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ORIGINAL ARTICLE

Immunohistochemical Expression of Epidermal Growth Factor Receptor in Different Histopathological Grades of Muco-epidermoid Carcinoma of Salivary Glands

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ABSTRACT

Objective: To determine the immunohistochemical expression of Epidermal Growth Factor Receptor (EGFR) in different histopathological grades of mucoepidermoid carcinoma (MEC) in salivary glands.

Patients and Methods: This cross-sectional study was conducted from August 2015 to September 2016 at Armed Forces Institte of Patholgy Rawalpindi (AFIP), to determine the immunohistochemical expression of Epidermal Growth Factor Receptor (EGFR) in different histopathological grades of mucoepidermoid carcinoma (MEC) in salivary glands. Thirty cases of MEC were retrieved from record files along with their paraffin blocks at AFIP, Rawalpindi. New histological diagnosis was made on freshly prepared Hematoxylin and Eosins section followed by application and analysis by immunostaining. Chi-square test was used to find the effect of EGFR on different grades of MEC.

Results: Out of 30 cases, 24 cases were positive for EGFR. In case of low-grade mucoepidermoid carcinoma, 8 cases were weak positive, whereas remaining six were negative. Out of eight cases of intermediate grade mucoepidermoid carcinoma, 3 were week positive, whereas remaining five are strong positive. In high grade mucoepidermoid out of eight cases seven were strong positive. P-value for EGFR was calculated as .036. EGFR expression increased with increase in grade of tumor.

Conclusion: The expression of EGFR increased with increase in grade of tumor.

Key words: EGFR, Mucoepidermoid carcinoma, Salivary Glands

Author`s Contribution
[1-2] Conception, synthesis, planning of research and manuscript writing Interpretation and discussion
[3] Data analysis, interpretation and manuscript writing, Active participation in data collection.

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Introduction

Tumors of salivary glands have an important place in oral and maxillofacial pathology, having incidence of 5% around world.[1] Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of salivary glands, accounting for 15.3% of all tumors and 56.9% of malignant tumors .[2] This tumor is composed of three intermixed type of cells: mucin-producing cells, intermediate cells or clear cells, and squamoid cells.[3] Mucoepidermoid carcinoma shows a variety of biological behavior that is correlated with histopathological grades of

tumor.[4] All treatment plans are based exclusively on histopathological grades. Number of microscopic grading systems based on specific microscopic parameters have been described to find the grades of mucoepidermoid carcinoma.[5] EGFR is a "tyrosine kinase receptor" of ErbB family. EGFR is a membrane glycoprotein and has an extracellular ligand -binding domain, a transmembrane lipophilic part and an intracellular protein kinase domain. EGFR is present on chromosome 7p12 and in many types of cancers. It is involved in proliferation, angiogenesis and metastasis of cancer cells. EGFR encodes membrane glycoprotein that is activated by phosphorylation.[6-8]

In many cases of MEC of salivary glands, EGFR protein is strongly expressed.[9] In high grade of MEC, the oncogenic glycoprotein MUC1 is greatly expressed.[10] MUC1 react with EGFR and cause activation of MAPK in mouse model. In MEC of salivary glands, ERK1/2 MAPKs expression is high in high grade MEC.

Patients and Methods

This cross-sectional study was conducted from August 2015 to September 2016 The study included thirty cases of mucoepidermoid carcinoma. The data was collected from clinical histories given with each case. Blocks were cut and stained with Hematoxylin and Eosin stains. Necrosed, scanty and autolysed tissue samples were excluded. After diagnosing on microscopy, histopathological grading was done according to Auclair et al and Goode criteria.[11,12]

Expression of EGFR on different grades of MEC was calculated by evaluating the percent of positive stained cells under the objective lens of power 40 with microscope.[12] Positive staining appeared as a linear to finely granular pattern in cell membrane and adjacent cytoplasm. Chi-square test was used to find out the association of EGFR with different grades of tumor. P value >0.05 was taken as significant

Results

Among 30 cases, 23 patients were males and remaining 7 were females. Anatomically, 22 patients had tumor in parotid glands, while 4 had in submandibular areas. Other tumors were in palate, retromolor area, and in posterior 1/3 of tongue. Most of patients had age between 40 to 60 years.

Immunohistochemical labeling patter:EGFR was applied to all 30 cases of Mucoepidermoid carcinoma. Both membranous and cytoplasmic stainings were considered. Among thirty cases eight cases were negative (-), while 24 were positive. Out of 24 positive 16 were weak positive (+), while 8 were strong positive (++). The low grade MEC was diagnosed in 14 cases, out of these 6 cases were negatively stained (-) and remaining 8 were weak positive (+). In intermediate grade

MEC, 3 cases were weak positive (+) while 5 cases were strong positive (62.5%), where as in high grade MEC one case was weak positive (12.5%) while the rest 7 were strong positive (87.5%) Chi-square test was applied to evaluate the association of EGFR and grades of tumor. P value of .036 was calculated and was significant. (Table 3).

Table 1: Scoring System

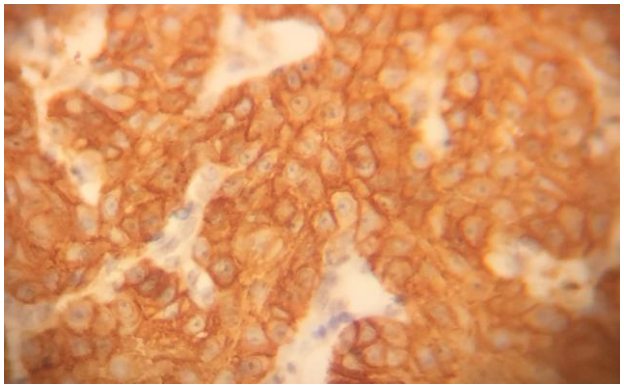
Intra cystic component <20%	2 Points
Neural invasion present	2 Points
Necrosis	2 Points
Mitosis (4 or more per 10 HPF)	3 Points
Anaplasia	4 Points
The quantitative grading system by these scores is:	
Low grade	0-4points
Intermediate grade	5-6points
High grade	7-14points

Table 2:Score Assessment of Immunoreactions

Score	Assessment
Negative	<5% of positive cells
Week positive	5 -50%of positive cells
Strong positive	>50% of positive score

Table 3: Expression of EGFR in different grades of tumors

Grades	**>50% (++)**	**5-50% (+)**	**<5% (-)**	**Total**	**P-value**
Low	0	8	6	14	0.036
Intermediate	5	3	0	8	
High	5	1	0	8	
Total	10	12	6	30	



igure 1: Strong membranous positivity of EGFR in High grade Mucoepidermoid carcinoma (40x100)

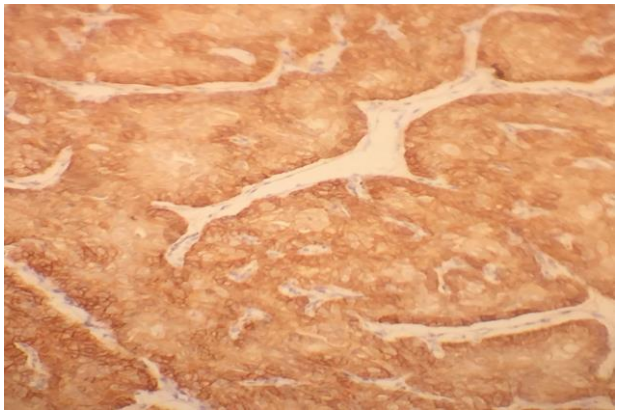


Figure: 2 High membranous positivity of EGFR in High grade MEC (10x10 Magnification)

Discussion

The EGFR/ErbB1 is a gene located on chromosome 7p12. This gene encodes membrane glycoprotein that is activated by phosphorylation. This activation induces a downstream signalling transduction cascade.[13] It is over expressed in many tumors like head and neck tumors, glioblastoma, lung, breast, ovaries and bladder. In the present study, we evaluated the expression of EGFR on different histopathological grades of MEC.

There are few studies present in literature showing expression of EGFR on MEC. In study conducted by Khiavi et al in 2012, out of 40 patients 2 were negative (4.3%), 12 week positive (26.1%) and 32 were strong positive (69.6%). The EGFR expression was cytoplasmic that is contrary to present study, as it had both cytoplasmic and membranous expressions. In another study conducted by Al-Ani in 2012[14], out of seventeen patients all were EGFR immunopositive. No statistical significant correlation was seen among marker and grading systems. According to above mentioned study, 9 cases were weak positive and remaining 8 cases were strong positive. EGFR in this study showed membranous expression.

In 2010, Lujan et al conducted a study to check relation of EGFR expression in salivary glands MEC of high grade.[15] Out of 42 cases, 34(79%) cases were positive for protein expression. Expression of EGFR was high in high grade MEC, so it was more positive in aggressive tumors. They considered only continuous membranous staining of EGFR as strong positive. In contrast, we considered both cytoplasmic and membranous staining.

In a study conducted by Hoyek-Gebeily et al in 2007, in which they checked the prognostic significance of EGFR in MEC of the salivary gland, 75% of cases are positive for EGFR staining.[16] They considered only membranous staining and found high expression of EGFR in high grade so have poor prognosis.

Conclusion

Expression of EGFR is strongly positive in high grade MEC and in few cases of intermediate grade MEC. In low grade MEC, EGFR has both negative and week positive expression. EGFR showed both membranous and cytoplasmic expression.

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