Expression of EMMPRIN/CD147 and Ki-67 in oral squamous cell carcinoma: An immunohistochemical study

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Abstract: Background Oral squamous cell carcinoma (OSCC) is the most frequent malignancy of the oral cavity, highly invasive with unfavorable prognosis and unimproved 5-year survival rate for at least two decades. An elevated level of EMMPRIN in cancer tissues have been correlated with tumor invasion in numerous cancers including oral cavity and larynx. Ki-67 is a specific marker of proliferation and the expression of which is strictly associated with cell proliferation and used to measure the growth fraction of cells in human tumors. Objectives: The aim of this study was to evaluate the immunohistochemical expression of EMMPRIN/CD147 and Ki67 markers in OSCC and to correlate the expression of either marker with each other and with the clinico-pathological parameters of OSCC. Methods: Thirty five formalin-fixed, paraffin-embedded tissue blocks of OSCC were included in this study. H&E stain was done for each block for reassessment of histological examination. The expressions of EMMPRIN and Ki67 were detected by immunohistochemical method. Results: The expression of EMMPRIN and Ki-67 were positive in all OSCC cases. EMMPRIN high expression score was observed in 26 cases (74.3%). No significant relationships were found between clinicopathologic factors and this protein except for clinical stage, and histological grade (P=0.047 and 0.005 respectively). The high expression of EMMPRIN was associated with higher grade and advanced stage of OSCC. On the other hand, Ki67 with high proliferation score was observed in 17 cases (48.5%) of 35 OSCC. Significant relationship was found between Ki67 and histologic grade (P=0.003). Also a statistically significant correlation was found between EMMPRIN high expression and Ki67 high proliferation scores (P=0.001). Conclusion: Increased expression of EMMPRIN in more than two third of cases with statistical significant association with proliferative marker highlight the importance of EMMPRIN in cancer progression, indicating that EMMPRIN could be an attractive target for immunotherapeutic approaches in a group of patients with OSCC.

Key words: EMMPRIN/CD147; Ki67; Oral squamous cell carcinoma; immunohistochemistry

1. Introduction

Head and neck cancer is the sixth most common cancer, representing 3% of all localizations. In 48% of these cases, the tumors were located in the oral cavity and 90% are squamous cell carcinomas (Jemal et al., 2009 & Olimid et al., 2012).

Oral squamous cancer cell carcinoma (OSCC) ranks among the top ten most frequently cancers, and is highly invasive with bad prognosis; despite the recent advances in cancer therapy, the 5-year survival rate of patients has remained at < 50% (Specenier and Vermorken, 2010). Little is known about of the molecular events that govern OSCC initiation, progression and metastasis. Development of OSCC is a complex and multistep process, with transformation from oral premalignant dysplastic lesion to OSCC. Progression is generally known to involve the intervention of proteinases (Siqueira et al., 2010).

During SCC progression, subsets of SCC cells undergo an epithelial-to-mesenchymal transition (EMT) to become highly invasive. The extracellular matrix metalloproteinase inducer (EMMPRIN) contributes to EMT by activating local matrix metalloproteinase (MMPs) (Siu et al., 2013) and through transforming fibroblasts to cancer associated fibroblasts (CAFs) (Xu et al., 2013).

Extracellular matrix metalloproteinase inducer (EMMPRIN), is a transmembrane glycoprotein of the immunoglobulin superfamily, also known as CD147, has been identified as a tumor-cell membrane protein that stimulates (MMP) production in stromal fibroblasts. EMMPRIN is overexpressed in various tumor cells including those in head and neck carcinoma, and is also known to promote tumor invasion and lymph node metastasis (Yang et al., 2013).

It is well understood that transition of the normal oral epithelium to dysplasia to malignancy is featured by increased cell proliferation. Discovery of various proliferation markers has enabled the detection of the hyperactive state of the epithelium, the basal layer is the only proliferative compartment for normal oral epithelium, and hence, any sign of
proliferative cellular activity beyond the basal layer should be considered as a warning sign (Dwivedi et al., 2013).

Ki-67 is a nuclear protein expressed in the G2- and M-phases of actively dividing cells. This antigen is a proliferation marker that correlates with the presence and severity of epithelial dysplasia. It provides significant information about the degree of aggressiveness and prognosis of (OSCC) (Patel, et al., 2014).

The purpose of this study was to evaluate the immunohistochemical expression of EMMPRIN/CD147 and Ki67 markers in oral squamous cell carcinoma and to correlate the expression of either marker with each other and with the clinico-pathological parameters of OSCC.

2. Patients and Methods

This retrospective study included 35 biopsies of OSCC were retrieved from archives of Histopathology laboratory at AL-Zahraa hospital, Al-Azhar university, Cairo, Egypt and private laboratory, during the period from 2008 -2011. All cases were selected on the basis of availability of paraffin blocks with sufficient amount of tissue for re-cut, histopathological re-examination and immunohistochemical staining. As the material of this study was archival paraffin blocks with no direct contact to the patient, who were unknown to us, there is no need for patient approval or consent. The clinical data related to the selected cases were prospectively collected in a computerized database.

Histopathological examination:

All specimens were formalin- fixed, routinely processed, and embedded in paraffin. Three 5-um thick sections were prepared from each tissue block, one of them stained with hematoxylin and eosin for histopathological examination to confirm the diagnosis of cases. Tumor stage was classified according to the 7th edition of the classification of malignant tumors of American Joint Committee on Cancer (Brandwein-Gensler & Smith, 2010) and graded according to the WHO classification (2005) into well-differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3) OSCC (Barnes et al., 2005). In addition, evaluation of lymph node metastasis (negative or positive), surgical margin, perineural and lymphatic invasion were carried out.

Immunohistochemical study

a) Immunohistochemical staining

Two sections were prepared from each case on positively charged slides and subjected to immunohistochemical staining using the streptavidin – biotin alkaline phosphate methods for expression of monoclonal antibodies for EMMPRIN (mouse monoclonal sc-21746 antibody; dilution 1:100; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) and Ki67 (mouse monoclonal sc-21743 antibody; dilution 1:50; Dako-cytomation). The sections were placed in an oven at 50 °C for 30 min and were deparaffinized in xylene, rehydrated in graded alcohol dilution, washed in PBS, incubated with 0.3% hydrogen peroxide to block endogenous peroxidase activity, washed in PBS again and boiled in citrate buffer solution (pH 6.0) using a microwave for 10 min at 60°C for antigen retrieval. After cooling at room temperature, the sections were incubated with primary antibody overnight in a humidified chamber. Rinsed with PBS, the sections were incubated for 30 min at 37 with biotinylated secondary antibody and streptavidin conjugated to horseradish peroxidase, respectively. After three rinses with PBS, the sections were incubated with diaminobenzidine substrate, then rinsed with distilled water and counterstained with hematoxylin.

Positive control for two antibodies was normal buccal mucosa. Negative controls were prepared by omitting the primary antibody under identical test condition.

b) Interpretation of immunohistochemical staining EMMPRIN (CD147) scoring

Cytoplasmic and membranous staining for EMMPRIN was accepted as positive. Each slide was evaluated according to staining extent and intensity. The extent of staining was calculated as the percentage of stained cells and was scored semiquantitatively, using a 0 to 4 scale for expression, where 0 = no expression, 1 = 1-25%, 2 = 26-50%, 3 = 51-75% and 4 = 76-100%, staining intensity was also categorized into three groups, where 1 = weak, 2 = moderate and 3 = strong. Staining extent and intensity scores were added to give combined scores that were then allocated to 4 groups in which the categories were: 0-1, negative staining; 2-3, weak staining; 4-5, moderate staining; and 6-7, strong staining (Kefeli et al., 2010).

For statistical purposes, staining in cancer cells was further divided into two groups; low expression and high expression scores according to (score 2-3 and 4-5) and (score 6-7) respectively.

Ki-67 scoring

Semiquantitative evaluation marking was performed in accordance with (Maheshwari et al., 2013) in this respect, presence of brown precipitate at the site of target antigen (nucleus) was indicative of positive immunoreactivity. Those histological section with uniform and good intensity staining were assessed for scoring from 1-3.

1- +++ - High proliferation >50% positive cells.
2-++ - Moderate proliferation 30-50% positive cells.
3- + - Low proliferation 10-30% positive cells.
Statistical analysis:
Data were collected, revised, coded and entered to the statistical package for social science (SPSS) version 17. The qualitative data were presented as number and percentages and compared together using Chi-square test while the quantitative data were presented as mean, standard deviations and ranges and the comparison between more than two groups were done by using One Way Analysis of Variance (ANOVA) test. The confidence interval was set to 95% and the margin of error was set to 5%. Differences were considered statistically significant when $P$ is 0.05 or less, highly significant when $P$ is less than 0.01 and not significant when $P$ is more than 0.05.

3. Results
Clinicopathological results
This study was carried out on 35 OSCC cases. The age of patients range from 22 to 75, the most of the cases 24 (68.6%) aged were above 60 years with males predominance 25/35 (71.4%). The most common site was the tongue 14/35 cases (40%). Clinicopathological data of the studied cases are displayed in Table (1).

Table 1 – Clinicopathological parameters of 35 OSCC

| Clinicopathologic parameters | Frequency | Percent%
|-----------------------------|-----------|---------
| Age                         |           |         |
| Age > 60 years              | 24        | 68.6%   |
| Age < 60 years              | 11        | 31.4%   |
| Gender                      |           |         |
| Female                      | 10        | 28.6%   |
| Male                        | 25        | 71.4%   |
| Site                        |           |         |
| Check                       | 7         | 20%     |
| Floor                       | 6         | 17.1%   |
| Hard palate                 | 3         | 8.6%    |
| Lip                         | 5         | 14.3%   |
| Tongue                      | 14        | 40%     |
| Stage                       |           |         |
| Stage I                     | 5         | 14.3%   |
| Stage II                    | 13        | 37.1%   |
| Stage III                   | 5         | 14.3%   |
| Stage IV                    | 12        | 34.3%   |
| Histologic grade            |           |         |
| Grade I                     | 15        | 42.8%   |
| Grade II                    | 10        | 28.6%   |
| Grade III                   | 10        | 28.6%   |
| LN metastasis               |           |         |
| Negative                    | 20        | 57.2%   |
| Positive                    | 15        | 42.8%   |
| Surgical margin             |           |         |
| Negative                    | 20        | 57.2%   |
| Positive                    | 15        | 42.8%   |
| Perineural invasion         |           |         |
| Negative                    | 25        | 71.4%   |
| Positive                    | 10        | 28.6%   |
| Lymphatic invasion          |           |         |
| Negative                    | 27        | 77.1%   |
| Positive                    | 8         | 22.9%   |

Immunohistochemical results
EMMPRIN expression and its correlation with clinicopathologic factors
All studied cases of OSCC (100%) showed positive EMMPRIN immunoreactivity with variable amounts ranging from low to high expression. In normal oral mucosa, staining was localized to the keratinocyte cell membrane with a slightly enhanced reactivity in the basal cell layer. In tissue sections of OSCC, antibodies to EMMPRIN reacted with the cell membrane throughout the entire specimen. Cytoplasmic and membranous staining pattern were acquired by tumor cells, also expressed in the adjacent connective tissue cells mainly fibroblasts and endothelial cells. Twenty six (74.3%) cases were with high expression and 9 (25.7%) cases were with low expression scores. Correlation of EMMPRIN immunohistochemical expression with different clinicopathological variables in the studied cases showed a significant positive associations between EMMPRIN high expression with pathological stage and tumor grade ($P=0.047$ and 0.005 respectively). EMMPRIN expression was found to be significantly associated with an increasing invasiveness of the tumor. Similarly, low-grade tumors (G1) were associated with low EMMPRIN expression scores, whereas high-grade tumors (G2 and G3) showed higher expression scores. However no significant correlation with other clinicopathologic parameters (Table 2) (Fig 1, A-D).
Table 2: Correlation between EMMPRIN/CD147 expression and clinicopathological characteristics in OSCC cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EMMPRIN (CD147)</th>
<th>Chi-square test</th>
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<tr>
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<td>Low Expression score</td>
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<td>Age</td>
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<td>Age&gt;60 years</td>
<td>7</td>
<td>77.8%</td>
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<tr>
<td>Age&lt; 60 year</td>
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<td>Gender</td>
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<td>Female</td>
<td>3</td>
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<td>Male</td>
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<td>Site</td>
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<tr>
<td>Check</td>
<td>3</td>
<td>33.3%</td>
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<tr>
<td>Floor</td>
<td>2</td>
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<td>Hard palate</td>
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<td>Lip</td>
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<td>Tongue</td>
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<td>LN</td>
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<td>Lymphatic invasion</td>
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<td>Stage II</td>
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<td>Grade III</td>
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Fig. (1): Immunohistochemical staining of EMMPRIN/CD147 expression in OSCC tissues. (A, B) Low focal expression EMMPRIN score in grade I OSCC (X200, 400). (C) High diffuse EMMPRIN expression score in grade II OSCC with peritumoral fibroblasts staining (X200). (D) High membranous EMMPRIN expression score in grade III OSCC (X400).
Ki-67 expression and its correlation with clinicopathologic factors

Ki-67 expression was identified at nuclear level in all analyzed cases. Eighteen cases (51.4%) were with low and moderate proliferation scores and 17 cases (48.6%) were with high proliferation score presenting high intensity at level of invasive front. Statistical analysis demonstrated a significant positive association between high Ki-67 immunostaining scores and tumor grade \((P = 0.003)\) i.e. the more the increase of the tumor grade, the higher the Ki-67 expression score. The Ki-67 staining pattern in these poorly differentiated tumors showed a more uniform distribution, as compared with the stratification revealed by the Ki-67 pattern in the well-differentiated tumors. No significant associations were detected between Ki-67 expression and other clinicopathological characteristics. (Table 3) (Figs 2, A-D).

<table>
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<th>Table 3- Correlation between Ki-67 expression and Clinicopathological characteristics in OSCC cases</th>
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Fig. (2): Immunohistochemical staining of Ki67/MIB1 in OSCC tissue. (A) Ki-67 moderate proliferation score in grade I OSCC. The carcinoma cells in the periphery of the nests stain strongly for Ki-67 more than in the center of the nests. (X200). (B) Ki-67 expression at level of invasive front (arrow) (X100). (C), (D) Ki-67 high proliferation score in grade III OSCC. Carcinoma cells form small clusters or nests without differentiation or keratin pearls. The carcinoma cells in the nests are diffusely stained strongly for Ki-67. The tumor stroma is negative for Ki-67 staining (x400).

Correlation between EMMPRIN and Ki 67 expression in OSCC

The correlation between EMMPRIN and Ki67 immunostaining scores is shown in Fig. 3. Overall, a significant positive correlation was observed between Ki67 and EMMPRIN expression in OSCC ($P=0.001$). Most of cases with EMMPRIN high expression scores presented with high Ki67 proliferation scores (Table 4).

4. Discussion

Oral squamous cell carcinoma (OSCC) is the most frequent type of cancer of the head and neck area. Better understanding of the molecular mechanisms regulating tumor invasion and metastasis for OSCC may lead to more effective treatment options (Huang et al., 2014). In the current work, it has been chosen as a subject of study.

| Table 4 Correlation between EMMPRIN and Ki 67 expression in OSCC |
|----------------|----------------|----------------|---------------|
| EMMPRIN (CD147) Scoring | Ki67 scoring | Chi-square test |
| | Low & Moderate proliferation | High proliferation | $X^2$ | $P$-value |
| Low expression | 9 | 50.0% | 0 | 0.0% | 11.442 | 0.001 |
| High expression | 9 | 50.0% | 17 | 100.0% |
| Total | 18 | 100.0% | 17 | 100.0% |

Fig. 3: Significant positive correlation between EMMPRIN and Ki-67 expression scores in OSCC.
Oral carcinogenesis is a multistep phenomenon whose progression is segregated into the early and late stages. Earliest morphological changes are potentially malignant oral lesions of leukoplakia and erythroplakia with dysplasia. A series of molecular events bring about this progression from normal to dysplasia to carcinoma in situ to invasion and eventual metastasis, that is associated with controlled proteolysis, and involves interactions between the tumor cells and the extracellular matrix (ECM) mediated by various soluble and cell surface molecules including EMMPRIN (Shrestha et al., 2014). The role of EMMPRIN in tumor growth and invasion was illustrated by the accelerated growth and increased invasiveness of EMMPRIN-overexpressing human breast cancer cells (Lescaill et al., 2012).

Being an important factor in epithelial-connective tissue interactions, EMMPRIN might be involved in OSCC progression and metastasis, so this study has been chosen to evaluate expression of EMMPRIN in OSCC and correlate with cellular proliferation and clinicopathologic parameters.

In the current work, all the examined cases of OSCC showed positive EMMPRIN immunoreactivity with high expression in more than two-thirds of the cases (74.3%). This suggests that EMMPRIN play an important role in oral tumor progression. Similarly, the high EMMPRIN positivity has been reported in OSCC by Monteiro et al. (2014), and many cancers including; hepatocellular carcinoma (Zhang et al., 2007), cervical cancer (Ju et al., 2008) and lung adenocarcinoma (Siens et al., 2008). Lower expression rate has been reported by Huang et al. (2009) in tongue squamous cell carcinomas (67%), Zhang et al. (2012) in OSCC (65.71%), also reported by Gou et al. (2014) in laryngeal carcinoma (87.5%).

In the present study, EMMPRIN showed cytoplasmic and membranous staining patterns for the positive cells. This result is in accordance with studies done by Piao et al. (2012) and Yang et al. (2013) who examined its immunohistochemistry in hypopharyngeal carcinoma and salivary duct carcinoma respectively. This expression pattern can be attributed to EMMPRIN's structure, as it has a cytoplasmic and membranous domain which was previously described by Iacono et al. (2007).

Our results showed EMMPRIN expression was significantly associated with histological grade. Moderate and poorly differentiated tumors showed EMMPRIN high expression than well differentiated tumors. This result is supported by study done by Monteiro et al. (2014) who observed that the expression of EMMPRIN protein in well-differentiated tumors was lower than that in moderately and poorly differentiated tumors in OSCC. Also in accordance with Feng et al., 2013 who found the same association in esophageal cancer, colon cancer, cervical cancer, lung cancer, ovarian cancer, and hepatocellular carcinoma. These observations strongly suggest that the EMMPRIN might be actively involved in the growth, invasion and metastasis of OSCC. Furthermore, the measurement of EMMPRIN levels may assist in predicting patients’ prognosis. Conflicting result done by Huang et al. (2009) in tongue SCC.

In the current study we observed that EMMPRIN high expression was noted with advanced clinical stage. This result is in line with Huang et al. (2009), emphasizing that EMMPRIN, plays a crucial role in tumor progression, invasion and metastasis in head and neck squamous cell carcinoma so it may represent a useful biomarker for prognostic evaluation. Uncontrolled proliferation of cells is one of the most important biological mechanisms associated with oncogenesis, a number of studies indicating that proliferation has prognostic value in a variety of tumors. Ki-67 is one of the mitotic indicators in proliferative activity of tumors. Expression of Ki-67 in mean of proliferative activity of tumor cells is one of the indicators for tumor invasion potential and invasive activity of cancers related to degree of malignant neoplastic cells (Motta et al., 2009). In our study, all the cases showed Ki-67 expression. A similar observation was reported by Raju et al. (2005); Dragonier et al. (2012). The present work showed a statistically significant relationship between Ki-67 and tumor grading. The highest Ki-67 expression was found in poorly differentiated squamous cell carcinoma and presenting high intensity at the tumoral invasion front which is the most important area for prognostic determination of oral cancer. It consists of many molecular and morphological characteristics that reflect tumor progression better than other parts of the tumor. Several molecular events of importance for tumor spread such as gains and losses of adhesion molecules, secretion of proteolytic enzymes, increased cell proliferation and initiation of angiogenesis occur at the invasive front. Results similar to those found in this study was reported in previous studies in OSCC (ARUL et al., 2011; Humayun and Prasad, 2011; Maheshwari et al., 2013; Dwivedi et al. 2013). The expression of Ki-67 is correlated with the grading of OSCC as it depicts the growth fraction of the tumor and its proliferative status increased according to the aggressiveness of the tumor. Conflicting results on the relationship of Ki67 with OSCC grade observed by studies done by Roland et al. (1994); Bettendorf & Herrmann (2002).

Hence, the present study suggests that the Ki-67 expression in OSCC is significant and useful in predicting histologic grade of differentiation,
prognosis of the lesion and determining survival rates. To explore the mechanism about the regulatory effect of EMMPRIN on tumor growth, we examined expression of Ki-67, a good proliferation marker and consequently found a significant positive correlation between the two parameters, high EMMPRIN expression has been related to high Ki-67 scoring (p=0.001) suggesting that increased EMMPRIN expression in cancer cells might be associated with adverse disease outcome. Similar results shown by previous studies (Yang et al., 2010; Zhao et al., 2013; Monteiro et al., 2014). Yang et al.(2006) reported a mechanism by which EMMPRIN provides resistance of cancer cells to anoikis, a form of apoptosis induced by loss of matrix or cellular attachment and often defective in tumor cells that are of epithelial origin and show that the effect of EMMPRIN appears to result from MAP kinase-mediated down-regulation of a BH3-only proapoptotic protein, Bim. Mariëb et al.(2004) documented that upregulated EMMPRIN expression stimulates hyaluronan production by elevating hyaluronan synthases, which is closely related to the anchorage-independent growth of cancer cells. These results supported the opinion that EMMPRIN might enhance tumor growth of carcinoma by disrupting the balance between apoptosis and proliferation. Silencing EMMPRIN in head and neck squamous carcinoma (HNSCC) cells was shown to result in significant suppression of tumor growth(Lescaille et al., 2012).

In conclusion, this study showed increased expression of EMMPRIN in more than two third of cases with statistical significant association with proliferative marker. This finding highlight the importance of EMMPRIN in cancer progression, indicating that EMMPRIN could be an attractive target for immunotherapeutic approaches in a group of patients with OSCC and could thus be considered as an objective and effective marker to predict the invasion and prognosis of OSCC. Further functional studies are needed to clarify the efficacy of anticancer therapy targeting these signal factors.

References:

12/21/2014