

A comparison between the concentration of mast cells in squamous cell carcinomas of the skin and oral cavity

Comparação entre a concentração de mastócitos em carcinomas espinocelulares da pele e da cavidade oral*

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Abstract: **FUNDAMENTOS:** The lethality of squamous cell carcinomas (SCC) of the skin is considered low. SCC in the mouth is usually associated with poor prognosis. Current evidence suggests that mast cells in the normal tissue contribute to the tumorigenesis of SCC, probably by promoting angiogenesis.

OBJECTIVE: The aim of this study was to compare the concentration of mast cells in SCC of the mouth and skin and evaluate whether there is a correlation with the degree of differentiation of these tumors.

MATERIAL AND METHODS: Thirty cases of SCC of the skin and 34 of the mouth were investigated. Toluidine blue staining was used to identify mast cells in blocks containing the central portion of the neoplasm.

RESULTS: A concentration of between 0 and 10 mast cells was found in one single case of SCC of the skin and there were no cases of SCC of the mouth with concentrations of mast cells in the tumor >201. In the majority of cases of SCC of the mouth (47%; n=16), mast cell concentration was between 0 and 10, with a concentration >51 mast cells in 80% of cases of SCC of the skin. All the cases of SCC of the mouth with a concentration of mast cells between 100 and 200 and 80% of those with a concentration of 51-99 were located on the lip. The concentration of mast cells was unrelated to the degree of differentiation of the tumor.

CONCLUSION: The concentration of mast cells is lower in SCC of the mouth except when the tumor is located on the lip. This may reflect a lower need for cell activation in the microenvironment to improve vascularization in oral cancer.

Keywords: Squamous cell carcinoma; Mast cells; Skin; Mouth

Resumo: **FUNDAMENTOS:** A letalidade dos carcinomas espinocelulares (CECs) de pele é considerada baixa. Os CECs de boca têm prognóstico ruim. Evidências atuais sugerem que os mastócitos, residentes no tecido normal, contribuem para a tumorigênese dos CECs, provavelmente por promoverem angiogênese.

OBJETIVO: Comparar a concentração de mastócitos em CECs da pele e da boca e avaliar se há correlação com o grau de diferenciação desses tumores.

MATERIAL E MÉTODOS: Foram analisados 30 casos de CEC de pele e 34 casos de CEC de boca. A coloração de azul de toluidina, para evidenciar os mastócitos, foi realizada nos blocos com a área central da neoplasia.

RESULTADOS: Apenas um caso de CEC de pele apresentou concentração de mastócitos de 0-10 e nenhum caso de CEC de boca apresentou concentração maior que 201 mastócitos no tumor. A maioria dos CECs de boca tem concentração de mastócitos entre 0 e 10 (47% - n = 16); 80% dos CECs de pele têm concentração acima de 51 mastócitos. Todos os casos de CEC de boca com concentração entre 100 e 200 mastócitos e 80% daqueles com concentração entre 51 e 99 eram de lábio. A concentração de mastócitos não está relacionada ao grau de diferenciação do tumor.

CONCLUSÃO: A concentração de mastócitos é menor nos CECs de boca, exceto nos de lábio, podendo refletir uma menor necessidade de ativação de células do microambiente para melhorar a vascularização nos cânceres de boca..

Palavras-chave: Boca; Carcinoma de células escamosas; Mastócitos; Pele

Received on 16.09.2009.

Approved by the Advisory Board and accepted for publication on 22.05.2010.

* Study conducted at the Universidade do Oeste Paulista (UNOESTE), Presidente Prudente, São Paulo, Brazil.

Conflict of interest: None / *Conflito de interesse: Nenhum*

Financial funding: None / *Suporte financeiro: Nenhum*

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INTRODUCTION

Squamous cell carcinomas (SCC) are malignant neoplasias that originate in the squamous epithelium and may be well-differentiated, moderately differentiated, poorly differentiated or undifferentiated. These tumors may occur in the skin (the most common site), mouth, larynx, esophagus or cervix, sites covered by squamous epithelium, or within the context of squamous metaplasia when the original epithelium is transformed into a squamous epithelium, as found in cases of bronchial SCC.¹

The number of new cases of nonmelanoma skin cancer (squamous and basal cell carcinomas) in Brazil in 2008 was estimated at 55,890 in males and 59,120 in females.² The lethality of nonmelanoma skin cancer is considered low; however, in some cases in which diagnosis is delayed, this cancer may lead to ulcerations and severe physical deformity.^{2,3} There is, almost certainly, considerable under-registration as a result of under-diagnosis and also because prognosis is excellent with this type of neoplasia and the likelihood of complete cure is high if the condition is treated adequately and opportunely.²

The majority of skin cancers result from excess sun exposure.^{2,3} The American Cancer Society estimated that in 2007 more than a million cases of basal cell and squamous cell carcinomas and around 60,000 cases of melanoma were associated with ultraviolet (UV) radiation.²

Oral cancer includes cancers of the lip and the oral mucosa (buccal mucosa, gums, soft and hard palate, tongue and the floor of the mouth). Lip cancer is more common in white individuals and the lower lip tends to be affected more often than the upper lip.² Malignant neoplasias of the oral cavity are more common in males and in individuals in the south and southeast of Brazil compared to the rest of the country.² Factors that may lead to mouth cancer include age >40 years, smoking (pipes or cigarettes), alcohol ingestion, poor oral hygiene and the use of badly fitting dentures.² In cases of lip cancer, sun exposure is the principal culprit.^{2,4}

Unlike malignant skin neoplasia, prognosis is poorer with tumors located in the oral cavity and morbidity and mortality are high due to the intense vascularization in this region that facilitates dissemination of the neoplastic cells. In addition, treatment may result in mutilation to patients.^{2,5}

Many cell types located in the stromal microenvironment have been found to be involved in the tumorigenesis of various types of tumors. Leukocyte infiltration into the tissues is a common finding in many physiological and pathological conditions. Specific populations of leukocytes infiltrating the squamous epithelia, with premalignant or malignant

keratinocytes, were recently described as playing a significant role in the pathogenesis of squamous cell carcinomas.⁶

Mast cells are found in the normal connective tissue. The density of these cells varies from one organ to another; however, they are consistently well represented in the respiratory tract. Mast cell hyperplasia has been found in many tumors, although the significance of this finding remains unclear.⁷ Recent data suggest that mast cells may play opposing roles in tumor biology and that the microenvironment may polarize these cells to render either a promoting or inhibiting effect on tumors.^{1,8}

Angiogenesis, an important prognostic factor in many tumors, is a complex event mediated by angiogenic factors released by the neoplastic cells or by the host's immune cells. Among the host's immune cells, mast cells have been associated with tumor progression by promoting angiogenesis.⁹ Recently, tryptase from mast cells was identified as another potent proangiogenic factor in the tumors and its role has been studied in various forms of cancer.¹⁰ A study conducted by Sawatsubashi et al.¹¹ suggests that SCC cells and mast cells may control the angiogenic response through vascular endothelial growth factor (VEGF) release.

Although mast cells are associated with promoting angiogenesis in some malignant tumors, particularly those situated in the aerodigestive tract, little is known of their effect on oral SCC.¹² Some studies have shown a significant correlation between mast cell density and microvessel density in preneoplastic lesions and in oral SCC^{12,13} and have suggested that mast cells may increase angiogenesis in these tumors via tryptase.¹²

OBJECTIVE

The objective of this study was to conduct a comparative analysis of mast cell density in squamous cell carcinomas of the skin and mouth and to evaluate whether there is a correlation with the degree of differentiation of these tumors.

MATERIAL AND METHODS

A retrospective study was performed on a selection of 64 anatomopathological reports following the surgical removal of squamous cell carcinomas, 30 of which referred to skin tumors and 34 to cases of oral cancer. All exams were performed between 2005 and 2008. Cases in which skin punch biopsy was performed were excluded from this study, since they do not permit evaluation of the entire lesion (tumor margin and central area).

Data related to the age of the patients, tumor

site and degree of differentiation (well-differentiated, moderately differentiated or poorly differentiated) were retrieved from the pathology report.

Paraffin blocks containing the central area of the tumor were selected and submitted to toluidine blue staining (Merck, Darmstadt, Germany) to investigate for mast cells. Mast cells were counted by two trained observers (ACGP and GAN) in 10 magnified fields on each slide (40x objective), corresponding to an area of around 1 mm². Quantification was first performed on the central area of the tumor and then in the tumor-free margins as a control. Mast cell density was divided into 5 categories: 0-10, 11-50, 51-99, 100-200 or >201 mast cells in 10 magnified fields.

Statistical analysis was carried out using the SPSS (Statistical Package for the Social Sciences) software package, version 15.0. The likelihood ratio test (LRT) was used to compare proportions in view of the low frequencies expected. The t-test was used to compare means when the distribution of the variable was normal; otherwise, the equivalent Mann-Whitney (MW) nonparametric test was used. Correlation was tested using Pearson's coefficient when the distribution of the variables was normal or Spearman's rho coefficient when it was not. The normalcy of variables was tested using the Kolmogorov-Smirnov (KS) test. To control for possible confounding factors, multiple linear regression was performed using the backward elimination method to select variables, the response variable being mast cell density in the tumor. Significance level was defined as 0.05%.

This study was approved by the Internal Review Board of the *Universidade do Oeste Paulista* (UNOESTE) under approval letter #112/08.

RESULTS

The majority of patients (92.2%; n=59) were over 50 years of age. Most cases (73.5%; n=25) of squamous cell carcinoma situated in the mouth and the majority of the patients with SCC of the skin (53.3%; n=16) were male.

In the majority of cases of SCC of the mouth (35.2%; n=12), the tumor was situated on the lip. In the cases of skin tumors, most (56.6%; n=17) were located on the head or neck.

In 57.85% of all cases (n=37), the tumor was well-differentiated. In the cases of SCC of the mouth, most of the tumors (58.8%; n=20) were well-differentiated, while one was well-differentiated with a verrucous presentation and 13 (38.2%) were moderately differentiated. With respect to the skin tumors, 56.6% (n=17) were well-differentiated and 33.3% (n=10) were moderately differentiated.

Mean mast cell density in the central area of the skin tumors was 116.7 cells/mm², whereas in the cases

of SCC of the mouth, mean density was 46.8 cells/mm². The normalcy test for this variable revealed a normal distribution (p=0.14; KS test), with the difference between the means being statistically significant (p=0.0001, t-test). Mean mast cell density at the tumor-free margin in the cases of skin cancer was 115.5 cells/mm² compared to 53.9 cells/mm² in the case of oral cancer (p=0.74; KS test and p=0.0001; t-test). When the cases of tumors situated on the lip and those of the oral cavity were analyzed separately, mast cell density in the central area of the tumor was 108.5 and 13.1 cells/mm², respectively, (p=0.07, KS test and p=0.000051, t-test), while in the tumor-free margin, density was 138.5 and 7.8 mast cells/mm², respectively, (p = 0.00, KS test and p=0.00001, MW test).

There were no cases of SCC of the mouth in which density was >201 mast cells/mm² in the central area of the tumor (Graph 1). In the majority of cases of SCC of the mouth, mast cell density was between 0 and 10 (47%; n=16) (Figure 1). All the cases of SCC₂ of the mouth with density of 100-200 mast cells/mm² (n=7) and 80% (n=4) of those with a density of 51 to

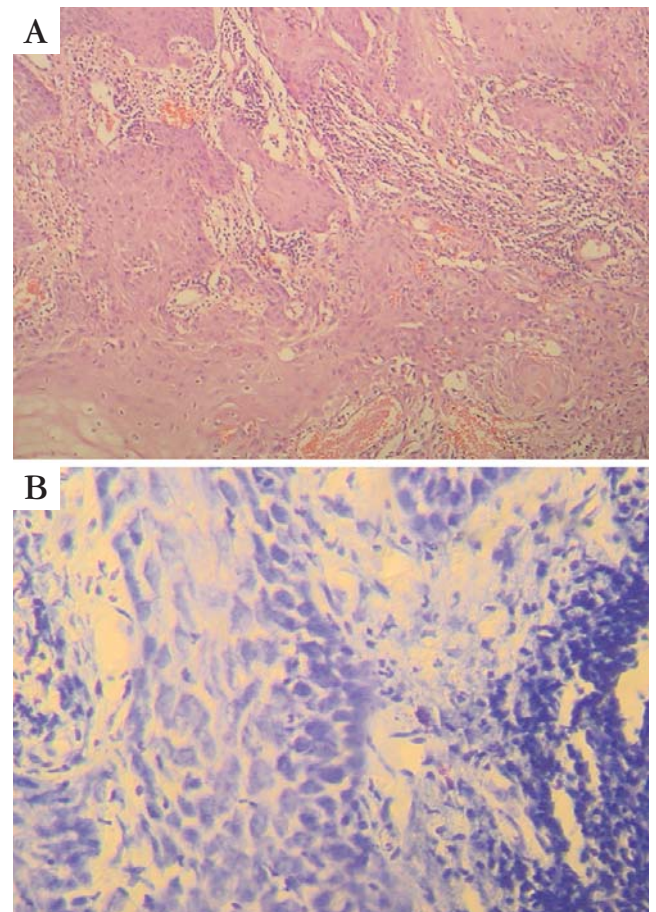
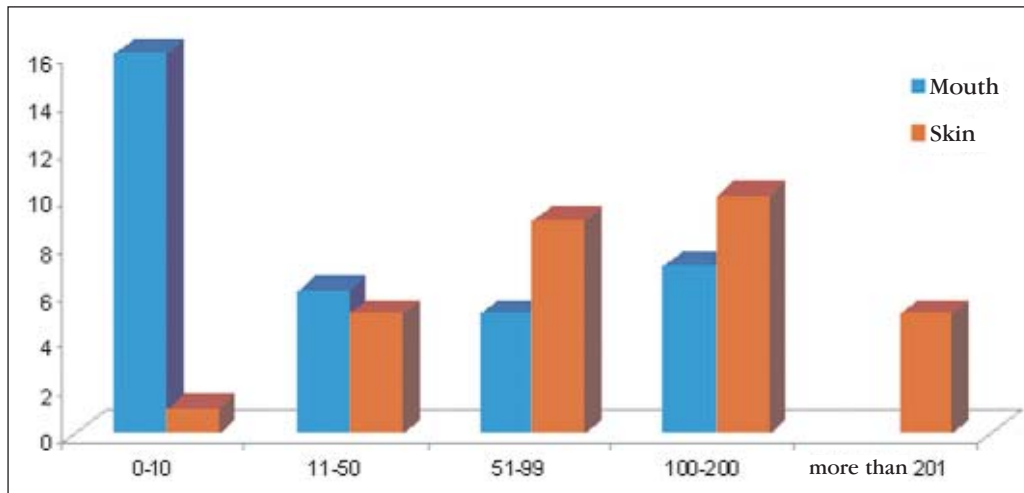


FIGURE 1: Well-differentiated SCC situated on the floor of the mouth. A. Hematoxylin-eosin, magnification 200x. B. Mast cell density 0 – 10 cells/mm² (toluidine blue staining, magnification 400x)



GRAPH 1: Distribution of squamous cell carcinomas of the mouth and skin according to mast cell density (n=64) (p=0.001)

99 mast cells/mm² were situated on the lip (Graph 2). Only one case of SCC of the skin had a density of 0-10 mast cells/mm² in the central area of the tumor. The majority of cases (80%; n=24) had a density >51 mast cells/mm² and 50% (n=15) had >100 mast cells/mm² (Graph 1, Figure 2). There was a statistically significant difference between the mast cell density in the central area of the tumor in cases of SCC of the mouth and that of tumors involving the skin (p=0.001). Furthermore, there was a statistically significant difference in mast cell density between cases of SCC of the lip and those of tumors situated in other parts of the mouth (p=0.03; LRT).

In the only case of SCC of the skin in which mast cell density was 0-10 cells/mm² in the central area of the tumor, mast cell density at the tumor-free margins was identical. In the cases in which mast cell density in the tumor was between 100 and 200 mast cells/mm², density was between 51 and 99 mast cells/mm² at the margin in 30% of cases, between 100 and 200 mast cells/mm² in 50% of cases and >201 mast cells/mm² in 20% of cases. The correlation between mast cell density in the tumor (p=0.59; KS) and at the margin (p=0.49; KS) was not statistically significant (p=0.079 and r=0.326). With respect to SCC of the lip, in the only case with density between 0 and 10 mast cells/mm², density was 51-99 at the margin. Of the cases with a density of 100-200 mast cells/mm² in the tumor, 57.1% had 100-200 mast cells/mm² at the margin, while in 42.9% of cases, density was >201 mast cells/mm². No significant correlation was found between mast cell density in the lip tumor (p=0.08, KS test) and at the margin (p=0.84, KS test) (p=0.129 and r=0.464). In the majority of cases of SCC of the oral cavity (93.3%) in which mast cell density in the central area of the tumor was between 0 and 10 mast cells/mm² and in those with a density of 11-50 cells/mm² (83.3%), density at the

margins was 0-10 cells/mm². In the cases of oral cancer, the correlation between mast cell density in the tumor (p = 0.04, KS test) and in the margin (p=0.01, KS test) was statistically significant (p=0.001 and Spearman's = 0.7444). In 10 cases of SCC of the skin

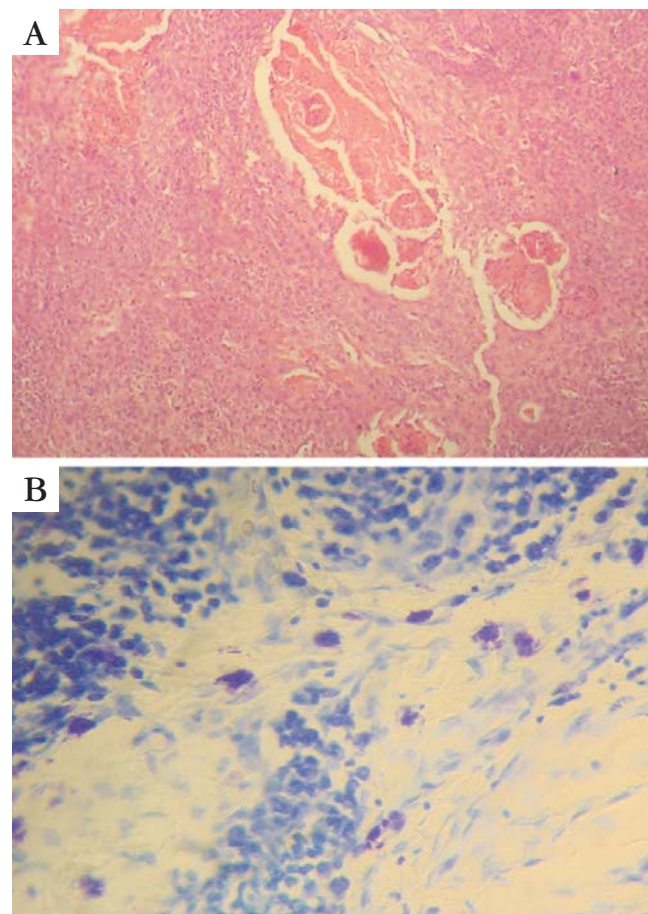
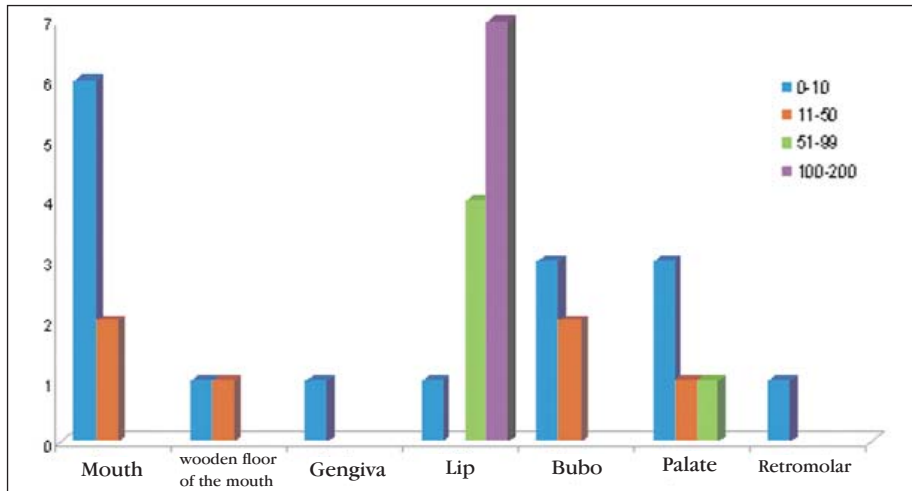


FIGURE 2: Well-differentiated SCC of the skin. A. Hematoxylin-eosin, magnification 200x. B. Mast cell density > 201 cells/mm² (toluidine blue staining; magnification 400x).



GRÁAPH 2: Distribution of squamous cell carcinomas of the mouth according to the site affected and mast cell density (n=34) ($p < 0.05$).

(30%), 7 cases of SCC of the lip (58.3%) and 2 cases of SCC in the oral cavity (9.1%), mast cell density was higher at the margins than in the central area of the tumor (Figure 3).

There was no statistically significant association between mast cell density in the central area of the tumor and the degree of differentiation of the tumors, either in the skin, the lip or in the oral cavity, nor between density at the tumor-free margin in any of the sites and the degree of differentiation ($p > 0.05$) (Graph 3).

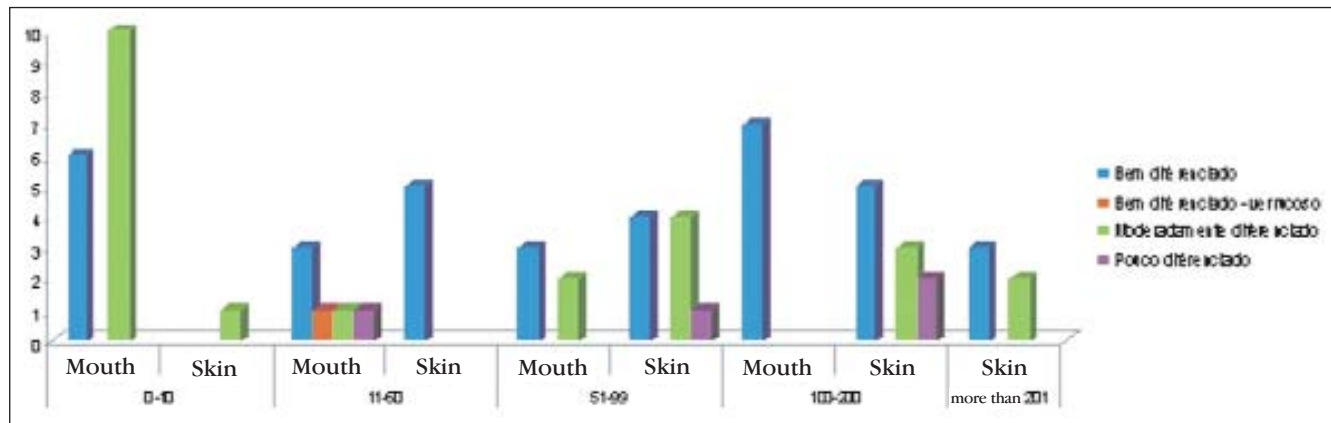
Multiple linear regression was performed to control for possible confounding factors in mast cell density in the tumor in relation to the site (skin, lip or oral cavity), age-group, sex, degree of differentiation or mast cell density at the margin. The backwards elimination method was used to select the variables, with exclusion criteria $p \geq 0.10$. The model showed an adjusted R^2 of 0.532, i.e. 53.2% of the variation in mast cell density in the tumor was explained by the variables in the model. There were no problems with autocorrelation of the residues, as shown by the Durbin-Watson test result of 1.88, and multicollinearity was acceptable, since the variance inflation factors (VIF) for the predictive variables were: sex = 1.10; site = 1.81 and mast cell density at the margin = 1.76. Analysis of the standardized residues showed no outliers. According to the adjusted model, mean density was 40.12 mast cells/mm² greater in females compared to males ($p = 0.006$). Mean mast cell density in the tumor was 0.48 times higher than at the margin in each case, irrespective of the site affected by the tumor ($p = 0.00001$).

DISCUSSION

In the present study, there was a predominance of SCC of the mouth in male patients, while SCC of

the skin occurred in approximately similar proportions in males and females. This predominance of SCC of the mouth in males may be explained by the fact that the principal cause of these tumors is smoking, the incidence of which is greater in the male population compared to females. The principal cause of SCC of the skin is solar radiation, which is common to both sexes. Both SCC of the skin and of the mouth are more common in patients over 50 years of age, as found in the present study.

Mast cells may tend to accumulate around skin neoplasias.¹ Few studies have failed to find any increase in mast cells in these tumors.¹⁴ Current evidence suggests that mast cells contribute to the tumorigenesis of skin neoplasias through four different mechanisms. 1) Immunosuppression. Ultraviolet B (UVB) radiation, the most significant trigger of skin neoplasias, activates mast cells. Following exposure to skin radiation, trans-urocanic acid in the epidermis is isomerized to cis-urocanic acid, which stimulates the release of neuropeptides by C-nerve fibers. These neuropeptides promote histamine release by the mast cells, leading to immunosuppression of the cell immune system. 2) Angiogenesis. Mast cells are the major source of vascular endothelial growth factor (VEGF) in basal cell carcinomas and melanomas. VEGF is the most powerful angiogenic factor and induces release of other angiogenic factors through the endothelial wall of the matrix. The proteases of the mast cells reorganize the stroma to facilitate migration of the endothelial cells. In addition to heparin, proteoglycan, predominantly from the mast cells, contributes to vascular invasion in metastases. 3) Degradation of the extracellular matrix. Through its own proteases and indirectly by interacting with other cells, mast cells participate in the degradation of the extracellular matrix, which is necessary in order



GRAPH 3: Distribution of squamous cell carcinomas of the mouth and skin according to the degree of differentiation of the neoplasia and mast cell density (n=64) (p> 0.05)

for the tumor to disseminate. 4) Mitogenesis. Mast cell mediators, including fibroblast growth factor-2 and interleukin 8 are mitogenic for melanoma cells.^{1,15}

Studies conducted in vivo have shown sequential infiltration and degranulation of mast cells during carcinogenesis in SCCs and have demonstrated a strict correlation between mast cell activation and the different phases of hyperkeratosis, dysplasia, carcinoma in situ and invasive oral carcinoma.⁵

Matrix metalloproteinases (MMPs) constitute a family of zinc-dependent endopeptidases capable of essentially degrading components of the extracellular matrix. These enzymes may be produced by different types of skin cells such as fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells and eosinophils. In general, MMPs are not expressed constitutively in the skin but are induced temporarily in response to exogenous signals, such as various cytokines, growth factors, extracellular matrix interactions and alterations in cell-to-cell contact. Currently, much evidence points to the significant role of MMPs in the proteolytic remodelling of the extracellular matrix in various physiological situations, including the development of tissue morphogenesis, tissue repair and angiogenesis. On the other hand, MMPs also play an important pathogenic role in the excessive destruction of connective tissue components, e.g. in rheumatoid arthritis, osteoarthritis, chronic ulcers, skin photoaging, periodontitis and in the invasion of tumor cells and metastases.^{16,17}

MMP-9, predominantly expressed by neutrophils, macrophages and mast cells, is overexpressed in angiogenic dysplasias and in invasive carcinomas of the epidermis in animal models for multi-step tumorigenesis. Transgenic rats lacking MMP-9 presented a reduction in keratocyte proliferation at all the stages of the neoplasia and a decrease in the inci-

dence of invasive tumors. However, those carcinomas that originate in the absence of MMP-9 lack keratinocyte differentiation, which is indicative of a more aggressive tumor with poorer prognosis.¹⁶ Therefore, MMP expression by mast cells may be one more factor that contributes to the aggressiveness of the SCC.

Oliveira Neto et al.⁸ showed a reduction in the number of mast cells in premalignant and malignant lesions of the oral cavity and suggested that this fact may be associated with a failure in the migration of these cells, possibly reflecting an important modification in the microenvironment during tumor initiation and progression.

In the present study, an inversely proportional correlation was found between SCC of the skin and mouth in relation to mast cell density, i.e. in cases of skin SCC mast cell density was high in the tumor in 80% of cases, while in the mouth mast cell density was low in 47% of cases. SCC of the lip proved to be an exception within the group of oral SCCs, since in the majority of cases mast cell density was high (between 100 and 200 cells/mm²), similar to the mast cell density found in cases of SCC of the skin, as reported by Rojas et al.⁴

Mean mast cell density in the cancer-free tissue is much higher in cases involving the skin and lip (115.5 and 138.5 cells/mm², respectively) compared to those involving the oral cavity where a mean of 7.8 mast cells/mm² was found. These results are in agreement with the findings of other studies showing an increase in the prevalence of dermal mast cells in skin that has been chronically exposed to the sun.¹⁵

In a study conducted by Costa et al.,¹⁸ mast cell density in cases of SCC of the lip and in actinic cheilitis was significantly greater compared to that found in normal lip mucosa. In the present study, mast cell density was higher in the tumor-free margin compared

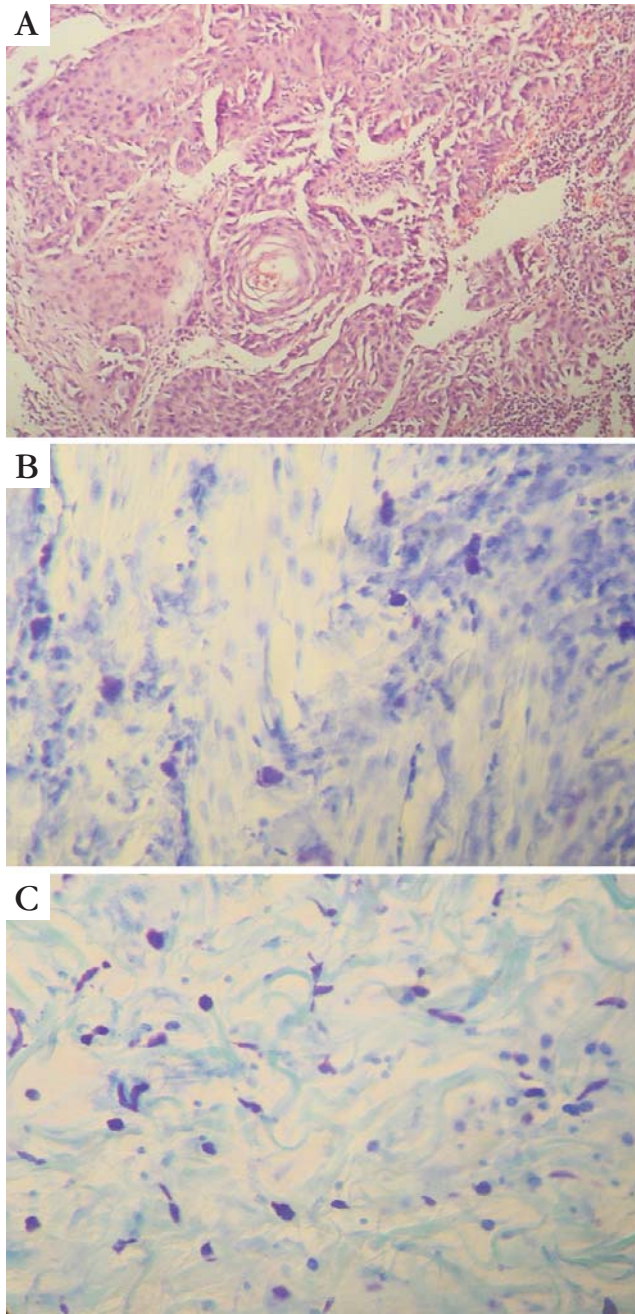


FIGURE 3: Moderately-differentiated SCC of the skin. **A.** Hematoxylin-eosin; magnification 200x. **B.** Mast cell density of 100 - 200 cells/mm² in the central area of the tumor (toluidine blue staining; magnification 400x)

to the central area of the tumor in 58.3% of cases of SCC of the lip. The difference between the two studies may lie in the fact that the former used normal mucosa from other patients without SCC as a control, while in the present study the adjacent mucosa from the surgical, cancer-free margins of the SCC was used as control.

Naik et al.¹⁹ reported an inverse association between mast cell density and the degree of anaplasia and the number of mitotic figures in SCC of the cervix, suggesting that these cells may be related to the degree of differentiation of these tumors.

In the present study, mast cell density in the tumor and in the cancer-free margins was not found to be associated with the degree of differentiation of the SCC, suggesting that mast cell density may be related to external stimuli such as ultraviolet B radiation, for example, or to a need for greater angiogenesis or difficulty in collagen degradation in certain areas.

In this study, mast cell density was much higher in female patients. This finding may be explained in part by the greater exposure of women to natural or artificial ultraviolet radiation in tanning for esthetic purposes. However, this does not explain the fact that mast cell density was also higher in the oral cavity of women, suggesting that there may be other mechanisms of recruitment and activation of mast cells related to the female gender.

This study evaluated mast cell density in SCC of the skin and mouth and correlated mast cell density with the degree of tumor differentiation. Studies comparing mast cell density, the quantity of vessels in the tissue and the concentrations of chemical mediators released by mast cells may add towards clarifying whether these cells contribute to the aggressiveness of the SCC.

CONCLUSION

The present study showed that mast cell density is almost 0.5 times higher in the tumor compared to the cancer-free margin irrespective of the site or degree of differentiation. This finding suggests that the increase in mast cell density in the tissue is important for the development of SCCs (growth and tissue invasion), but not for cell differentiation. □

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How to cite this article / *Como citar este artigo*: Parizi ACG, Barbosa RL, Parizi JLS, Nai GA. A comparison between mast cell density in squamous cell carcinomas of the skin and oral cavity. *An Bras Dermatol*. 2010;85(6):811-18.