Intraoral Mucoepidermoid Carcinoma of Salivary Glands: Lack of Association Among Clinicopathological Features and Immunoexpression of c-erbB-2 in 29 Cases

**Carcinoma Mucoepidermoide de Glândulas Salivares Intraoral:
Factores Clínicos y Patológicos e Imunoexpresión de c-erbB-2 en 29 Casos**

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SUMMARY: The association among clinicopathological features and c-erbB-2 oncoprotein expression was evaluated in twenty-nine cases of intra-oral mucoepidermoid carcinoma (MEC). MEC was prevalent in the female gender (79.3%), tumors were more frequent in ages between 21 and 40 years (48.3%), and the palate was the most commonly affected site (72.4%). Microscopically, 27 cases (93.1%) were classified as low grade of malignancy. The c-erbB-2 expression was considered positive in 9 (31%) cases and no significant association ($p>0.05$) was found among protein expression and gender nor between patient age and site or histological grade of the lesion. c-erbB-2 expression in MEC may reflect intrinsic biologic properties of salivary gland neoplasms and may be linked to histogenesis and cellular differentiation.

KEY WORDS: c-erbB-2; Her-2/neu; Immunohistochemistry; Mucoepidermoid carcinoma; Salivary gland neoplasms.

INTRODUCTION

The c-erbB-2 proto-oncogene, also known as Her-2/neu, is located on chromosome 17 and encodes a cell-surface transmembrane glycoprotein known as p185neu. Its intracellular component has a tyrosine kinase activity, whereas the extracellular domain may act as a growth factor receptor because of its considerable homology with epidermal growth factor receptor (Nguyen *et al.*, 2003). The c-erbB-2 oncoprotein is involved in matrix degradation and proteolytic activity as well as in the increase in vessel permeability, endothelial cell growth, proliferation, migration, and differentiation (Verbeek *et al.*, 2003; Sanderson *et al.*, 2006) inducing and maintaining oncogenesis in a great number of human malignancies.

The amplification and/or overexpression of c-erbB-2 in human tumor tissue has been associated with a poor prognosis in ovarian, endometrial and breast carcinoma (Weed *et al.*, 2004). Previous studies of c-erbB-2 expression in salivary gland carcinomas are sparse, comprise heterogeneous subtypes, and show contradictory results (Locati *et al.*, 2005).

Mucoepidermoid carcinoma (MEC) is the most common malignant neoplasm of major and minor salivary glands (Lopes *et al.*, 2006). MEC is reported to manifest variable biologic aggressiveness, basically showing correlation with its histological features and is graded by a 3-tiered system (Auclair *et al.*, 1992).

Conflicting results have been reported with regard to c-erbB-2 overexpression in mucoepidermoid carcinoma, with reported rates ranging from absent to 38% (Sugano *et al.*, 1992; Press *et al.*, 1994; Suzuki *et al.*, 1998). Different conclusions may be attributed to the varying techniques used, criteria applied to determine positive c-erbB-2 expression, the diversity of lesions and the limited number evaluated in some studies.

Few papers evaluating only one type of oral salivary gland tumors are available. Thus, the aim of this study was to analyze a series of intraoral MEC for expression of the c-erbB-2 oncoprotein and its possible association with the clinicopathologic features of the sample.

MATERIAL AND METHOD

The protocol of this study was approved by the Committee of Bioethics in Research at the Universidade Federal de Minas Gerais, UFMG (COEP-UFMG 345/05).

Patients. From 1953 to 2006 forty cases were diagnosed as MEC from the files of the Oral Pathology Department, School of Dentistry, Universidade Federal de Minas Gerais. For this study only the intraoral MEC surgically treated with adequate material for microscopic and immunohistochemical

analysis corresponding to 29 cases were analyzed. Sinonasal and maxillary tumors were not included in the sample. Clinical information about age, gender, and site were obtained from the biopsy records.

Histopathology. Histopathological diagnosis was revised in new hematoxylin-eosin-stained sections and tumors were graded as low, intermediate, or high according to the histologic grading method of Auclair *et al.*

Table I. Clinicopathological features of mucoepidermoid carcinoma of salivary glands

Case	Age (years)	Gender ^a	Site	Malignancy grade	c-erbB-2/neu expression
1	34	F	Retromolar area	Low	Negative
2	23	F	Buccal mucosa	Low	Negative
3	31	F	Floor of the mouth	Low	Positive (2+)
4	35	F	Palate	Intermediate	Negative
5	20	M	Palate	Low	Positive (2+)
6	35	F	Palate	Low	Positive (2+)
7	53	M	Palate	Low	Positive (2+)
8	66	F	Palate	Low	Negative
9	26	F	Palate	Low	Negative
10	60	M	Palate	Low	Positive (2+)
11	25	F	Palate	Intermediate	Positive (2+)
12	53	F	Palate	Low	Negative
13	14	M	Palate	Low	Negative
14	40	F	Palate	Low	Negative
15	55	F	Palate	Low	Negative
16	65	M	Retromolar area	Low	Negative
17	41	F	Palate	Low	Positive (3+)
18	64	F	Floor of the mouth	Low	Negative
19	73	F	Palate	Low	Negative
20	14	F	Palate	Low	Negative
21	43	F	Palate	Low	Negative
22	32	F	Palate	Low	Negative
23	16	F	Palate	Low	Negative
24	21	F	Retromolar area	Low	Positive (2+)
25	48	F	Retromolar area	Low	Negative
26	55	M	Palate	Low	Negative
27	23	F	Buccal mucosa	Low	Positive (2+)
28	36	F	Palate	Low	Negative
29	28	F	Palate	Low	Negative

aF: feminine / M: masculine

Immunohistochemistry (IHC). IHC was performed with a standard, monoclonal antibody CB11 (Novocastra Laboratories, Newcastle Upon Tyne, UK). Briefly, 4 μ m sections were dewaxed in xylene and hydrated with graded ethanol. Blocking of endogenous peroxidase and avidin-biotin activity were performed (Miller *et al.*, 1999). The slides were placed in a 10 mM ethylenediaminetetraacetic acid (EDTA) buffer, pH 8.0, heated to 96 °C in a steamer for 25 minutes, incubated with the primary antibody for 18h at room temperature, and diluted 1:200 in a 1% bovine serum albumin (BSA). After washing in the Tris-HCl buffer, sections were incubated for 30 min at room temperature with biotinylated multi-link swine anti-goat, mouse, and rabbit immunoglobulin (LSAB kit, Dako, Carpinteria, CA, USA). The reactions were revealed by applying 0.01% diaminobenzidine tetrahydrochloride (DAB) (Sigma-Aldrich, St. Louis, MO, USA) and 0.03% H₂O₂. The sections were counterstained with Mayer's haematoxylin and mounted in Permount (Fisher Scientific, NJ, USA). In situ intraductal carcinoma of the breast was used as a c-erbB-2 positive control and negative controls were obtained by the omission of the primary antibody.

Evaluation of the immunohistochemical staining. Tumors were scored on a 0-3+ scale, as follows: 0, staining in <10% of tumor cells or no staining; 1+, faint and partial membrane staining in $\geq$ 10% of tumor cells; 2+, weak to moderate complete membrane staining in $\geq$ 10% of tumor cells; or 3+, moderate to strong complete membrane staining in $\geq$ 10% of tumor cells. Scores of either 2+ or 3+ were defined as c-erbB-2 overexpression. The slides were independently evaluated by two observers (VFB, MCFA) with neither prior discussion nor knowledge about the clinical features and malignancy grade. Discrepancies were solved by consensus.

Statistical analysis. Significance was evaluated by the Chi-square test using the SPSS program with a $p < 0.05$ significance level (SPSS, 2003).

RESULTS

From 22688 oral biopsies submitted during period between 1953 and 2006, 40 (0.18%) MEC were diagnosed being 29 located in minor

salivary glands. Tumors were more common in the third and fourth decades of life (48.3%), with predilection for females (79.3%). The palate was the most commonly affected site, with 21 cases (72.4%). Other intraoral sites included the retromolar area (4), the buccal mucosa (2), and the floor of the mouth (2). The majority of MECs (27 cases) were classified as low grade of malignancy.

c-erbB-2 positive staining of cell surface membranes (2+ or 3+) was identified in 9 cases (31%) of our series. All positive cases also expressed cytoplasmic staining. Both patterns (cell surface membrane/cytoplasmic staining) were observed in mucous, intermediate and epidermoid cells (Figure 1A). Neither staining was observed in adjacent normal salivary gland nor in the stroma. No significant association ($p > 0.05$) was found among protein expression and gender nor between patient age and site or histological grade of the lesion.

Fig.1. Membranous (arrows) and cytoplasmic (arrowheads) immunoexpression of c-erbB-2 in MEC of mucous, intermediate and epidermoid cells (100x).

DISCUSSION

MEC is the most common malignancy of salivary glands and presents a diverse age distribution (Auclair *et al.*; Lopes *et al.*). However, there are few articles with a significative number of cases (Lopes *et al.*). In our series, patients demonstrated an earlier average age of occurrence, with a peak of incidence in the third and fourth decades of life, whereas previous studies described a prevalence in fifth and sixth decades of life (Auclair *et al.*; Lopes *et al.*). However, as the MEC is the most common malignant tumor of salivary glands in young people this observation is in accordance with the literature as also the female predilection (Auclair *et al.*; Triantafillidou *et al.*, 2006).

Most of the studies show that the palate is the most common site of occurrence (Lopes *et al.*; Kokemueller *et al.*, 2005). In our series the results were similar with 21 (72.4%) cases affecting the hard palate. Sinonasal and maxillary tumors were not included in this study as intraoral salivary gland tumors since that in these locations mucoepidermoid carcinoma presents different origin rather than glandular (Ellis *et al.*, 1991).

Microscopically, most intraoral MEC were classified as low grade of malignancy (27cases - 93.1%), followed by intermediate (2 - 6,9%) and no case of high-grade as expected. Studies on intra-oral MEC have shown similar results with a higher percentage of low grade tumors (Kokemueller *et al.*; Lopes *et al.*). Low grade tumors seem to arise more often in minor salivary glands, which according to some authors are detected at earlier stages, probably due to the less aggressive growth in addition to a better visible tumor site. High grade tumors, on the other hand, seem to arise more often in major salivary glands (Kokemueller *et al.*).

Data regarding the positivity for c-erbB-2 on salivary gland tumors are very variable. Kärjä *et al.* (1994) described positivity in 44% of cases, including malignant and benign tumors. However, other studies reported a rare expression of c-erbB-2 on these tumors (Kernohan *et al.*, 1991; Shrestha *et al.*, 1992).

Concerning MEC, there had been only individual case descriptions of c-erbB-2 expression (Kernohan *et al.*; Shrestha *et al.*) before a study of Press *et al.* These authors observed the gene amplification and protein overexpression of c-erbB-2 in 21% and 38% of MEC respectively. Cho *et al.* (1997) showed a similar prevalence. However, some authors described a far greater rate, with almost 80% of the MEC positive for c-erbB-2 in their series, although the

criteria for analysis of positivity was not presented (da Cruz Perez *et al.*, 2004; Lopes *et al.*). We observed c-erbB-2 membranous expression in 9 (31%) of cases in our series which is in accordance with previous report (Press *et al.*).

We suppose that reasons for this contradictory results are associated with the immunohistochemistry technique, in special with the primary antibody employed and with the subjective interpretation and semiquantitative nature of the results. There is no consensus about the best antibody for the evaluation of c-erbB-2 immunoeexpression (Hanna *et al.*, 2001). The CB11 antibody used here has shown the best concordance with FISH (fluorescent in situ hybridization) technique (Gouvea *et al.*, 2006). This antibody although less sensitive than the polyclonal antibody used in other reports (Lopes *et al.*; Gouvea *et al.*) is considered more specific (Kernohan *et al.*, Handra-Luca *et al.*, 2003; Kamio *et al.*).

Besides, in the present study a standardized method was employed for evaluation of positivity. The high percentage of previously observed positive cases (21 cases, 77.7%) (Lopes *et al.*) as compared to our series (9 cases, 31%) may be due to differences in methods of interpretation.

Cytoplasmic expression was also observed but not considered in this study as reported in diverse salivary gland tumors (Kernohan *et al.*). Although the significance of this cytoplasmic staining remains unknown, Cheng *et al.* (2005) suggested that this pattern reflects degenerated c-erbB-2 fragments with less functional ability. Further studies in order to clarify this point are warranted.

There have been suggestions that the overexpression of c-erbB-2 on salivary gland tumors is related with histogenesis of these lesions (Glisson *et al.*, 2004; Rivière *et al.*, 1991; Gibbons *et al.*, 2001, Rosa *et al.*, 1997). MEC is composed of varying proportions of mucous, epidermoid, columnar, intermediate and clear cells (Auclair *et al.*) and is though to arise from the salivary excretory duct (Ellis *et al.*). Glisson *et al.* suggested that c-erbB-2 has a higher frequency of overexpression in tumors derived from excretory duct (e.g. MEC) than that from intercalated duct. For Rivière *et al.* the expression of c-erbB-2 on salivary gland tumors may reflect accident of genomic reconstitucional events occurring within the differential pathway of mioepithelial/epithelial cells which justify the overexpression of this oncogene in tumors of intercalated duct origin.

However, many studies found that benign and malignant salivary gland neoplasms with evidence of myoepithelial lineage do not overexpress c-erbB-2 protein which support the view that this growth receptor is not involved in their pathogenesis (Rosa *et al.*, Shrestha *et al.*; Kamio *et al.*). In contrast, the c-erbB-2 is expressed by high grade carcinomas as salivary duct carcinoma, high grade carcinoma, and exclusively by the malignant component of carcinoma ex pleomorphic adenoma (Johnson *et al.*, 2008; Nabili *et al.*, 2007; Matsubayashi & Yoshihara, 2007). Although the latter may present myoepithelial derivation, carcinoma ex pleomorphic adenoma probably acquired a particular biological behavior in the longstanding process of malignant transformation. Moreover, Gibbons *et al.* demonstrated a clear difference in the molecular phenotypes of MEC and adenoid cystic carcinoma with only MEC overexpressing c-erbB-2. This provides further support to the existence of distinct molecular mechanisms in salivary gland carcinogenesis associated with the overexpression of c-erbB-2.

Despite the small sample studied our results demonstrated no association among c-erbB-2 expression and demographic or histological grades of MEC. Press *et al.* reported that male gender was significantly associated with neu oncogene amplification and overexpression in MEC. Cho *et al.* and Nguyen *et al.* reported that c-erbB-2 expression was more frequent in high grade tumors than in low grade.

The majority of MEC in minor salivary glands are histologically classified as low grade of malignancy and an association with the c-erbB-2 immunopositivity could be not demonstrated. However, in the study of Lopes *et al.* c-erbB-2 positivity was predominantly observed in low-grade MEC and differently of other studies, negativity for c-erbB-2 correlated with lowest survival rates. Suzuki *et al.* also demonstrated that the overexpression of c-erbB-2

on MEC of parotid gland was associated to a poor prognosis independently of the histological grade.

Thus, our findings may suggest the lack of association among clinicopathological features and the immunoeexpression of c-erbB-2. Moreover, the significance of c-erbB-2 expression in MEC may reflect intrinsic biologic properties of salivary gland neoplasms (Nguyen *et al.*). A greater number of studies involving large series with specific histologic subtypes are necessary to highlight the role of c-erbB-2 in the pathogenesis of salivary gland neoplasms.

CONCLUSION

Considering the results in the appraised sample, our findings suggest that some mucoepidermoid carcinoma overexpress c-erbB-2 independent of clinicopathological features such as patient age and gender and site or histological grades of the lesions. This overexpression may be due to the process involving histogenesis and celular differentiation. Our data suggest that further investigation is indeed warranted to better assess the role of c-erbB-2 immunoeexpression in pathogenesis of mucoepidermoid carcinomas of salivary glands.

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RESUMEN: Fueron evaluados 29 casos de carcinoma mucoepidermoide intraoral en sus aspectos clínico-patológicos, además de la expresión de la oncoproteína c-erbB-2. El carcinoma mucoepidermoide fue predominante en las mujeres (79,3%), siendo más frecuente en individuos entre 21 y 40 años de edad (48,3%). El paladar fue el sitio más comunmente afectado (72,4%). Microscópicamente, 27 casos (93,1%) fueron clasificados como de baja malignidad. La expresión del c-erbB-2 se consideró positiva en 9 (31%) casos y no fue observada ninguna asociación significativa ($p>0,05$) entre la expresión de la proteína y género, ni entre la edad de los pacientes y el sitio o el grado histológico de la lesión. La expresión de la c-erbB-2 en el carcinoma mucoepidermoide puede mostrar las propiedades biológicas intrínsecas de las neoplasias de las glándulas salivales.

PALABRAS CLAVE: c-erbB-2; Her-2/neu; Inmunohistoquímica; Carcinoma mucoepidermoide; Neoplasmas de las glándulas salivales

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