ORIGINAL ARTICLE

FREQUENCY OF CD44 EXPRESSION IN DIAGNOSED CASES OF ORAL EPITHELIAL DYSPLASIA AND SQUAMOUS CELL CARCINOMA

Zumrud Momin[1], Noshaba Rahat[2], Humera Shahzad[2], Marvi Umair[3], Raima Kaleemi[4], Asma Khursheed[5]

[1]Department of Pathology, Mekran Medical College, Turbat-Pakistan
[2]Department of Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center Karachi-Pakistan
[3]Department of Pathology, Sir Syed College of Medical Sciences Trust, Karachi-Pakistan
[4]Department of Radiology, Jinnah Postgraduate Medical Center Karachi-Pakistan
[5]Sindh Blood Transfusion Authority, Karachi-Pakistan

Background: Oral cavity cancer is one of the most widespread head and neck cancers in the world. 90 percent of oral cavity cancers are squamous cell carcinoma (SCC). Oral Potentially Malignant Disorder (OPMD), are well known to develop into squamous cell carcinoma. CD44 is a glycoprotein present on the cell surface and plays a vital role in cancer cell invasion, migration, metastasis of cancers and prognosis. The present study aims to detect the frequency of CD44 immunomarker expression in epithelial dysplasia and squamous cell carcinoma samples and correlates the expression with histologic grades of this lesion. **Methods:** Cross sectional study at the Department of Pathology, BMSI, JPMC, Karachi between 01-01-2018 to 31-12-2021. 95 patients diagnosed on morphological characterization of the lesion as squamous cell carcinoma/dysplasia were selected by using non-probability purposive sampling technique, among them 41 were diagnosed as epithelial dysplasia and 54 as SCC and were subjected to immunohistochemistry. **Results:** A total of 95 cases were selected. The mean age was 49.32 years. The majority of cases were seen in 4th and 5th decades. 69 (72.6%) were males and 26 (27.4%) were females with male to female ratio 2.65:1. The closest site was buccal mucosa 75(78.9%). Among 41 cases of dysplasia, 36 showed membranous positivity for CD44 (87.8%), and 45 showed positive membranous CD44 immunoreactivity (83.3%) among 54 cases of squamous cell carcinoma. **Conclusion:** Increased frequency of CD44 expression was found with increasing grades of dysplasia and squamous cell carcinoma, which may be a possible indicator of malignant transformation and can serve as a prognostic biomarker for oral SCC.

Keywords: CD44, Oral potentially malignant disorder, Squamous cell carcinoma

Citation: Momin Z, Rahat N, Shahzad H, Umair M, Kaleemi R, Khursheed A. Frequency of CD44 expression in diagnosed cases of oral epithelial dysplasia and squamous cell carcinoma. J Ayub Med Coll Abbottabad 2023;35(4 Suppl 1):762–8.
DOI: 10.55519/JAMC-S4-11864

INTRODUCTION

Oral cavity cancer is one of the most widespread head and neck cancers in the world. Although the prevalence of oral cancer has decreased globally due to less chewing habits and geological heterogeneity, until now it is the most common cancer in South Asia.[1] The five-year survival rate of this cancer lies below 50%. This is chiefly because most cancer cells have progressed to an untreatable stage at the time of diagnosis.[2] According to Globocan, it ranked 1st and 2nd commonest malignancy among males and females of Pakistan respectively after breast cancer.[3] As much as 90 percent of oral cavity tumours are SCC.[4] The precancerous lesion, also known as Oral Potentially Malignant Disorder (OPMD), is chiefly demonstrated by erythroplakia, leucoplakia, oral submucosal fibrosis, Proliferative Verrucous Leucoplakia and lichen planus (PVL), are well known to develop into SCC.[5] Oral epithelial dysplasia (OED) is a precancerous lesion of oral mucosa with an unreliable course of progression.[6] Leucoplakia is the most common lesion with different grades of epithelial dysplasia and has the potential to lead to invasive OSCC. The frequency of carcinomatous changes in leucoplakia varies from 15.6–39.2%.[7] Changes in molecules and genes may precede the changes in the morphology of benign tissues.[8] Therefore, prediction of its actual malignant transformation in individual cases is quite a difficult task. Hence, the right way for early detection would be to establish markers. By this, early detection of changes in the genes of lesions is

quite a possibility. It may also help to detect the lesions that grow into a malignant stage.[9]

Cluster differentiation-44(CD44) is a multi-functional and multi-structural transmembrane glycoprotein. It is a hyaluronan receptor, which is an important part of the extracellular matrix. It is also a coreceptor for various growth factors and cytokines.[10] The latest research indicates that tumours consist of a small portion of cancerous cells known as Cancer Stem Cells (CSCs). These cells are the primary cause of tumour initiation and progression. By molecular studies, it has been identified that CD44 is a CSC marker in SCC.[11] Using this biomarker, the diagnosis of squamous cell carcinoma in the initial stage gives an approach to preventive treatment by suppressing the disease in the early stage.CD44 plays a vital role in cancer invasion and metastasis.[9]

In humans, the gene of CD44 contains 19 exons. Among these, the initial 5 and the later 5 exons invariably generate the standard CD44 (CD44s). On the other hand, the 9 middle exons (called "variable" exons) go through alternative splicing to generate splicing variants (CD44v isoforms).[10]. It is a tumour-developing biomarker, it causes the initiation of tumours in many tumours involving increased expression in oral SCC. The ligand most specific for the activation of CD44 is hyaluronic acid (HA). It binds to CD44 causing structural changes that favour the binding of adaptor molecules to the intra-cellular cytoplasmic tail of CD44. This leads to cells indicating enhanced cell adhesion, migration, and proliferation. The tracts activated by the binding of CD44, and HA include Ras, MAPK and PI3K pathways.[12]

Increased expression of this marker is correlated with poor prognosis in breast, pancreatic, and lung tumours, gliomas and head and neck squamous cell carcinoma.[13] CD44 expression occurs chiefly in the basal region in normal surface epithelium. As dysplasia develops and grows, CD44 expression moves toward the upper layers, imparting its role in the initial stages of tumour development.[2]

The present study aims to evaluate the frequency of immune-expression of CSC marker, CD44 in oral dysplastic and malignant squamous cell carcinoma samples and also correlates the expression with histologic grades of this lesion.

MATERIAL AND METHOD

A cross-sectional retrospective study that involved histopathologically diagnosed tissue cases of oral epithelial dysplasia and SCC that were received at the department of histopathology, BMSI, between 01-01-2018 to 31-12-2021. Properly formalin-fixed, paraffin-embedded incisional and excisional oral biopsies specimens of more than 18 years of age which were histopathologically confirmed as oral epithelial dysplasia and squamous cell carcinoma were included. Cases of less than 18 years of age, inadequate material and metastatic carcinomas were excluded. H and E-stained slides of selected cases were re-examined by a senior pathologist (having more than 10 years of experience) and the diagnosis was reconfirmed. Grading of epithelial dysplasia and SCC was done according to the World Health Organization grading system as mild, moderate and severe for dysplasia[14] and well differentiated, moderately differentiated and poorly differentiated for SCC.[11] The paraffin-embedded tissue blocks were retrieved from the archives after obtaining permission from the Ethical Review Board (ERB) of JPMC. The sample size was calculated by using open EPI software by following Yousaf *et al*. (2019).[15]

The calculated sample size was 74. The sample size was enhanced to 95.

The immunohistochemical staining of CD44 was performed on 4 µm thick sections of selected blocks which were cut and mounted on slides coated with Poly-L-Lysine. The procedure for immunostaining was performed according to the manufacturer's recommendations. Deparaffinization and rehydration of sections were done by lowering concentrations of alcohol. Antigen unmasking was done using tris Hcl buffer PH 9.0 in the steamer. After peroxidase blocking, the sections were stained with purified CD44 Rabbit monoclonal primary antibody (Catalogue no: REF 22468) in 1:100 dilution followed by incubation with secondary antibody. The sections were treated with Di-aminobenzidine chromogen for visualization. Sections of normal skin tissue were taken from the concerned department as a positive control. Immunostains were reviewed by 02 senior pathologists of the pathology department of JPMC. Brown membranous staining of CD44 in lining epithelium above the basal layer in

dysplasia[9] and in tumour cells in SCC[11] was labelled as positive. Scoring was done according to the percentage of positive cells, e.g. 51–100% positive cells scored as; 3+. 31–50% of positive cells scored as; 2+. 11–30% of positive cells scored as; 1+ and less than 10% of staining was considered as negative. Immunoreactivity in selected groups for CD44 was graded as 1+ (weak), 2+ (moderate), 3+ (strong).[11]

SPSS version 21 was used for data analysis. Frequencies and percentages were estimated for continuous variables such as the age of patients, and categorical variables such as gender, site, histological grade, and presence of CD44 expression. By using the chi-square test, ≤0.05 was considered as significant p-value.

RESULTS

In the current study, a total of 95 diagnosed cases were selected for CD44 immunoreactivity, including 41 of dysplasia and 54 of SCC. Dysplasia was further categorized as mild moderate and severe, in which 13 cases were mild dysplasia, 15 were moderate dysplasia and 13 cases of severe dysplasia. Among the diagnosed squamous cell carcinoma cases 17 were well differentiated, 17 moderately differentiated and 20 were poorly differentiated type. Among total 95 cases, 69 (72.6%) were males and 26 (27.4%) were females. Male to female ratio is 2.65:1. (Chart. 1). Male: Female ratio= 2.65:1. Mean age was 49.32 (±12.73) years. There was a wide variation of age ranging from a minimum of 21 years to a maximum of 80 years. The majority of cases were in their 4th and 5th decades. (Chart. 2) The most common site of oral epithelial dysplasia and SCC was buccal mucosa 75 (78.9%) followed by lip and tongue 7.4% and 6.3% respectively. (Chart.3)

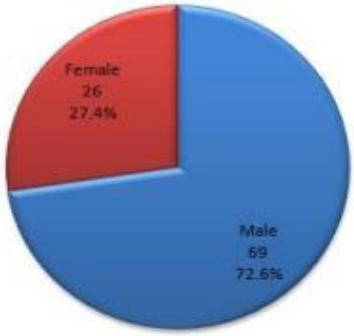

Chart-1: Gender distribution

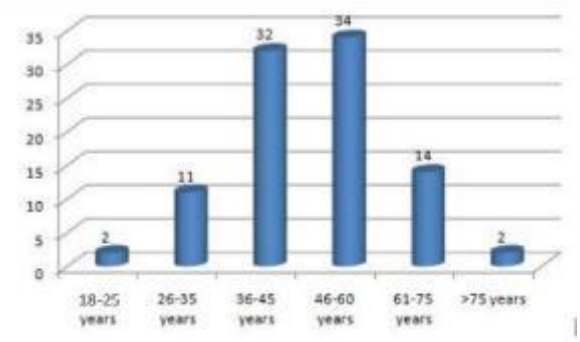

Chart-2: Age distribution

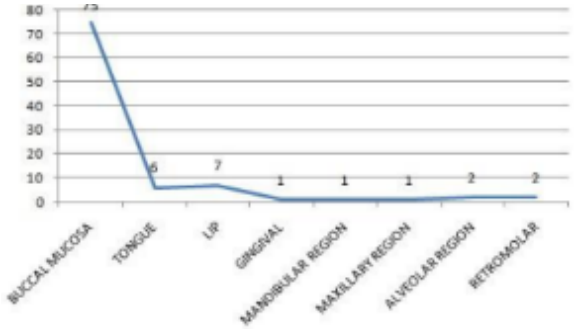

Chart-3: Site of lesion

Table-1: CD44 Immunoreactivity in selected cases of morphological grades of dysplasia and SCC (n=95)

Morphology	Grades	CD 44 immunoreactivity				Total	*p*-Value
		0	1 +	2 +	3 +		
Dysplasia	Mild	1(7.7%)	10(76.9%)	2(15.4%)	0(0%)	13(100%)	
	Moderate	1(6.7%)	4(26.7%)	6(40%)	4(26.7%)	15(100%)	
	Severe	5(12.19%)	3(23.1%)	1(7.7%)	6(46.2%)	13(100%)	
	Total	5(12.19%)	17(41.46%)	9(21.95%)	10(24.39)	41(100%)	0.005
OSCC	Well differentiated	2(11.8%)	9(52.9%)	5(29.4%)	1(5.9%)	17(100%)	
	Moderately differentiated	4(23.5%)	2(11.5%)	6(35.3%)	5(29.4%)	17(100%)	0.021
	Poorly differentiated	3(15%)	1(5%)	6(30%)	10(50%)	20(100%)	

	Total	9(16.66%)	12(22.22%)	17(31.48%)	16(29.63%)	54(100%)	

p-value < 0.05 was considered statistically significant

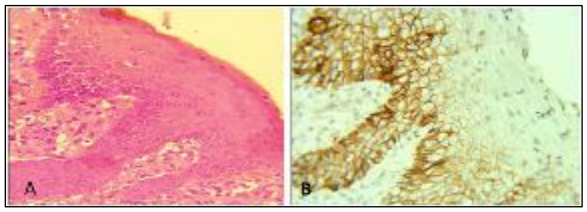

Figure-1: Mild dysplasia, Sp no. 20-1117 (A) H&E X 40 (B) Positive CD44

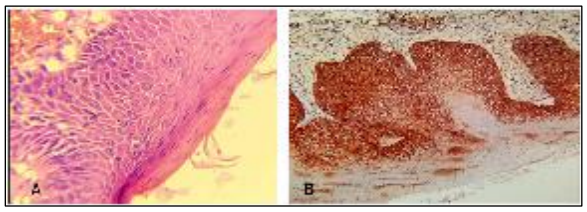

Figure 2: Moderate dysplasia, Sp no. 19-1962 (A) H&E X 40 (B) Positive CD44

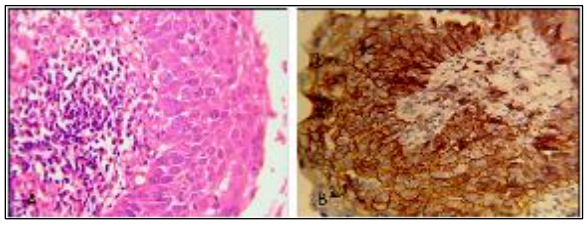

Figure-3: Severe dysplasia, Sp no. 20-622 (A) H&E X 40 (B) Positive CD44

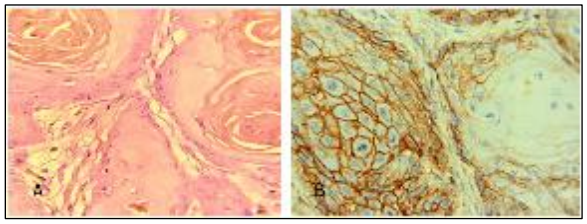

Figure-4: Will differentiated SCC, Sp no. 21-1249 (A) H&E X 40 (B) Positive CD44

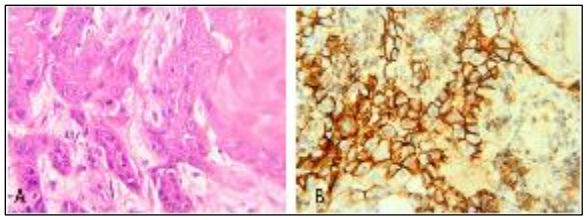

Figure-5: Moderately differentiated SCC Sp no. 18-3142 (A) H&E X 40 (B) Positive CD44

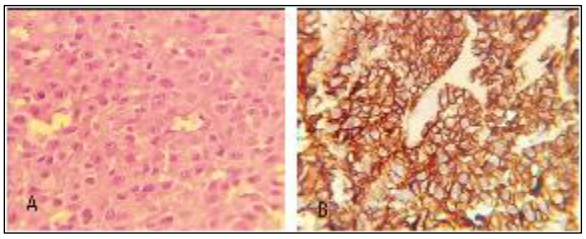

Figure-6: Poorly differentiated SCC, Sp no. 21-1082 (A) H&E X 40 (B) Positive CD44

Among 41 dysplasia cases, 36(87.8%) showed membranous positivity for CD44, In the 13 cases of mild dysplasia, most cases, that is, 10(76.9%) showed weak (1+) positive immunoreactivity for CD44. Among 15 cases of moderate dysplasia, the bulk of the cases, 6(40%) showed moderate (2+) positive immunoreactivity. In the 13 cases of severe dysplasia, most of the cases, 6(46.2%), showed strong (3+) positive membranous CD44 immunoreactivity. In a total of 54 cases of squamous cell carcinoma, 45(83.3%) showed positive membranous CD44 reactivity. Among well-differentiated cases 9 (52.9%) showed weak (1+) positive immunoreactivity, among moderately differentiated tumours, 6(35.3%) cases showed moderate (2+) and among poorly differentiated carcinoma, 10(50%) cases showed strong (3+) positive membranous immunoreactivity for CD44. (Table.1)

DISCUSSION

The incidence of oral SCC differs across the world, with the highest number in the Indo-Pak subcontinent. Identifying the pattern of occurrence of this tumour concerning gender, age, size distribution, tumour grade and immunohistochemical marker is essential in making the therapeutic decision.

This study found that the occurrence of epithelial dysplasia and SCC was more common in men as compared to women. Singh *et al*. (2020) in India also found that dysplasia was more common in males.[16] The male-to-female ratio of dysplasia and squamous cell carcinoma in the current study was 2.65:1. A Closely similar ratio was observed by Barma *et al*. (2020) in Bangladesh which was 2.3:1 in SCC.[17] The commonest racial, environmental and habitual factors could be responsible for similar

findings. However, some studies gave a higher male-to-female ratio. For instance, Sriwardena *et al*. (2020) and Anwar *et al*. (2020) gave male-to-female ratios of 3:1and 5:1 respectively[1,18] and Dzudzilo *et al*. (2021) observed male to female ratio of 11:1.[19] The reason why males are affected more than females is that smoking and chewing habits are more common among men than women.[20]

The mean age of the patients in the current study was 49.32(±12.73). A quite similar mean age was presented by Anwar *et al*. (2020) in Pakistan, which was 47.62 in SCC[1], However, e Costa *et al*. (2021) in Brazil found that the mean age of the patients was 58.93 which slightly differed from that of the present study.[21] In Pakistan and other Asian nations, the early onset of carcinoma is possibly due to their chewing habits of pan, *gutka* and *naswar* at early ages as compared to Brazil and other Western countries.

Lin *et al*. (2021) and Barma *et al*. (2020) observed that the commonest site of OSCC was buccal mucosa. Singh *et al*. (2020) and Dzudzilo *et al*. (2021) also found buccal mucosa was the commonest site in dysplasia, these results concur with recent research showing buccal mucosa as the most common site of dysplasia and SCC occurrence.[16,17,19,22]

Regarding the frequency of CD44 among these cases, 41 cases of dysplasia, 36(87.8%) showed positive membranous CD44 immunostaining. It was observed that with the increase of the grades of dysplasia, the strength of the positivity of the CD44 marker also increases (Sp no. 20-1117 (B), 19-1962 (B), 20-622 (B)). These results support those of Ghazi *et al*. (2020) in India, who reported higher expression of CD44 in dysplastic lesions as compared to non-dysplastic oral lichen planus. Another study conducted by Ghazi *et al*. (2021) observed higher expression of CD44 in dysplastic leucoplakia compared to non-dysplastic leucoplakia. He also suggested that higher expression of CD44 as a CSC marker may show the role of this marker in the malignant transformation and carcinogenesis process of those premalignant lesions.[9,23]

In the present study, 54 cases of SCC were selected for CD44 immunostaining. Among these, 45 (83.3%) showed positive membranous immunostaining for CD44. Higher expression was observed in oral squamous cell carcinoma with higher grade. In well-differentiated cases CD44 positive cells were seen in peripheral cells of tumour nests and pearls, (Sp no. 21-1249 (B)) and in poorly differentiated cases diffuse intense positivity was observed in malignant cells (Sp no. 21-1082 (B)). These results are consistent with those of Khamis *et al*. (2017) who observed, that well-differentiated cases of OSCC showed weak positive membranous immunostaining in the peripheral epithelial cells forming the epithelial nests and pearls, and the poorly differentiated OSCC demonstrated the highest number and greatest intensity of CD44 immunopositivity.[24] Another study conducted by Saghravinian *et al*. (2017) in Iran, observed higher CD44 immunoreactivity in high-grade squamous cell carcinoma.[11] Work done by Boxberg *et al*. (2018) observed the association of CD44 with tumour aggressiveness and epithelial-mesenchymal transition.[25]

Negative expression of CD44 in a few cases of high-grade dysplasia and SCC was found in the present study, however, no literature was available to compare regarding negative expression of CD44 in high-grade dysplasia. These findings may be because of the presence of a specific isoform of CD44 which can be better detected by their specific antibodies. It is recommended that various isoforms of this marker should be separately examined so that specific isoforms for these lesions can be confirmed.

Kaza *et al*. (2018) found half of the cases of poorly differentiated SCC showed negative CD44 expression, they assessed that different patterns of expression in varying grades of OSCC were associated with the presence of highly pleomorphic cells with a weak similarity to the parent tissue, and a total absence of immunostaining was associated with undifferentiated SCC.[26] The significance of CD44 might have been different with univariate analysis if the number of cases increased.

This study found that the expression of CD44 correlates with poor histological grades of dysplasia and SCC. The higher expression of CD44 with the severity of these lesions reflects the intense proliferative activities and invasiveness of these lesions.

5-mG2a-f, a monoclonal anti-CD44 antibody was used in recent trial-based research by Takei *et al*. (2020) In vivo analysis of this antibody revealed significantly reduced tumour development in mouse xenografts oral cancer cells in comparison to control mice. They concluded that CD44 is present in large amounts in OSCC and could be an excellent therapeutic target.[27]

Presently, several new antibodies against CD44 are under preclinical trials for anti-cancer stem cell therapy.[10] Further studies regarding cancer stem cells as a therapeutic target in cancer management will increase therapeutic success. There were a few limitations of the study, the calculated sample size was low, and the study was retrospective which limits the knowledge of dysplasia expression of CD44 in transformation to squamous cell carcinoma. We also were lost in following up with the patient's concerning treatment and cure. However, to my knowledge, this is the first study done on the Pakistani population with SCC and dysplasia using CD44. We are planning for further study with a larger sample size and a prospective study design with follow-up will be of high benefit to express the value of CD44.

CONCLUSION

This study discovered an increased frequency of CD44 expression in cases of dysplasia and squamous cell carcinoma (SCC), with these rates rising with higher grades of dysplasia and SCC signifying its importance as a prognostic biomarker for oral SCC.

This study found that the expression of CD44 correlates well with poor histological grades of dysplasia and SCC. The higher expression of CD44 with the severity of these lesions reflects the intense proliferative activities and invasiveness of these lesions.

Expression of the CD44 with rising grades of dysplasia may well be a foretelling indication of any preceding malignant transformation and may thus act as biomarkers for oral cancer growth.

AUTHORS' CONTRIBUTION

ZM: Primary and corresponding author, literature search, conceptualization, study design, data collection, data analysis, data interpretation, write-up. NR: Conceptualization and study design. MS: conceptualization and study design. MU: Data collection. RK: Data interpretation, write-up, proofreading. AK: Data interpretation.

REFERENCES

1. Anwar N, Pervez S, Chundriger Q, Awan S, Moatter T, Ali TS. Oral cancer: Clinicopathological features and associated risk factors in a high risk population presenting to a major tertiary care center in Pakistan. PLoS One 2020;15(8):e0236359.
2. Su YF, Chen YJ, Tsai FT, Li WC, Hsu ML, Wang DH, *et al*. Current insights into oral cancer diagnostics. Diagnostics (Basel) 2021;11(7):1287.
3. International Agency for Research on Cancer. Pakistan. The Global Cancer Observatory. [Internet]. (2021c, March). [cited 2023 March]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/586-pakistan-fact- sheets.pdf
4. Sakurai K, Tomihara K, Yamazaki M, Heshiki W, Moniruzzaman R, Sekido K, *et al*. CD36 expression on oral squamous cell carcinoma cells correlates with enhanced proliferation and migratory activity. Oral Dis 2020;26(4):745–55.
5. Coletta RD, Yeudall WA, Salo T. Grand challenges in oral cancers. Fron Oral Health 2020;1:3.
6. Jaber MA, Elameen EM. Long-term follow-up of oral epithelial dysplasia: A hospital based cross-sectional study. J Dent Sci 2021;16(1):304–10.
7. Bavle RM, Paremala K, Soumya M, Reshma V, Sudhakara M. Immunohistochemical expression of p63 in oral premalignant disorders and its correlation with oral squamous cell carcinoma. J Datta Meghe Inst Med Sci Univ 2020;15(2):255.
8. Borse V, Konwar AN, Buragohain P. Oral cancer diagnosis and perspectives in India. Sens Int 2020;1:100046.
9. Ghazi N, Saghravanian N, Ghazi A, Shakeri MT, Khajehbahrami H. CD44 expression in dysplastic and non-dysplastic oral lichen planus. Int J Cancer Manag 2020;13(1)e98061.
10. Xu H, Niu M, Yuan X, Wu K, Liu A. CD44 as a tumor biomarker and therapeutic target. Exp Hematol Oncol 2020;9(1):1–4.
11. Saghravanian N, Anvari K, Ghazi N, Memar B, Shahsavari M, Aghaee MA. Expression of p63 and CD44 in oral squamous cell carcinoma and correlation with clinicopathological parameters. Arch Oral Biol 2017;82:160–5.
12. Chen C, Zhao S, Karnad A, Freeman JW. The biology and role of CD44 in cancer progression: therapeutic implications. J Hematol Oncol 2018;11(1):64.
13. Wang YY, Vadhan A, Chen PH, Lee YL, Chao CY, Cheng KH, *et al*. Cd44 promotes lung cancer cell metastasis through erk–zeb1 signaling. Cancers 2021;13(16):4057.
14. Ranganathan K, Kavitha L. Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. J Oral Maxillofac Pathol 2019;23(1):19.
15. Yousaf A, Mahmood S, Faraz R, Quader Q. Annual cancer registry report-2018, of the Shaukat Khanum Memorial Cancer Hospital & Research Center, Pakistan. 2018; p.1–28.
16. Singh S, Singh J, Chandra S, Samadi FM. Prevalence of oral cancer and oral epithelial dysplasia among North Indian population: A retrospective institutional study. J Oral Maxillofac Pathol 2020;24(1):87.
17. Barma P, Khalil I, Yeasmin T. Rural profile of oral squamous cell carcinoma (OSCC) survival patients attending in tertiary level hospital in Bogura: a hospital based retrospective observational study. Update Dent Coll J 2020;10(1):3–5.
18. Siriwardena BS, Karunathilaka HD, Kumarasiri PV, Tilakaratne WM. Impact of histological and molecular parameters on prognosis of oral squamous cell carcinoma: analysis of 290 cases. Biomed Res Int 2020;2020:2059240.

19. Dzudzilo M, Kleina R, Čēma I, Dabuzinskiene A, Svirskis Š. Expression and localisation of cd44 antigen as a prognostic factor of oral leukoplakia. InProceedings of the Latvian Academy of Sciences. Section B. Nat Exact Appl Sci 2021;75(2):68–74.
20. Pervez S, Jabbar AA, Haider G, Ashraf S, Qureshi MA, Lateef F, *et al*. Karachi cancer registry (KCR): Age-Standardized incidence rate by age-group and gender in a Mega city of Pakistan. Asian Pac J Cancer Prev 2020;21(11):3251–8.
21. Costa AM, Pontes FS, Souza LL, Lopes MA, Santos-Silva AR, Vargas PA, *et al*. What is the frequency of floor of the mouth lesions? A descritive study of 4,016 cases. Med Oral Patol Oral Cir Bucal 2021;26(6):e738.
22. Lin NC, Hsien SI, Hsu JT, Chen MY. Impact on patients with oral squamous cell carcinoma in different anatomical subsites: a single-center study in Taiwan. Sci Rep 2021;11(1):1–9.
23. Ghazi N, Saghravanian N, Shakeri MT, Jamali M. Evaluation of CD44 and TGF-B expression in oral carcinogenesis. J Dent 2021;22(1):33.
24. Khamis AK, Fouad HA, Raslan HS, Fata MM, Fayad AI. Diagnostic and prognostic value of cancer stem cell marker CD44 and soluble CD44 in the peripheral Blood of patients with oral Squamous cell carcinoma. Open Sci J 2017;2(3):2–23.
25. Boxberg M, Götz C, Haidari S, Dorfner C, Jesinghaus M, Drecoll E, *et al*. Immunohistochemical expression of CD44 in oral squamous cell carcinoma in relation to histomorphological parameters and clinicopathological factors. Histopathology 2018;73(4):559–72.
26. Kaza S, Kantheti LP, Poosarla C, Gontu SR, Kattappagari KK, Baddam VR. A study on the expression of CD44 adhesion molecule in oral squamous cell carcinoma and its correlation with tumour histological grading. J Orofac Sci 2018;10(1):42–9.
27. Takei J, Kaneko MK, Ohishi T, Hosono H, Nakamura T, Yanaka M, *et al*. A defucosylated anti CD44 monoclonal antibody 5 mG2a f exerts antitumor effects in mouse xenograft models of oral squamous cell carcinoma. Oncol Rep 2020;44(5):1949–60.

Submitted: March 5, 2023	*Revised: November 4, 2023*	*Accepted: December 26, 2023*

Address for correspondence:

Zumrud Momin, Pathology Department Teaching Hospital Kech (Turbat)-Pakistan
Cell: +92 322 815 4858
Email: zumrudmomin18@gmail.com