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IMMUNOHISTOCHEMICAL EXPRESSION OF C-KIT (CD117) PROTIEN IN SALIVARY GLAND TUMORS

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ABSTRACT

Background: Salivary gland neoplasms (SGNs) are the next most common neoplasms of mouth after squamous cell carcinoma. C-kit was soon defined as type III receptor tyrosine kinase. As together with is ligand stem cell factor play an important role in the hematopoiesis, gametogenesis and melanogenesis. C-kit is driving oncogene in the most human tumors. Over activation of downstream signaling pathways is consequence of unregulated c-kit resulting in dysregulation of cell growth and cancer formation.

Objective: the aim of the present work was to determine the immunohistochemical expression of c-kit in most common benign and malignant cases of salivary gland neoplasms. Moreover, correlation of the immunoexpression of this marker with the histopathlogical grades of the studied lesions.

Material and Methods: Thirty two paraffin blocks for pleomorphic Adenoma (PA), Warthin's tumor, mucoepidermoid carcinoma (MEC) and Adenoid cystic carcinoma (ACC) were investigated in this study, with eight for each neoplasm were immunostained for c-kit.

***Results*:** positive c-kit expression in all the studied cases with variable degrees of immunoreactivity.

Conclusion: High grade MEC and solid pattern of ACC showed the strongest immunoreactivity, which might play a more distinct role in tumor aggressiveness.

KEY WORDS*: Salivary gland neoplasm*. immunohistochemistry: c-kit.

INTRODUCTION

SGNs may be broadly categorized into benign and malignant. Most of SGNs (80%) originate in the parotid gland, 10-15% in the submandibular gland and the remainder in the sublingual and minor salivary glands. About 80% of parotid neoplasms are benign. On the other hand, about half of submandibular gland neoplasms, most sublingual and minor SGNs are malignant. The vast majority of SGNs are epithelial in origin, rarely the interstitial connective tissue components of major salivary glands give rise to primary neoplasms whose behavior is similar to that of their extra glandular counterparts (*Lee et al, 2011*).

Pleomorphic adenoma (PA) and Warthin's tumor are the most common benign SGN (*Chahin&*

Kaufman, 2008)while the most common malignant neoplasms of the major and minor salivary glands are mucoepidermoid carcinoma (MEC) and adenoid cystic carcinoma (ACC) (*Smith, 2008*).

There is an increased interest in determining the molecular abnormalities that occur in SGNs with the hope that doing so will lead to proper diagnosis, prognosis as well as the discovery of effective therapeutic targets. One possibility involves transmembrane receptor tyrosine kinase c-kit which plays a critical role in initiation and development of many tumor types, including those arising in the head and neck (*Tetsu et al., 2010*).

C-kit was originally identified as a viral oncogene (v-kit) responsible for the transforming of the hardy–Zuckerman IV feline sarcoma virus. The c-kit receptor is 145-160 kDa cell membrane protein that is also called kit, CD117, or mast / stem cell growth factor receptor (SCFR). In human, kit gene is mapped to chromosome 4q12 (*Tetsu et al, 2010*). It is like all members of subclass III has **two intracellular tyrosine kinase domains** divided by a kinase insert domain and a c-terminal domain. A **single transmembrane domain** is believed to have a helical confirmation, and **a ligand–binding extracellular domain** composed of five immunoglobulin-like domains share in the structure of c-kit (*Li et al, 2007*).

Stem cell factor (SCF), also known as kit ligand (kit–L), steel factor, or mast cell growth factor, is a cytokine that binds to the c-kit receptor.The essential role of both SCF and c-kit was demonstrated by the previous studies on experimental animals by *Dahlen et al. (2001)*. They showed that mice lacking either SCF or cell surface c-kit were non-viable and died. Furthermore, mutations that altered the production of SCF or diminished the tyrosine activity of c-kit were associated with a variety of phenotypic abnormalities including macrocytic anemia, sterility, lack of pigmentation and mast cell deficiency.

SCF forms a non-covalent dimer that binds to two c-kit monomers and promotes c-kit dimer formation. The activated receptor becomes autophosphorylated on a number of tyrosine residues, mainly located outside the kianse domain, which serves as docking sites for signal transduction molecule such as Src homology 2 (SH2) or phosphotyrosine binding (PTB) (*Lennartsson & Rönnstrand, 2006*). Stimulation of c-kit activates a wide array of signaling pathways as PI3-K, Ras/Raf/Map kinase, Src kinase. This explains the diverse functions of c-kit in different tissues (*Roskoski, 2005)*. As together with SCF, c-kit is a key controlling receptor for a number of cell types. It is required for normal hematopoiesis, gametogenesis and melanogenesis *(Rönnstrand, 2004)*.

C-kit is a driving oncogene in most human tumors. Over activation of downstream signaling pathways is a consequence of unregulated c-kit, resulting in dysregulation of cell growth and cancer formation. This can take place through different mechanisms including overexpression of c-Kit**,** Gain-of-Function Mutations and Autocrine Loop (*Edling & Hallberg, 2007)*.

Inhibitors of oncogenes are proteins expected to show anti-tumor effect, possible with fewer side effects than those associated with conventional anticancer chemotherapy. Imatinib mesylate is a low molecular weight inhibitor of the c-kit kinase activity, thus inhibiting its signaling capability (*Hotte et al, 2005)*.

C-kit is expressed in a variety of normal tissue includes mast cells, certain hematopoietic stem cells, germ cells, melanocytes, gastrointestinal cajal cells and subsets of neurons especially in cerebellum and neoplastic tissue including gastrointestinal tumors, hepatocellular carcinoma, small cell lung cancer and salivary gland adenoid cystic carcinoma (*Chung et al, 2005, Camps et al, 2006 and Jeng et al, 2000)*.

MATERIAL AND METHODS

Thirty two paraffin blocks of cases previously diagnosed as PA, Warthin's tumour, MEC and ACC (8 cases for each neoplasm) were chosen. All the cases were collected from the archival paraffin blocks of the Oral Pathology Department, Faculty of Oral and Dental Medicine and National Cancer Institute, Cairo University during the period from 2006 to 2010.

Immunohistochemical staining

Histological examination using hematoxylin and eosin stain was performed. For immunohistochemical examination, streptavidin- biotin method was used and each case was stained with (Rabbit polyclonal concentrated primary antibody CD117/c-Kit/ SCF-Receptor Ab-6 (Thermo Scientific, Cat. No. RB-1518-P0-0.1ml)).

Analysis of Results

For c-kit immunohistochemical evaluation, the histological sections were examined by (magnification 20x) Olympus CX21 microscope attached to a camera and computer. All the stained section were examined by Image J software (NIH, version v1. 45e, USA). The area percent and optical density of the positive cytoplasmic immunoreaction were measured in each lesion.

Statistical analysis

All the obtained data from the image analyzer were tabulated and presented as mean and standard deviation (SD) values. One way ANOVA was used to compare the area percentage and immunostaining intensity of c-kit among the examined SGNs and different patterns of ACC. Tukey's Multiple Comparison Test was used to perform a pair-wise comparison between each variant versus the other. Moreover, two tailed unpaired student t-test was employed to compare benign versus malignant SGNs and low versus high grades of MEC.

RESULTS

All the studied cases of PA (100%) demonstrated positive heterogeneous c-kit immunoreactivity. Most of the tumor cells showed moderate to strong cytoplasmic positivity (fig.1 A). While in all cases of Warthin's tumors moderate to strong cytoplasmic immunoreaction of c-kit was detected in both inner tall columnar cells layer and outer cuboidal cells layer (fig.1 B).

In low-grade MEC: In three out of eight cases, the epidermoid cells interposed between mucous cells showed strong cytoplasmic immunoreactivity. The mucous cells showed moderate positive cytoplasmic immunoexpression. On the other hand high grade MEC: All cases (5/8) showed strong homogenous cytoplasmic c-kit immunostaining in masses of epidermoid (fig.1 C).

In ACC a different immunohistologic pattern of staining was noted among the eight cases. Distribution of c-kit immunostaining was observed primarily in the cytoplasm although when cytoplasmic staining was strong, a membranous pattern of immunostaining was observed. Basaloid cells of small ducts and cells lining the cystic spaces in cribriform pattern showed moderate cytoplasmic c-kit immunoreactivity. As well as moderate cytoplasmic c-kit expression in the strand of tumor cells was observed in trabecular pattern. On the other hand, moderate c-kit immunoreaction was seen in the tumor cells of the duct like structures of tubular pattern. As well as some cells showed nuclear immunoreactions. The solid pattern showed strong homogenous cytoplasmic c-kit immunostaining in all basaloid cells. Nuclear reaction was observed also (fig.1D).

TABLE (1) **Anova test comparing area percentage of c-kit positive cells among all tested SGNs.**

	PA	Warthin's T	ACC	MEC
Mean± SD	11.09±4.89	22.8±6.5	19.3±13.3	28.9±8.33
P value	0.0023***			

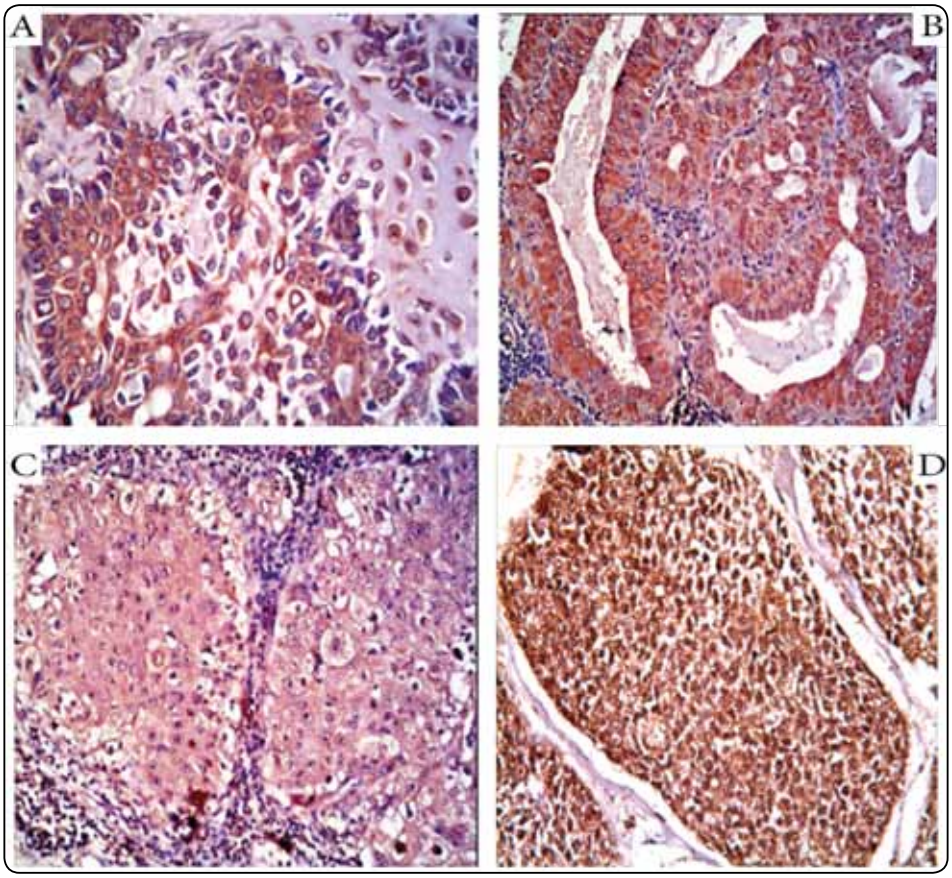

Fig.(1) Immunohistochemical reactivity of c-kit in epithelial cells forming epithelial masses or lining duct like structures in PA (A)(x400), Warthin's tumor showing homogenous strong c-kit expression in both layers of epithelial lining (B)(x200), high grade MEC demonstrating homogenous strong c-kit expression in epidermoid cells (C) (x200), solid pattern of ACC showing homogenous strong cytoplasmic and membranous c-kit expression in all basaloid cells (D)(x400).

TABLE (2) **Tukey's Multiple Comparison Test to compare area percentage among all tested SGNs.**

	PA	**Warthin's T**	**ACC**	**MEC**
PA	-------	ns	ns	**
WT	ns	--------	ns	ns
ACC	ns	ns	-------	ns
MEC	**	ns	*	---------

TABLE (3) **Anova test comparing immunostaining intensity of c-kit among all tested SGNs**

	PA	Warthin's T	ACC	MEC
Mean± SD	0.46±0.135	0.45±0.065	0.64±0.15	0.66±0.24
P value	0.0057***			

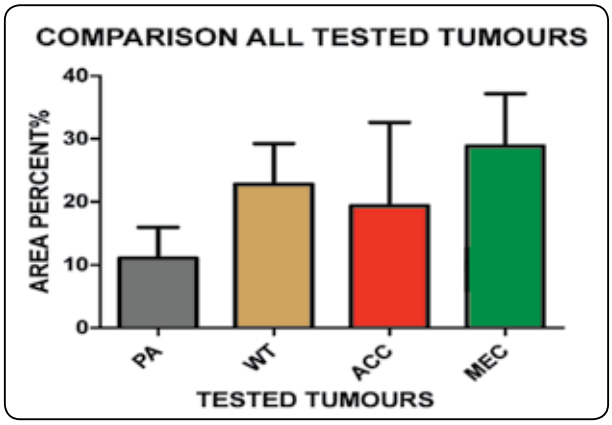

Fig. (1) A Bar chart demonstrating mean area percentage of c-kit immunostaining in all tested SGNs

TABLE (4) **Tukey's Multiple Comparison Test to compare immunostaining intensity among all tested SGNs.**

	PA	Warthin's T	ACC	MEC
PA	-------	ns	ns	*
WT	ns	--------	ns	*
ACC	ns	ns	-------	ns
MEC	*	*	ns	---------

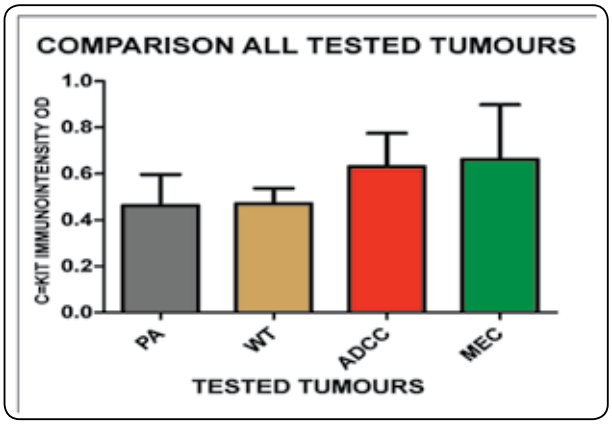

Fig. (2) A Bar chart illustrating mean immunostaining intensity of c-kit among all tested SGNs.

DISCUSSION

Our finding that all the examined tumors showed positive c-kit immunoreactivity with variable degrees of positivity revealed the role of c-kit in growth and development of these tumors. The observed cytoplasmic immunoreactivity in most of the tumor cells was in agreement with the findings of studies conducted by *Went et al. (2004), Andreadis et al. (2006), Negri et al. (2008) and Bell et al. (2010)*. On the other hand, the observation of nuclear immunoreactivity in few cases was in accordance with *Castillo et al. (2004)* who found intense and diffuse nuclear staining in some cases of sarcomatoid renal cell cancer. For the best of our knowledge, the nuclear expression was not reported in almost all the previous studies of c- kit. However, it could be explained as a different activation system of gene.

Concerning PA and Warthin's tumor, only limited information was available on the immunoexpression of c-kit protein. In PA, the stronger c-kit immunoreactivity observed in the inner cells of epithelial masses and intraluminal cells of some duct–like structures which was consistent with the previous immunohistochemical investigations of *Mino et al. (2003), Chandan et al. (2004), Went et al. (2004), Andreadis et al. (2006) and Choi et al. (2008)*. As well as *Kim et al. (2011)* who suggested that this pattern of c-kit expression reflected its role in the differentiation of the precursor cells of ductal cells.

In Warthin's tumor, positive cytoplasmic reaction in both outer tall columnar cell and inner cuboidal cell layers lining cystic spaces was in agreement with *Mino et al. (2003) and Andreadis et al. (2006)*. Moreover, we could explain this finding in line with *Ariada et al. (2005)* who hypothesized that of the histogenesis of Warthin's tumor is due to proliferation of salivary ductal cells that entrapped within the parotid lymph node. As well as, *Bell et al. (2010)* demonstrated highly c-kit immunoreactivity in salivary ductal cells. However, the uniform pattern of c-kit expression seen in this study for tumor cells may be suggestive for the potential role of c-kit in the pathogenesis of Warthin's tumor. However, further studies including larger number of cases will be needed.

The finding of positive cytoplasmic immunoreaction in MEC was in agreement with the results obtained by *Mino et al. (2003)*. On the contrary, it was in disagreement with *Jeng et al. (2000)* and *Andreadis et al. (2006)* who demonstrated negative c-kit immunoreaction in MEC. They explained their results that MEC might arise from precursor cells that did not express c-kit in normal salivary gland tissues, or due to using different polycolonal c-kit antibody or epitope retrieval modalities. Our result of stronger c-kit expression in epidermoid cells than

mucus cells in MEC, would indicate the role of c-kit in controlling differentiation and proliferation of epidermoid cells.

Our result that c-kit immunoreaction was higher in high grade than low grade MEC was not well supported by previous studies as no studies for the best of our knowledge evaluated the difference in c-kit expression between both grades of MEC. We could explain this finding in line with *Costa et al. (2011)* who observed that the high grade component exhibited solid sheets of dedifferentiated anaplastic cells and correlated c-kit immunoreactivity with worse and aggressive clinical course.

In ACC, our finding that the pattern & intensity of c-kit immunoexpression varied with its histological subtypes is in accordance with the previous results of *Penner et al. (2002), Edwards et al. (2003), Epivatianos et al. (2007), Pfeffer et al. (2007), Bell et al. (2010), Tetsu et al. (2010), Ahmed & Abu-hager (2010) and Meer et al. (2011)***.** The finding that the strongest reaction was seen in the solid variant of ACC compared to the cribriform, tubular, trabecular patterns indicated that c- kit expression was associated with loss of cellular differentiation in the solid pattern. Contrarily, *Freier et al. (2005)* exhibited contradictory results. They found that the c-kit expression in solid pattern was lower than other variants.

Findings of studies performed by *Penner et al, (2002), Ahmed & Abu-hager (2010) and Meer et al. (2011)*are parallel with our results on the localization of c-kit immunostaining in the luminal cells of the cribriform, tubular and trabecular patterns than abluminal cells (basal cells and myoepithelial cells). Moreover, their results are in accordancewith the present findings that revealed intense c-kit expression in all tumor cells of solid pattern. They explained that most of the tumor cells of the solid pattern of ACC which acquired intense c-kit immunoreaction were considered as modified myoepithelial cells. They explained the variable patterns and intensities of c-kit staining as a result of loss of cellular differentiation and correlated it with the worse clinical course of ACC. These findings were in line with *Zarbo et al. (2002)* and *Costa et al. (2011)* who found that loss of myoepithelial component was one of the major criteria to identify the dedifferentiation or high grade transformation in ACC.

The finding of stronger c-kit immunoexpression in high grade MEC and solid pattern of ACC, as well as the highly significant statistical difference in the area percentage as well as immunostaining intensity of positive c-kit immunoreactivity with the highest values in the same groups suggested the role of c-kit in more aggressive tumors. Also, it proposed the possible c-kit activity in association with tumor initiation and progression. Thus it can be used as a prognostic marker for worse clinical course. Furthermore, this implied the potential role for c-kit inhibitors in the management of SGNs. This is in accordance with *Castillo et al. (2004), Lorenzo et al. (2004), Camps et al. (2006) and Yasuda et al. (2007)*. They demonstrated that c-kit expression enhance the invasion in sarcomatoid renal cell carcinoma, prostate cancer, small lung cell cancer and pancreatic cancer respectively. This is also in agreement with *Tang et al. (2010)* who demonstrated that the overexpression of c-kit enhanced invasion, metastasis and was related to the malignant process.

On the contrary, *Aslan et al. (2005)* showed no correlation among degree and pattern of c-kit expression to local recurrence or distantmetastasis of tumor. Furthermore, *Chung et al. (2005)* demonstrated that c-kit positivity in hepatocellular carcinoma could be used as a good prognostic indicator and more recently, *Kim et al. (2011)* suggested that the loss of c-kit expression was associated with the malignant transformation of PA.

The area percentage of c-kit immunoreactivity was not helpful for differential diagnosis between the examined benign and malignant SGNs as it showed no significant difference. Contrarily,

the immunostaining intensity could be used as a helpful method to differentiate between them as it showed a highly significant difference. This is in agreement with *Mino et al. (2003) and Andreadis et al. (2006)*.On the other hand, it was in disagreement with *Chandan et al. (2004)* who demonstrated no difference in c-kit expression between PA and ACC.

Finally, in the current work, the area percentage and immunostaining intensity of positive c-kit immunoreactivity showed highly significant statistical difference among the different grades of MEC and the different histological patterns of ACC. Among the studied cases of MEC, the highest values of immunreactvity as measured by area percentage and immunointensity were found in high grade MEC. Similar results were obtained in the studied cases of ACC, where solid pattern of ACC showed the highest values of c-kit immunoreactivity. These findings may suggest that the high c-kit immunoexpression is associated with aggressive form of MEC and ACC as discussed before.

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