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Research Article

Immunohistochemical Evaluation of CD10 Expression in Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma: A Cross-sectional Study

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Abstract

Objectives: The objective of the study is to evaluate the expression of CD10 in oral epithelial dysplasia and oral squamous cell carcinoma (OSCC) and to determine its role as a potential biomarker in OSCC.

Methods: Immunohistochemical evaluation of 40 archival paraffin-embedded tissue specimens grouped into oral epithelial dysplasia and early invasive, well-differentiated, and moderately differentiated OSCC was conducted to determine and compare the CD10 expression among the groups. Stromal positivity of the CD10 expression was calculated and statistically analyzed at $p<0.05$.

Results: The results of the study showed that there was a statistically significant increase in the mean CD10 expression among the four groups. Intergroup comparison showed a statistically significant difference between oral epithelial dysplasia and OSCC while statistical significance was not observed in the various grades of OSCC.

Conclusion: CD10 expression could be used as an important biomarker for determining the progression of oral epithelial dysplasia and the overall prognosis of OSCC.

Keywords: Biomarker, CD10, oral epithelial dysplasia, oral cancer, immunohistochemistry

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OSCC is a significant cause of morbidity and mortality worldwide and accounts for most of the head and neck cancers in India.[1,2] The increased prevalence of OSCC could be attributed to various deleterious habits such as tobacco chewing and smoking and alcohol consumption.[3] In general, they arise de novo, but most of the cases are preceded by innocuous-looking lesions such as leukoplakia, erythroplakia, oral submucous fibrosis, and oral erosive lichen planus that are collectively referred to as oral potentially malignant disorders with increased potential for malignant transformation over a course of time.[4]

The cytological and epithelial alterations that are histologically evident in clinically diagnosed oral potentially malignant disorders are known as epithelial dysplasia, the grading of which serves as an important prognostic indicator of oral cancer. Various factors contribute to the malignant transformation of oral epithelial dysplasia into OSCC.[5] In recent years, the crosstalk between cancer cells and tumor stroma, which is highly responsible for the progression of tumors and their metastasis, has been increasingly unveiled. Mounting evidence shows that components of the tumor microenvironment including cancer-associated fibroblasts, vascular and lymphatic endothelial cells,

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extracellular matrix, and inflammatory immune cells are important modulators of tumor behavior in primary OSCC.[6] A better understanding of the contribution of the host stroma toward cancer progression will increase our knowledge about the growth-promoting signaling pathways and hopefully lead to novel therapeutic interventions targeting the tumor stroma.

CD10 has been used as a cell surface marker to differentiate certain hematological malignancies. The expression of CD10 is found to be deregulated in several other cancers.[7] The relevance of CD10 in OSCC has been scarcely reported in the literature, and till date, no literature data comparing the CD10 expression in oral epithelial dysplasia and OSCC exist. Understanding the potential role of CD10 as a tumor biomarker may pave the way for future directives in using CD10 to determine the prognosis and treatment of OSCC. Therefore, the aim of the present study is to evaluate the role of CD10 as a potential biomarker in oral epithelial dysplasia and OSCC.

Methods

An in vitro cross-sectional study was performed using archival paraffin-embedded tissue specimens, which were grouped as follows: Group I (oral epithelial dysplasia, n=10); Group II (early invasive squamous cell carcinoma (SCC), n=10); Group III (Well-differentiated OSCC, n=10); and Group IV (moderately differentiated OSCC, n=10). The selected tissue specimen was histopathologically confirmed for the diagnosis. Insufficient tissue specimens, clinically recurrent cases, and the presence of nonneoplastic inflammatory lesions were excluded from the study. Institutional ethics committee approval was obtained prior to the commencement of the study.

Immunohistochemical analysis of the selected specimen was conducted using Supersensitive Polymer-Horseradish peroxidase technique (Biogenex Life Sciences, San Ramon, CA, USA) with a monoclonal antibody directed against CD10. CD10 positivity was considered as brown cytoplasmic and/or membrane staining of stromal cells. Semiquantitative assessment of CD10 positivity was performed wherein the CD10 immunostained stromal cells were evaluated in 10 high power fields for every specimen and expressed as a percentage of positive cells. When stromal cells positive for CD10 was >10%, it was considered positive, and <10% was considered negative for CD10 reaction. Positive control for the immunohistochemistry analysis employed kidney tissue as supplied by the manufacturer, and for negative controls, histopathologically diagnosis cases of OSCC without primary antibody were used.

The obtained values were then statistically analyzed using Student's t-test. The Mann–Whitney test for abnormally distributed data, one-way ANOVA or the Kruskal–Wallis H test for continuous variables, and post hoc tests for pairwise comparison of significant results were performed. A value of $p<0.05$ was considered significant.

Results

The results of the study showed that there was a linear increase in the mean CD10 expression among the four groups (Fig. 1). One-way ANOVA showed a statistically significant increase in the expression of CD10 from oral epithelial dysplasia to poorly differentiated OSCC. Intergroup comparison also showed a statistically significant difference between oral epithelial dysplasia and OSCC, while statistical significance was not observed in the various grades of OSCC. The staining intensity was mild in oral epithelial dysplasia (Fig. 2), with a gradual increase in early invasive OSCC (Fig. 3), well-differentiated OSCC (Fig. 4), and moderately differentiated OSCC (Fig. 5).

Discussion

The molecular biology of OSCC is poorly understood, hampering the development of novel treatments and prognostication. The progression of potentially malignant disorders to SCC and its propensity to metastasize to locoregional sites remains enigmatic. An insight into the molecular alteration associated with OSCC will provide a better understanding of the basic mechanisms underlying its progression. CD10 can be a useful progression marker and an attractive molecular target for therapy.[8] To the best of our knowledge, this is the first study done to evaluate the CD10 expression in oral epithelial dysplasia and varying grades of OSCC.

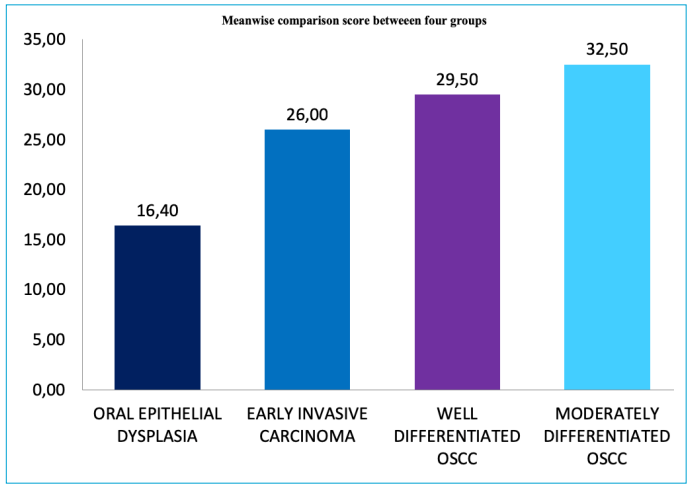

Figure 1. Mean-wise comparison of CD10 positivity between the groups.

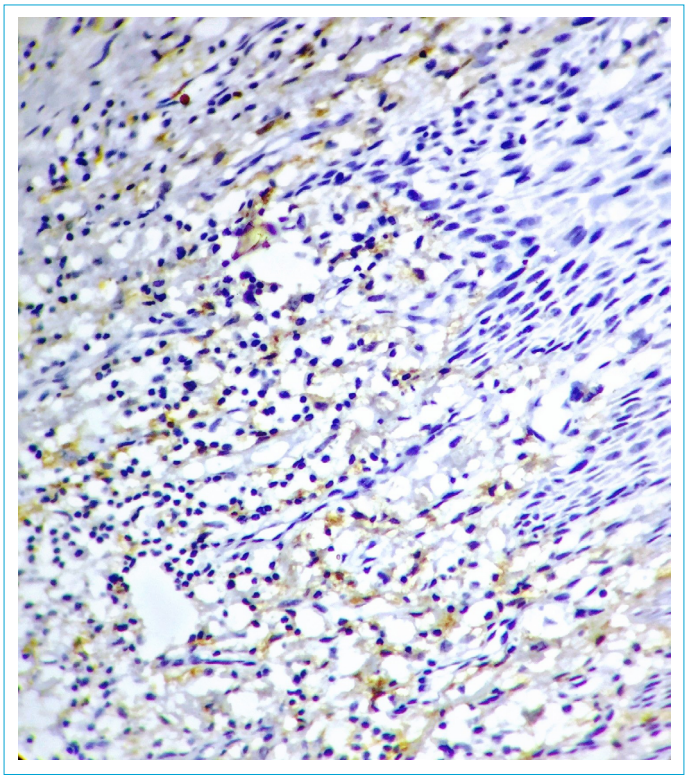

Figure 2. Photomicrograph (10×) showing mild immunopositivity in the subepithelial stroma of oral epithelial dysplasia.

The human CD10 antigen is a 100 kDa cell surface glycoprotein belonging to the peptidase M13 family. It is a zinc-dependent metallopeptidase that is expressed on the surface of a variety of normal hemopoietic and lymphoid cells (especially B lymphocytes), some epithelial cells, and neoplastic cells.[9] Earlier CD10 was used as a cell surface marker to identify and differentiate hematological malignancies, such as ALL, Burkitt lymphoma, and follicular germinal cell lymphoma.[7] Currently, it is also thought to play a significant role in cancer development and progression. The expression of CD10 was found to be deregulated in different cancers, either acting as a tumor suppressor or a tumor promoter. CD10 expression has been detected in peritumoral fibroblasts at the invasive front of various cancers, such as prostrate, breast, colorectal, and hepatocellular carcinoma.[10]

CD10 acts by cleaving amino acid peptide bonds of hydrophobic acids, causing the inactivation of a range of physi-

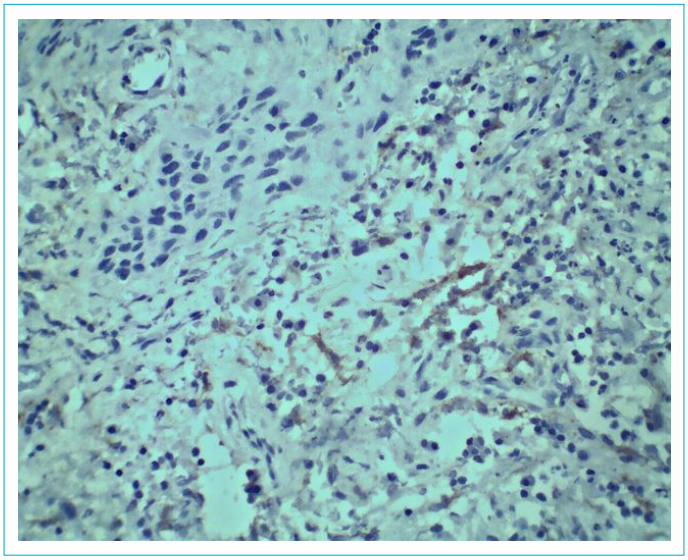

Figure 3. Photomicrograph (10×) showing mild CD10 immunopositivity in early invasive oral squamous cell carcinoma (OSCC).

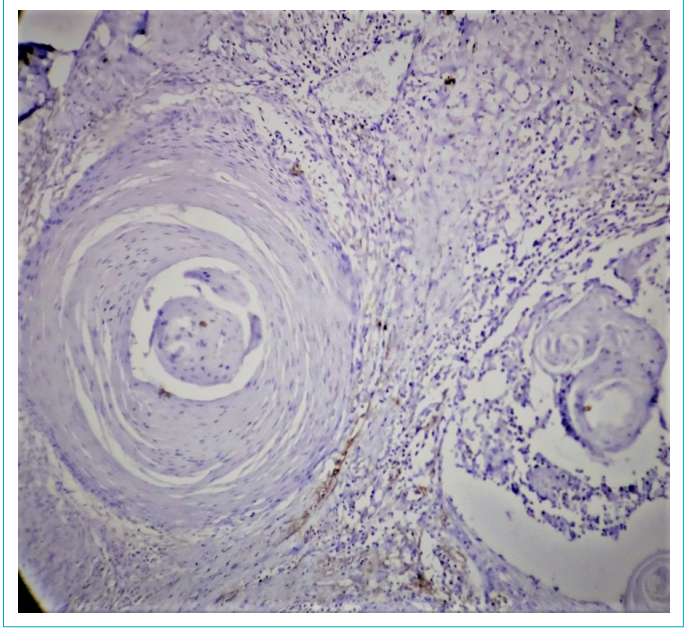

Figure 4. Photomicrograph (10×) showing moderate CD10 immunopositivity in well-differentiated OSCC.

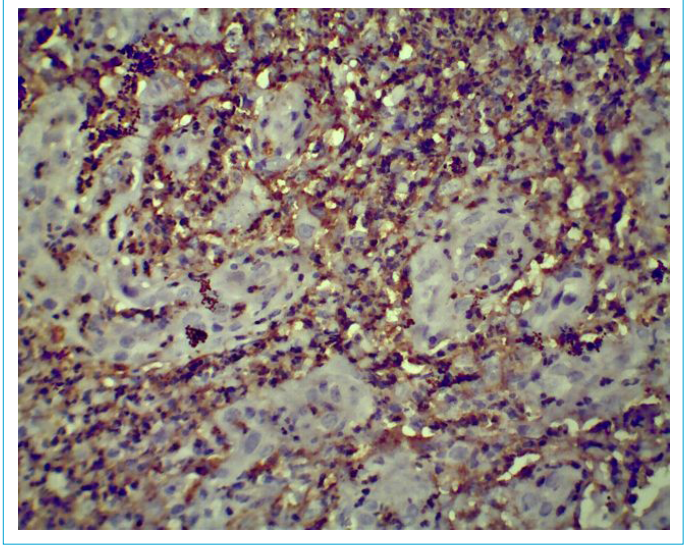

Figure 5. Photomicrograph (10×) showing intense CD10 immunopositivity in moderately differentiated OSCC.

ologically active neuropeptides. It metabolizes biologically active peptides such as bradykinin and oxytocin.[9] The enhanced accumulation of cleaved peptides leads to the proliferation of undifferentiated cells. CD10 targets outside the cell via its enzymatic activity at the intracellular level by interacting with various signaling pathways. The majority of malignancies show an upregulated expression of CD10 and its correlation with high tumor stage and severity.[10]

A study performed by Fukusumi et al. found that CD10 positive subpopulation was more refractory to treatment with radiation and chemotherapeutic drugs, such as cisplatin and fluorouracil, in comparison with CD negative subpopulation. CD10 positive cells are slow cycling compared with CD10 negative cells. Given that cancer stem cells are responsible for therapeutic resistance and are slow cycling mainly in G0/ G1 phase, it is hypothesized that CD10 can serve as a cancer stem cell marker of head and neck SCC (HNSCC). CD10 positive subpopulation in HNSCC acquires stem-cell-like properties and expresses higher levels of cancer stem cell marker OCT ¾. An elevated level of CD10 and OCT ¾ results in an increased tendency to form spheres implicated in the therapeutic resistance of HNSCC.[11]

The role of CD10 in tumor differentiation and growth in HNSCC has been reported by Piattelli et al. They studied CD10 expression in stromal cells of OSCC and found a highly significant correlation with lymph node status, presence of local recurrences, and histological grading.[12]

In the present study, a significant difference was found in the average immunopositivity of oral epithelial dysplasia (16.40%) and early invasive OSCC (26%). It was also significant between cases of dysplasia and moderately differentiated OSCC (32.50%). However, this difference was not significant between the grades of carcinoma as the mean positivity of well-differentiated SCC cases was 29.50% as compared with 32.50% in moderately differentiated carcinoma. This result contrasted with the study conducted by Helmy et al. who found a significant difference between various grades of carcinoma.[13] However, no statistical difference was found between the grades of cutaneous SCC by Fernandez-Flores.[14] In stromal cells, a gradual increase in the expression of CD10 was observed from dysplasia to early invasive carcinoma. The expression further increased according to the histopathological grade of OSCC. This might suggest that CD10 plays a role in the loss of differentiation of neoplastic cells.

A study observed that CD10 is expressed in stromal cells of more advanced primary melanomas and was associated with their higher proliferation rate suggesting that stromal cells may also have an important role in the progression of melanoma.[9] It is possible that the structural similarities of CD10 to matrix metalloproteinases may result in the creation of a conducive microenvironment by CD10 to facilitate cancer cell invasion and metastasis.

The proliferation of stromal cells is commonly seen when cancer cells invade and metastasize. The invasive and/or metastatic potential of several types of cancer cells is regulated by interactions with stromal cells. Certain literature findings have suggested that CD10 facilitates invasion and metastasis of breast cancer and can be labeled as a novel prognostic marker.[8,15] In the present study, all OSCC cases showed positive CD10 immunoreactivity in the stromal cells within the invasive area of the tumor. CD10 expression was detected in peritumoral fibroblast and inflammatory cells of the present study which was similar to other findings from the literature.[16]

In an investigation conducted to determine the role of CD10 in stromal cells of colorectal neoplasms at various stages of carcinogenesis, it was demonstrated that CD10 expression appeared to be associated with the transition of colorectal adenomas to carcinomas. Similarly, a gradual increase in CD10 expression from epithelial dysplasia to early invasive carcinoma and further grades of OSCC as evidenced by the present study might indicate the potential role of CD10 in the progression of oral epithelial dysplasia to OSCC.

Conclusion

The preliminary results obtained from the immunohistochemical analysis of archival tissue specimen used in the present study were encouraging in that higher CD10 expression was noted with the disease progression from oral epithelial dysplasia to increasing grades of OSCC which could be correlated with its worse prognosis. Stromal expression of CD10 can have an important role in the tumor invasion and help to stratify the different grades of OSCC. There is a possibility that CD10 could be an important contributing factor in the disease progression of epithelial dysplasia and different grades of OSCC as it facilitates the invasion and metastasis of the tumor. Further analysis with an increased sample size diversified over various grades of oral epithelial dysplasia and OSCC, as well as inclusive of lesions with and without metastasis may shed more light on the utility of CD10 as an important tumor biomarker.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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