RESEARCH ARTICLE

Association of podoplanin expression to histopathological grades of oral epithelial dysplasia and oral squamous cell carcinoma

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Abstract

Objective: To determine the expression of podoplanin, and to correlate it with histopathological grades in oral epithelial dysplasia and oral squamous cell carcinoma cases.

Methods: The retrospective, analytical, cross-sectional study was conducted at the City Laboratory, Peshawar, Pakistan, and comprised specimen block data of histologically diagnosed cases of oral benign lesions, dysplastic lesions and oral squamous cell carcinoma from January 2017 to August 2021. Two sections (4um) were cut from each specimen block for Haematoxylin and Eosin staining and immunohistochemistry. The slides were re-evaluated by two pathologists for confirmation of the diagnosis, and podoplanin marker was applied to cases selected using immunohistochemistry. Data was analysed using SPSS 22.

Results: Of the 80 cases identified, 68(85%) were analysed. There were 20(29.4%) benign cases; 11(55%) females and 9(45%) males with mean age 39.90±16.23 years, 20(29.4%) oral dysplastic cases; 14(70%) males and 6(30%) females with mean age 57.75±12.02 years, and 28(41.2%) oral squamous cell carcinoma cases; 17(61%) males and 11(39%) females with mean age 50.55±14.80 years. Podoplanin expression in oral epithelial dysplasia cases was significant (p=0.028), while it was not significant in the other 2 groups (p>0.05).

Conclusion: Podoplanin when used along with histopathological evaluation could aid as an adjuvant technique in the diagnosis and grading of oral epithelial dysplasia.

Keywords: Oral epithelial dysplasia, Oral squamous cell carcinoma, Podoplanin. (JPMA 74: 852; 2024)

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Introduction

In South Asia, oral squamous cell carcinoma (OSCC) is the most dominant form of cancer, accounting for nearly one-third of all cancers.[1] The development of OSCC usually occurs in a two-step process, with the initial presence of a precancerous lesion subsequently developing into cancer. These precancerous lesions are characterised by an altered epithelium and are classified by the World Health Organisation (WHO) histologically into mild, moderate and severe dysplasia as well as carcinoma in situ (CIS) based on the presence and severity of oral epithelial dysplasia (OED).[2] The malignant transformation potential (MTP) rates of the lesion with OED in several well-established studies range from 3% to 33% with a median follow-up of >7 years.[3]

Currently, histological assessment of OED in precancerous lesions is considered the gold standard for determining MTP risk.[4] However, studies indicate that there is no clear agreement on most of the clinical grading systems of OED. The accuracy of histopathological assessment of OED is largely subjective, with inter-observer and intra-observer variability.[5] Moreover, the quality of tissue and the site at which a biopsy is taken also impact its accuracy. Sometimes a mild dysplastic lesion may progress rapidly to OSCC, whereas a severe epithelial dysplasia may not develop into carcinoma.[6] In addition, there is also difficulty in differentiating between OED and some benign lesions exhibiting architectural and cytological abnormalities similar to OED, which can further complicate accurate diagnosis.[7]

Histopathologists also face challenges in accurately grading OSCC, which is important for determining prognosis and guiding treatment decisions. There is a correlation between histopathology and survival rates, with poorly differentiated tumours having a worse prognosis than well-differentiated ones.[8,9]

Therefore, studies have been conducted to identify objective markers that can aid in the diagnosis of OED and OSCC in addition to traditional histopathological assessment.[10] In most studies, protein detection is done using immunohistochemistry (IHC). Many studies have focussed on assessing the potential of IHC examination as a tool for diagnosing OED and OSCC. IHC does not require specialised equipment, does not require lengthy laboratory manipulation of tissue samples, permits evaluation of cell morphology during examination, and archival specimens can be used. Therefore, if proper markers are applied, IHC

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can be used in routine diagnosis of OED and OSCC.[11] One such promising marker that has recently gained interest is podoplanin (PDPN), a type 1 transmembrane sialomucin-like glycoprotein that is highly expressed in lymphatic endothelial cells, but not in blood endothelium.[12] PDPN expression has been reported in various carcinomas of the skin, lungs, uterus, oesophagus and oral cavity. PDPN has been found to be overexpressed in both OED and OSCC.[13] In OED, PDPN expression has been linked to the severity of the dysplastic changes, and it has been proposed as a potential biomarker for predicting the progression of OED to OSCC. In OSCC, PDPN expression has been associated with a more aggressive tumour phenotype.[14,15]

To the best of our knowledge, no study has assessed PDPN expression in OED and OSCC in Pakistan. Given that genetic makeup, habits, and socioeconomic conditions vary in different regions of the world, the present preliminary study aims to determine the pattern of podoplanin expression in OED and OSCC among the Pakistani population and to correlate PDPN expression to histopathological grades of OED and OSCC, thus serving as a basis for future prospective studies.

Materials and Methods

The retrospective, analytical, cross-sectional study was conducted at the City Laboratory, Peshawar, Pakistan, and comprised specimen block data of histologically diagnosed cases of oral benign lesions, dysplastic lesions and oral squamous cell carcinoma from January 2017 to August 2021. The specimen blocks of these lesions as well as data related to site, age, gender and histopathological diagnosis were retrieved from the institutional archives using convenience sampling technique. All the specimens were re-evaluated through haematoxylin and eosin (H&E) staining by two skilled oral pathologists. In case of difference of opinion, the cases were excluded. Also excluded were cases with deficient epithelial layers or having incomplete data.

Two sections were cut from each selected specimen block; one for H&E staining and the other for IHC. Tonsillar tissue was selected as a positive control to compare the staining intensity of PDPN expression.

Formalin-fixed paraffin-embedded tissue sections about 4um thick were cut and mounted on positively charged slides. The slides were deparaffinised by dipping in a series of xylene solutions, and then rehydrated with graded concentrations of alcohol. Antigen retrieval was achieved by immersing slides in antigen retrieval solution in coupling jar and heated in the microwave at 180°C for up to 30 minutes as part of the heat-induced epitope retrieval (HIER) method.[12] Endogenous peroxidase activity was blocked by immersing the slides in peroxidase blocking agent for 15 minutes at room temperature. the slides were incubated with monoclonal antibody against PDPN at 1:100 dilutions for 40-45 minutes. After each step of antigen retrieval, peroxidase blocking, and applying primary antibody, the slides were washed with distilled water and buffer solution. The sections were then incubated with horseradish peroxidase (HRP) for 40-45 minutes at room temperature. Optimal signal amplification was achieved by applying chromogenic substrate. The slides were checked under a microscope for staining and then washed with distilled water and buffer solution. Tonsillar tissue was used as a positive control to assess the staining intensity. Counterstaining with haematoxylin was the final step. The stained tissue sections were mounted with dibutyl phthalate in xylene (DPX) oil, and coverslip were placed.

Brown colour at the site of the target antigen was considered positive immunoreactivity. Cytoplasm and/or membrane immunoreactivity was considered to indicate positive PDPN expression. Immunostaining in oral benign and dysplastic lesions was scored as follows: 0=no expression observed in any part of the epithelium, 1=expression restricted to the basal layer of epithelium, 2=expression in a basal and suprabasal layer at one area, 3=suprabasal expression observed at 2 or 3 areas, and 4=expression observed at >3 areas. Lesions with scores equal or >2 were considered positive, and lesions with scores <2 were considered negative.[16]

In OSCC, immunostaining was scores as follows: 0=no expression observed in any part of tumour island, 1=expression in 0-25% of the tumour island, 2=expression in 25-50% of tumour island, 3=expression in 50-75% of tumour island, and 4=expression in 75-100% of tumour island. The staining intensity for OSCC was scored as 0=negative, 1=weak, 2=moderate, and 3=strong. The data was then converted to the immunoreactive score (IRS) by multiplying the quantity and staining intensity scores. The final scores were put on a scale ranging 0-12 as: 0-3=weak, 4-7=moderate, and >8=strong.[17]

Data was analysed using SPSS 22. Descriptive statistics were applied for demographics. Chi-square test was used as appropriate. The correlation between PDPN expression and histopathological grades of OED and OSCC was determined using Spearman rho. $P<0.05$ was considered statistically significant.

Results

Of the 80 cases identified, 68(85%) were analysed. There were 20(29.4%) benign cases; 11(55%) females and 9(45%) males with mean age 39.90±16.23 years, 20(29.4%) OED cases; 14(70%) males and 6(30%) females with mean age 57.75±12.02 years, and 28(41.2%) OSCC cases; 17(61%)

Table-1: Age, gender and site of lesions.

Variables	Study groups		
	Benign oral epithelial lesions (n=20)	Oral epithelial dysplasia (OED) (n=20)	Oral squamous cell carcinoma lesions (OSCC) (n=28)
Age (years)			
Minimum age	17	40	25
Maximum age	75	82	75
Mean±SD	39.90±16.23	57.75±12.02	50.55±14.80
Age groups			
<50 years	12(60%)	6(30%)	12(42.9%)
>50 years	8(40%)	14(70%)	16(57.1%)
Gender			
Male	9(45%)	14(70%)	17(60.7%)
Female	11(55%)	6(30%)	11(39.3%)
M: F	1:1.22	2.33:1	1.54:1
Site of lesions			
Lip	4	1	2
Tongue	3	5	8
Floor of mouth	2	1	4
Gingival	2	6	6
Buccal mucosa	9	7	8

SD: Standard deviation.

Table-2: Immunoreactivity score of podoplanin.

Histopathological Features	Tissue Podoplanin immunoreactivity			*p*-value (Chi-square Test)
	Negative n (%)	Positive n (%)	Total n (%)	
Benign oral lesions				
Benign epithelial proliferations	16 (80)	1 (5)	17 (85)	0.666
Benign connective tissue lesions	3 (15)	0 (0)	3 (15)	
Oral epithelial dysplasia (Binary grading system)				
Low grade dysplasia	9(45)	3 (15)	12 (60)	0.027
High grade dysplasia	2 (10)	6 (30)	8 (40)	
WHO Grading System of OSCC	**Strong expression**	**Moderate expression**	**Weak expression**	
WDSCC	5 (17.8)	4 (14.2)	3 (10.7)	0.093
MDSCC	4 (14.2)	1 (3.5)	3 (10.7)	
PDSCC	7 (25)	0 (0)	1 (3.5)	

WHO: World Health Organisation, WDSCC: Well-differentiated oral squamous cell carcinoma, MDSCC: Moderately-differentiated oral squamous cell carcinoma, PDSCC: Poorly-differentiated oral squamous cell carcinoma.

males and 11(39%) females with mean age 50.55±14.80 years (Table 1).

The pattern of PDPN expression in all the three groups was noted, and PDPN expression in OED cases was significant (p=0.028), while it was not significant in the other 2 groups (Table 2).

The correlation between the grade of OED and PDPN expression was positive, while the correlation of PDPN expression to histopathological grades of OSCC was also noted (Table 3).

Discussion

Oral cavity oncogenesis is caused by a series of progressive genetic mutations that lead to a progressive change in the oral mucosa from normal to dysplastic lesions and invasive cancer. In an attempt to overcome the subjectivity of OED histopathological grading, which frequently fails to predict malignant transformation, efforts have been made to associate particular genetic changes with histomorphological grades.[18] Several studies have proposed PDPN as a marker that has the potential to enhance the diagnosis of OED when combined with histomorphological evaluation. Additionally, PDPN plays a crucial role in assessing the MTP of oral potentially malignant lesions (OPMLs), a determination often elusive through histopathological evaluation alone.[19]

Table-3: Correlation of podoplanin expression with OED and OSCC grades.

Spearman's rho	No. of cases	Correlation Coefficient of PDPN expression	*p*-value
OED	20	-0.492	0.027
OSCC	28	-0.42	0.093

OED: Oral epithelial dysplasia, OSCC: Oral squamous cell carcinoma, PDPN: Podoplanin.

The current study observed that PDPN expression increased significantly from benign lesions to dysplastic lesions. In benign lesions, the expression was mostly negative. The results were in agreement with an earlier study conducted in Japan.[20] In the current study, one case of benign papillomatous lesion showed a higher PDPN expression (score 4), suggesting that this case might have had a high MTP although it was a benign hyperkeratosis of epithelium.[19]

In the present study, the expression of PDPN was variable in OED. More cases of high-grade dysplasia showed immunoreactivity for PDPN compared to low-grade dysplasia. This was in agreement with past studies.[21] However, 2 cases of high-grade dysplasia were PDPN-negative. This could be due to the possibility that biopsy was taken at a different clonal site than from which lesion had eventually developed.[21]

In high-grade dysplasia, few among PDPN-positive cases showed suprabasal PDPN expression (Figure-1). These cases could be correlated with the role of PDPN as a marker of cancer risk assessment in dysplastic lesions. Earlier studies conducted by Patil A et al[17] and Parhar S et al[22] have recognised an upward clonal expansion of abnormal cells within the epithelial layers of dysplastic lesions, indicating a significantly raised risk of cancer development. The ability to detect these cells ascending past the basal layers provides a hint into potential clonal expansion during tumorigenesis. Previous findings have recommended that tumour initiation and generation are attributed to a small, phenotypically distinct subset of clonogenic cells recognised as tumour-initiating cells (TICs), or cancer stem

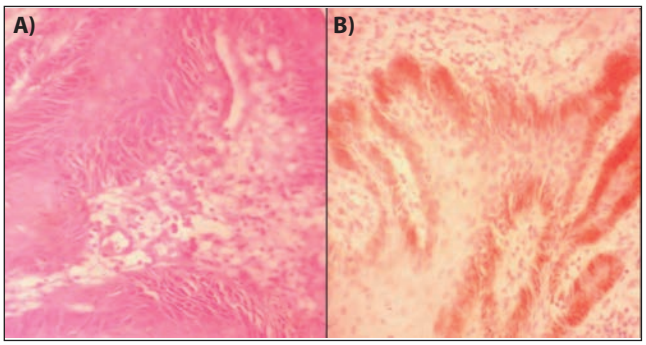

Figure-1: A) Section of moderate dysplasia (Haematoxylin and Eosin [H&E]), B) Section of moderate dysplasia with podoplanin (PDPN) score 3 (immunohistochemistry [IHC]).

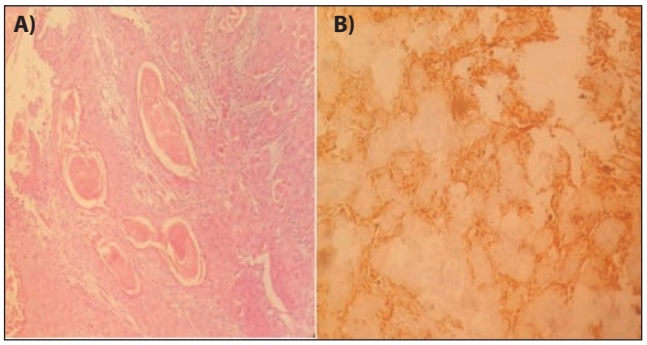

Figure-2: A) Section of well differentiated OSCC (Haematoxylin and Eosin [H&E]), B) Section of well-differentiated OSCC with podoplanin (PDPN) score 12 (immunohistochemistry [IHC]).

cells. PDPN is abnormally expressed in early oral tumorigenesis, and is identified as a new marker for TICs in OSCC, explaining its role in assessing cancer risk in premalignant lesions.[17,22]

In histopathological grades of OSCC, PDPN expression was not significant probably due to a small sample size. However, most cases of poorly-differentiated OSCC showed strong expression of PDPN compared to well-differentiated cases, indicating an association with less mature differentiation. The results were in agreement with a study by Ashoke Patel et al in which PDPN score was increasing with advancing grade of OSCC proposing its role in the progression of OSCC and its use as a biomarker for advanced grades of OSCC.[17] Prasad et al. also studied PDPN expression in different grades of OSCC, and concluded that its presence in tumour cells showed aggressiveness of tumour and helped in pathological diagnosis of OSCC.[23] In the current study, one case of poorly-differentiated OSCC showed weak staining hinting at potentially lower biological aggressiveness. In moderately-differentiated OSCC, the expression of PDPN was variable. Out of 8 cases, 4 were strongly stained, and 3 were weakly stained. In well-differentiated OSCC, more cases were strongly positive although well-differentiated OSCC is considered less aggressive (Figure-2). This might be because high PDPN expression is associated with higher risk of early metastasising.[24] This pattern of podoplanin expression in different grades of OSCC in the present study aligns with a previous study.[23] They proposed that PDPN staining becomes strong as a grade of OSCC increases playing role in the progression of OSCC. However, some studies showed contradictory results. A study by F.N Bartuli et al and S Parhar et al concluded that PDPN is involved in tumour initiation but not in the progression of OSCC. Therefore, more exhausting studies are required to assess the role of PDPN in OSCC.[22,25]

Table-4: Podoplanin expression in oral precursor lesions and oral squamous cell carcinoma (OSCC) in literature.

Frequency of immunohistochemical podoplanin protein expression in epithelial precursor lesions among cases of oral potentially malignant disorders			
No. of cases	**Frequency of cases with +ve podoplanin expression**	**Frequency of cases with -ve podoplanin expression**	**Reference**
Leukoplakia 15	9	6	Srinivasan et al. 2023[15]
Oral submucous fibrosis with dysplasia 30	18	12	Karunagaran et al. 2019[14]
Oral leukoplakia 30	23	7	D'Souza et al. 2016[27]
Oral leukoplakia 20	13	7	Deepa et al. 2017[27]
Oral leukoplakia 25	19	6	Aishwarya et al. 2021[12]

Frequency of immunohistochemical podoplanin protein expression in Oral squamous cell carcinoma					
No of cases	**Negative**	**Weak**	**Moderate**	**strong**	**Reference**
OSCC 45	1	8	20	16	Srinivasan et al, 2023[15]
OSCC 30	3	7	15	5	B Prasad et all. 2015[23]

OSCC: Oral squamous cell carcinoma

Correlations between PDPN expression and histo-pathological grades of OED were also observed in the current study, and the findings were close to an earlier study.[26] Similarly, in OSCC, a moderate positive correlation suggested elevated PDPN expression with advancing grades, which was in agreement with literature.[17,23] A table summarizing key findings from selected studies discussed above is provided (Table 4) for enhanced comprehension and comparison of our results with these investigations. The current study has limitations as it was a retrospective study with a small sample size. Prospective studies with appropriate follow-up and large sample sizes are recommended.

Conclusion

A high expression of PDPN was significantly correlated with increased grade of dysplasia, indicating that PDPN's role in OED diagnosis is more defined, and, if used along with histopathological evaluation, it can help in improving diagnosis and grading of OED. In OSCC, high PDPN expression represented immature status of differentiation process of OSCC, and may prove helpful in pathological

diagnosis for advanced grades of OSCC.

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Author Contribution:

HS: Literature search, study design, concept, data collection and drafting.
ASK: Literature search and data collection.
SHD: Study design, drafting and final approval.
KNA: Data analysis, result compilation.
SFT: Writing and data collection.