Original Article

Expression of HER2 in adenoid cystic carcinoma and mucoepidermoid carcinoma of salivary glands as a prognostic marker

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Objectives: To determine the expression of HER2 in adenoid cystic and mucoepidermoid carcinoma of salivary glands, if can be used as a prognostic marker as well as for therapeutic approach.

Methodology: Forty cases of mucoepidermiod carcinoma (n=20) and adenoid cystic carcinoma (n=20) were taken from various hospitals of Lahore. Relevant clinical data was recorded and blocks were examined for histological diagnosis. HER2 immunopositivity was assessed by immunohistochemistry. Tumors with (+2) to (+3) score were considered as positive for overexpression.

Results: Mean age was 32.35±13.674 and 41.50±12.224 while male to female ratio was 1.5:1 and 1:1.5 in mucoepidermoid carcinoma and adenoid cystic, respectively. Parotid gland was the common site in mucoepidermoid carcinoma, while minor salivary glands was the most affected site in adenoid cystic carcinoma. Both carcinomas were found on the right side mostly. In mucoepidermoid carcinoma, 40% were grade III and 35% and 25% were grade I and III, respectively. Out of 20 cases, 80% were grade I while 5% and 15% were grade II and grade III correspondingly in adenoid cystic carcinoma. Lymph node involvement was seen 45% of mucoepidermoid carcinoma while it was not present in adenoid cystic carcinoma.

HER 2 immunopositivity was seen as brownish membranous staining in 85% among 100 cases of both mucoepidermoid carcinoma adenoid cystic carcinoma. Statistically, significant association was found between HER2 expression and tumor grade.

Conclusion: Positive expression of HER2 in both mucoepidermoid and adnoidcyctic carcinoma shows the development and progression of carcinoma. It could be used as a prognostic marker and also for potential therapeutic approach. (Rawal Med J 201;43:354-357).

Key words: Mucoepidrmoid carcinoma, adenoid cystic carcinoma, HER2.

INTRODUCTION

The human epidermal growth factor receptor (HER) is a family of receptors that play a significant role in the pathogenesis of various human cancers. It regulates cell growth, survival, and differentiation through multiple signal transduction pathways. There are four main members of this family: HER-1, HER-2, HER-3, and HER-4, also called ErbB1, ErbB2, ErbB3, and ErbB4, respectively.[1]

The HER2 receptor is a 1255 amino acid, 185 kD trans membrane glycoprotein present at the long arm of human chromosome 17 (17q12).[2] HER2 is expressed in many tissues and its major role in these tissues is to facilitate excessive/uncontrolled cell growth and tumor genesis. HER2 has no recognized ligand but it can undergo heterodimerization with any of the other three HER proteins thus, participating in signal transduction cascade with varied effects that potentiate the malignant phenotype.[3] HER2 overexpression can be seen in different forms of cancers such as breast, stomach, ovary, uterine serous endometrial carcinoma, colon, bladder, lung, uterine cervix, head and neck, and esophagus. It is not only involved in the development of various cancers, but has also been strongly assessed for a therapeutic purpose.[4]

Salivary gland tumors are about 80% are benign, while malignant tumors are rare, containing less than 0.5% and about 5% of head and neck cancers.[5] Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignant tumor. Theses tumors are graded into low, intermediate and high grade, depending on adverse features like perineural, angiolymphatic invasion, coagulative

necrosis, high mitotic rate, cystic element >20 %, anaplasia and infiltrative growth.[6] Adenoid cystic carcinoma forms around 1% of all oral and maxillofacial malignant tumors and 21.9% among salivary gland malignancies.[7] It has three morphologic forms tubular, cribriform and a solid pattern. Increased local recurrence, high metastatic rate and mortality is seen in solid variant.[8] The aim of this study was to determine the expression of HER2 in adenoid cystic and mucoepidermoid carcinoma of salivary glands, if can be used as a prognostic marker as well as for therapeutic approach.

METHODOLOGY

This study was conducted at the Department of Morbid Anatomy and Histopathology University of Health Sciences, Lahore, Pakistan after the ethical approval from review board committee of university. We took paraffin embedded blocks of 40 cases containing both mucoepidermoid carcinoma (n=20) and adenoid cystic carcinoma (n=20) from Histopathology department of University of Health Sciences, King Edward Medical College/Mayo Hospital, Fatima Jinnah Medical College/ Ganga Ram Hospital and Sheikh Zayed Hospital, Lahore. The duration of study was six months. All were excisional biopsies of primary tumor. Clinical data including patient's age, gender, site and laterality was collected from the particular departmental records. To assure the diagnosis slides were looked by light microscope by at least three histopathologists.

Table 1. HER2 assessment scoring.

Score	0	+1	+2	+3
	Staining in _10% of tumor cells or no staining;	Faint and partial membrane staining in _10% of tumor cells	Weak to moderate complete membrane staining in _10% of tumor cells	Moderate to strong complete membrane staining in _10% of tumor cells

For immunohistochemistry, sections were incubated with a primary monoclonal anti HER2 antibody (DAKO) and DAB chromogen was applied to the sections followed by counter staining with hematoxylin. For assessment of HER2, slides were scored from 0 to +3. Scores of either +2 or +3 were marked as overexpression (Table 1). Chi square and Fisher' Exact test were applied to determine the association between grade of tumor and HER2 expression.

RESULTS

Mean age was 32.35±13.674 and 41.50±12.224 years in mucoepidermoid carcinoma and adenoid cystic carcinoma, respectively. There were 12 males and 8 females in mucoepidermoid carcinoma and 8 males and 12 females in adenoid cystic carcinoma patients.

In mucoepidermoid carcinoma, 70% (n=14) cases were seen involving parotid gland followed by minor salivary glands, submandibular salivary and sub-lingual glands, respectively. While in adenoid cystic carcinoma 80% (n=16) cases were reported in minor salivary glands followed by parotid and sublingual salivary glands respectively. Most cases were on right side.

Mucoepidermoid carcinoma grading was done on criteria by Auclair et al based on intracystic component, neural invasion, necrosis, mitosis and anaplasia.9 A total of 40% cases were graded as grade III while 35% and 25% were of grade I and II, respectively. Grading according to Spiro et al10 who proposed mostly tubular or cribriform with infrequent solid as grade I, mixed with significant solid (>50%) as grade II and only solid as grade III. Out of 20 cases, 80% were graded as I while 15% and 5% were of grade III and II, respectively. Among 20 cases, 45% showed lymph node involvement in mucoepidermoid carcinoma while it was absent in all cases of adenoid cystic carcinoma. Positive and overexpression of HER2 was seen both in mucoepidermoid and adenoid cystic carcinoma.

Table 2. HER2 immunoexpression in Mucoepidermoid and Adenoid Cystic Carcinoma.

HER 2 Expression Score	+3	+2	+1	0
Mucoepidermoid Carcinoma	15%	45%	35%	5%
Adenoid Cystic Carcinoma				

Among 20 cases of mucoepidermoid carcinoma, overexpression of HER2 (score +2 & +3) was seen in 60% (n=12) cases collectively. While in adenoid cystic carcinoma only 45% (n=9) cases showed overexpression (score +2 & +3) (Table 2). Statistically, significant association was seen between grade of tumor and HER2 expression ($p<0.05$).

DISCUSSION

Mucoepidermoid carcinoma is an epithelial malignant neoplasm having mucous, epidermoid, intermediate, columnar, clear, and oncocyticcells.[11] Adenoid cystic carcinoma is a malignant epithelial tumor and has different growth pattern mainly cribriform, tubular, and solid which can be seen within the same lesion.[12] Salivary glands tumors (SGTs) demonstrate significant discrepancies with regard to clinical facets, biology and clinical behavior.[13]

In present study, mean age was 32.35±13.674 and 41.50±12.224 which is similar to 42.3 years in salivary gland carcinomas observed by Vasconcelos et al.[14] Another study by Zaman et al reported mean age of 36.33years and 54.4 years for mucoepidermoid carcinoma and adenoid cystic carcinoma, respectively.[15]

Our observations showed parotid gland to be the common site of involvement followed by minor salivary glands, submandibular and sublingual salivary glands in mucoepidermoid carcinoma. Araya et al reported similar findings.[16] Out of 20 cases, 40% of MEC were graded as III followed by I (35%) and II (25%). Derek Kofi et al graded mucoepidermoid carcinoma into grade I (48%), grade II (45%) and grade III (7%) in his study.[17] Lymph node involvement was seen in 45% cases of mucoepidermod carcinoma while Derek Kofi et al reported it in only 10% cases.[17] Among 20 cases of adenoid cystic carcinoma, 80% were graded as I while 15% as grade III and only 1 % grade II. van Weert et al graded 49% cases of adenoid cystic carcinoma as II, 27% and 23% as grade III and I respectively.[18]

A number of molecular targets like HER-2 have been known now with rapid advances in molecular studies.[19] HER-2 protein shows an important role in pathogenesis of many cancers including breast, ovary, gastric, prostate, lung and head and neck cancers indicated by its overexpression.[20] HER-2 protein over-expression is also found in different types of salivary gland carcinomas like salivary duct carcinoma, adenocarcinoma and adenoid cystic carcinoma.[21] The mechanism of HER-2 protein overexpression is genomic amplification similar to breast cancer.[22]

In our study, the frequency of HER2 overexpresion was observed in 60% cases of mucoepidermoid carcinomas while Glisson et al found it in 21% cases.[23] The frequency of overexpression of HER2 was observed in 45% cases of adenoid cystic carcinoma in present study while only 4% cases of adenoid cystic carcinoma showed immunopositivity in study by Glisson et al.[23] Overexpression of HER-2 in salivary gland cancer is associated with high-grade malignancy and poor prognosis.[21]

CONCLUSION

Positive expression of HER2 in both mucoepidermoid and adenoidcyctic carcinoma showed development, aggressive behavior and progression of carcinoma. It is usually associated with poor prognosis and aggressive behavior. Thus, it could be used as a prognostic marker and also for potential therapeutic approach.

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