshetty, and Kumar,2015, Hamalainen,et.al.,2019).

The risk of malignant transformation of OLP to OSCC is 0.4 to 5% in a mean period of four years; thus, it can be stated that LP is a preneoplastic lesion (Shen et.al.,2012, Sargolzaei, and Mohamadian,2017). Expression of several markers in OLP can increase the risk of its malignant transformation to OSCC as ALDH1, BCL2, P53, BAX, COX2, MMP, CD133, E-cadherin and PCNA (Sousa,et.al.2009, Li and Cui,2013, Li and Cui,2013). Moreover, these factors are rarely expressed in healthy mucosal tissue, moderately in LP and highly in OSCC; thus, their expression is an indicator of higher potential for malignancy (Li and Cui,2013). Perturbed expression of the cell adhesion molecule N-cadherin is a hallmark of EMT that resulting in the acquisition of an aggressive tumor phenotype (Mrozik,et.al.2018).

Although the recent protocols in the treatment of OSCC it still the most prevalent oral cancer and unfortunately the 5 years survival it still in a low rate (Chaw,et.al.2012). Improving the prognosis of OSCC starts from early detection and treatment in the precancerous stage (Chaw,et.al.2012). N cadherin has a central role in oral carcinogenesis. It is capable to function as a potential therapeutic target and a prognostic tool in clinical management of OSCC (Di Domenico, et.al.,2011). Finally, disturbance in cell adhesion molecule N cadherin, cell to cell connections and epithelial permeability, contributing to oral lichen planus pathogenesis.

Summary and Conclusion:

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OLP is considered as a premalignant lesion; therefore, patients should be monitored in order to identify ominous signs of malignant transformation into very early stages. It is of paramount importance to understand the pathogenesis of OLP and establish what determines its progression to OSCC, as well as to monitor it adequately. N-cadherin was differentially expressed in OSCC, normal oral mucosa, premalignant lesions and OLP. N-cadherin can differentiate between behavior of OLP, premalignant lesions and OSCC, proved that OLP is potentially malignant disease.

Fund:

Nil

Conflict of interest:

No conflict of interest.

5. References:

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