

**UNIVERSIDADE FEDERAL DA PARAÍBA  
CENTRO DE CIÊNCIAS DA SAÚDE  
DEPARTAMENTO DE CLÍNICA E ODONTOLOGIA SOCIAL  
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA- NÍVEL MESTRADO  
COM ÁREA DE CONCENTRAÇÃO EM DIAGNÓSTICO BUCAL**

**RACHEL REINALDO ARNAUD**

**DENSIDADE DE MASTÓCITOS EM LESÕES DE QUEILITE ACTÍNICA**

**JOÃO PESSOA  
2011**

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Federal da Paraíba para obtenção do título de Mestre em Diagnóstico Bucal.

**Orientador(a):** Prof.(a) Dr.(a) Maria Sueli Marques Soares

**Co-Orientador(a):** Cláudia Cazal Lira

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**2011**

**A744d** Arnaud, Rachel Reinaldo.

Densidade de mastócitos em lesões de queilite actínica / Rachel Reinaldo. – João Pessoa: [s.n.], 2011.

70 f. : il.

*Orientadora: Maria Sueli Marques Soares.*

*Coorientadora: Cláudia Cazal Lira.*

*Dissertação (Mestrado) – UFPB/CCS.*

1. Mastócitos. 2. Queilite actínica. 3. Carcinoma de células escamosas.

*BS/CCS/UFPB*

*CDU: 616.31-006(043.3)*

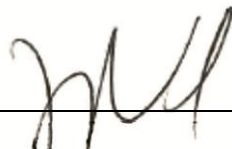
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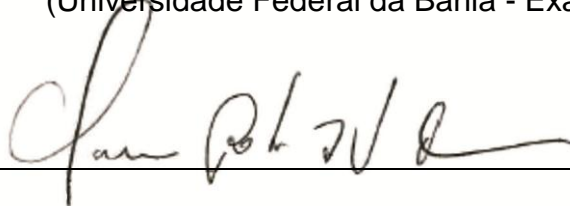
Data da Defesa : 05/12/2011

**Banca Examinadora**



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Prof . Dr . Jean Nunes dos Santos  
(Universidade Federal da Bahia - Examinador)



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Prof <sup>a</sup>. Dr <sup>a</sup>. Claudia Roberta Leite Vieira de Figueiredo  
(Universidade Federal da Paraíba - Examinadora)

---

Prof <sup>a</sup>. Dr <sup>a</sup>. Maria Sueli Marques Soares  
(Universidade Federal da Paraíba - Orientadora)

**JOÃO PESSOA**  
**2011**

## DEDICATÓRIA

Dedico este trabalho à Deus, aos meus pais  
e aos meus irmãos, razão de tudo que eu faço  
e acredito.

## AGRADECIMENTOS

À Deus, por ser Presença em minha vida e luz nos meus caminhos.

Aos meus pais, Reinaldo e Socorro, pelo amor incondicional.

Aos meus irmãos pela amizade, afeto e companheirismo constantes. Ao meu irmão Reinaldo, um agradecimento especial, pelos ensinamentos de vida e exemplo de honestidade, responsabilidade e perseverança.

Aos meus familiares e cunhados, pelas demonstrações de carinho.

Aos meus sobrinhos, pelo simples fato de existirem e sorrirem para mim.

À minha orientadora, mestre e amiga, Prof<sup>a</sup>. Dr<sup>a</sup>. Maria Sueli Marques Soares, pela contribuição, experiência, incentivo e paciência dedicados durante o desenvolvimento deste trabalho.

À Prof<sup>a</sup>. Claudia Cazal Lira, pelos ensinamentos e valiosa contribuição a este estudo.

Ao Prof. Frederico Barbosa de Sousa, por disponibilizar o Laboratório de Microscopia e Imagem Biológica – CCS/UFPB para análise dos dados.

Aos professores da Disciplina de Estomatologia, por ampliarem meus conhecimentos e despertarem em mim o interesse pela Estomatologia.

Ao Hospital Napoleão Laureano, pelo fornecimento dos casos de Queilite Actínica usados no presente estudo.

Ao laboratório de Patologia da UFPB, pelo fornecimento de material usado no presente estudo.

Aos funcionários do laboratório de Histologia e Patologia da UFPB, pela contribuição nos cortes e colorações deste trabalho.

A todos que direta ou indiretamente contribuíram para que esse trabalho fosse realizado.

Obrigada a todos vocês.

*“A mente que se abre a uma nova idéia jamais voltará ao seu tamanho original.”*

Albert Einstein

## RESUMO

O objetivo do estudo foi avaliar a densidade de mastócitos nas lesões de queilite actínica e sua correlação com os processos de inflamação e displasia epitelial, comparando a controle normal. Para o grupo queilite actínica, selecionaram-se 33 casos de registrados no Serviço de Cirurgia de Cabeça e Pescoço do Hospital do Napoleão Laureano, PB. E para o controle, 9 blocos com diagnóstico de mucocele. Os blocos parafinados foram cortados e corados em Hematoxilina e Eosina e por Azul de toluidina. A contagem dos mastócitos foi realizada em 8 campos por espécimes. Realizou-se análise estatística descritiva e aplicaram-se testes U de Mann-Whitney, Kuskall-Wallis, Qui-Quadrado e o coeficiente de Spearman, considerando  $p < 0,05$ . No grupo queilite actínica, 57,6% apresentaram algum grau de displasia epitelial, sendo 39,4% displasia leve, 15,2% moderada e 3% severa. Em 21,2% da amostra foi observado carcinoma de células escamosas de lábio. A presença de elastose solar foi observada em 81,8% dos casos e algum grau de inflamação em 84,9%, sendo 39,4% leve, 15,2% moderado e 30,3% intenso. Os mastócitos estavam presentes em 87,8% dos casos. A média de mastócitos no grupo queilite actínica foi de  $17,42 \pm 10,43$  células/ $\mu\text{m}^2$  e no controle  $1,78 \pm 1,64$  células/ $\mu\text{m}^2$ , com diferença estatisticamente significante ( $p < 0,001$ ). A densidade dos mastócitos foi significativamente maior nos casos de carcinoma com  $p = 0,001$ . Houve correlação estatisticamente significante entre densidade de mastócitos e os processos de displasia ( $p = 0,004$ ) e infiltrado inflamatório ( $p = 0,000$ ); e entre displasia epitelial e infiltrado inflamatório ( $p = 0,002$ ). O aumento da densidade dos mastócitos sugere uma possível participação dessas células no processo de transformação maligna da lesão.

**Palavras-chave:** Mastócitos, Queilite actínica, Carcinoma de células escamosas.

## ABSTRACT

The objective of this study was to evaluate the density of mast cells in the lesions of actinic cheilitis and its correlation with the processes of inflammation and epithelial dysplasia. We selected 33 cases of actinic cheilitis recorded in the Department of Head and Neck Surgery, Hospital Dr. Laureano Napoleon, PB. The paraffin blocks were cut and stained with hematoxylin and eosin and toluidine blue. The count of mast cells was performed in 8 fields per case and final reading with the average value expressed. Analysis was descriptive and inferential statistics, and tests were applied to the Mann-Whitney U, Kuskall-Wallis test, chi-square and Spearman coefficient, considering  $p < 0.05$ . Of the total sample, 57.6% had some degree of epithelial dysplasia, mild dysplasia was 39.4%, 15.2% moderate and 3% severe. In 21.2% of the sample was observed squamous cell carcinoma of the lip. The presence of solar elastosis was observed in 81.8% and some degree of inflammation in 84.9%, as well as 39.4% mild, 15.2% moderate and 30.3% intense. Mast cells were present in 87.8% of cases. The average number of mast cells in specimens of actinic cheilitis was  $17.42 \pm 10.43$  cells /  $\mu\text{m}^2$  and normal mucosa  $1.78 \pm 1.64$  cells /  $\mu\text{m}^2$ , and this difference was statistically significant ( $p < 0.001$ ). The density of mast cells was significantly higher in cancer cases with  $p = 0.001$ . There was a statistically significant correlation between the density of mast cells and the processes of dysplasia ( $p = 0.004$ ) and inflammatory cell infiltration ( $p = 0.000$ ) and between epithelial dysplasia and inflammatory cell infiltration ( $p = 0.002$ ). The increased density of mast cells suggests a possible role of these cells in the malignant transformation of the lesion.

**Key-words:** Mast cells, Actinic cheilitis, Squamous cells carcinoma.

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# 1 INTRODUÇÃO GERAL

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A queilite actínica (QA) é uma importante lesão bucal com potencial de transformação maligna podendo originar carcinoma de células escamosas (CCE) de lábio (VAN DER WALL, 2009); e que afeta grande número de pessoas que se expõem excessivamente à radiação solar (PERUZETTO, 2006).

A radiação ultravioleta (UV) tem propriedade imunomoduladora e inflamatória. Estudos mostram que os mastócitos estão significativamente aumentados na pele exposta a radiação UV (GONZALEZ, MORAN, KOCHEVER, 1999). O mesmo fato foi evidenciado em lesões de Q.A (ROJAS et al., 2004) e em carcinoma de lábio (ROJAS et al., 2005) . Autores como Rojas et al. (2004) apontam a necessidade de estudos que possam analisar a contribuição dos mastócitos no processo de malignização da QA.

Os mastócitos são células de grande impacto sobre o microambiente tecidual e reconhecidas como importantes efectoras nas alterações causadas pela radiação ultravioleta (UV) na pele, acredita-se que contribuem no microambiente lesional facilitando a carcinogênese e metástase (HUANG et al., 2008).

Acredita-se que no microambiente tumoral haja fatores capazes de influenciar vários processos celulares tais como o crescimento, morte, diferenciação, migração e invasão, de modo que, o infiltrado inflamatório tumor-associado pode contribuir para a tumorigênese (BALKWILL, MANTOVANI, 2001). E, neste contexto, a participação dos mastócitos tem sido questionada e estudada por vários autores.

Em modelo experimental de carcinogênese ficou evidenciado o aumento da densidade de mastócitos associado ao desenvolvimento de carcinomas, pois estas células atuam na regulação da angiogênese durante os estágios pré-maligno e

maligno da carcinogênese (COUSSENS et al., 1999). A presença de mastócitos e sua distribuição em lesões com potencial de transformação maligna e em lesões malignas indicam possível associação dessas células com a severidade das lesões, bem como com o aumento da imunossupressão provocada pela radiação UV (GOMES et al., 2008; ARAÚJO et al., 2010). Por outro lado, outros estudos sugerem que os mastócitos exercem efeito tumoral antagônico e apresentam efeito inibitório sobre a proliferação de ceratinócitos (HUTTUNEN et al., 2001; THEOHARIDES; CONTI, 2004).

Considerando o acima exposto nos propusemos no presente estudo analisar a densidade dos mastócitos em QA segundo as características histológicas da lesão e comparando com a mucosa normal.

**2 OBJETIVOS**

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## **2.1 OBJETIVO GERAL**

O objetivo do presente estudo foi verificar a participação dos mastócitos no processo de transformação maligna da QA para CCE através da determinação da sua presença e densidade nos diversos graus de displasia, carcinoma e outros achados histológicos como a presença do processo inflamatório.

## **2.2 OBJETIVOS ESPECÍFICOS**

- Correlacionar à densidade dos mastócitos em QA e mucosa normal.
- Correlacionar à densidade dos mastócitos com os diversos graus de displasia epitelial e CCE.
- Correlacionar à densidade dos mastócitos com a presença de infiltrado inflamatório.
- Descrever a localização tecidual dos mastócitos em lesões de QA.

**3 CAPÍTULOS**

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Estes capítulos são compostos por 3 artigos. O primeiro, descrito no Capítulo 1, é uma revisão sistemática intitulada “Mast cell participation on malignant transformation of Actinic Cheilitis: A systematic review.” que foi submetido à avaliação para publicação no periódico International Journal of Dermatology; o segundo, descrito no Capítulo 2, é um artigo original intitulado “Actinic cheilitis: histopathological evaluation of 44 cases.”, que foi submetido à avaliação no periódico Pathology and Oncology Research; e o terceiro, descrito no Capítulo 3, é um artigo original intitulado “Density of mast cells in lesions of actinic cheilitis”, que foi submetido à avaliação no periódico Archives of Dermatological Research.



Artigo em processo de envio para periódico International Journal of Dermatology.

**Mast cell participation on malignant transformation of Actinic Cheilitis: A systematic review.**

SOARES MSM<sup>1</sup>

ARNAUD RR<sup>2</sup>

LIRA CC<sup>3</sup>

Universidade Federal da Paraíba

<sup>1</sup> Associated Professor, Department of Clinical and Social Dentistry, School of Dentistry, Universidade Federal da Paraíba, João Pessoa, Brazil;

<sup>2</sup> Postgraduate student, Department of Clinical and Social Dentistry, School of Dentistry, Universidade Federal da Paraíba, João Pessoa, Brazil;

<sup>3</sup> Adjunct Professor, Department of Clinical and Social Dentistry, School of Dentistry, Universidade Federal da Paraíba, João Pessoa, Brazil;

**Keywords:** mast cell, actinic cheilitis, carcinogenesis.

## **Abstract**

**Background:** No one knows the role of mast cells in the pathogenesis and malignant transformation of actinic cheilitis (AC) as well as in the carcinogenesis of squamous cell carcinoma of the lip (SCC).

**Objective:** Assess the relationship of the presence of mast cells in the pathogenesis and malignancy of QA through a systematic literature review.

**Methods:** Electronic search was performed on the primary information basis Medline (via PubMed), Embase and Cochrane Central Clinical Trials for full-text articles, in English, published until August 2011 and that cited the level of association between mast cells and the process of malignancy of AC and / or lip cancer. Terms employed were: mast cell and actinic cheilitis, and mast cell and lip cancer. The search was limited to the titles of the articles. The Newcastle-Ottawa scale for qualifying the articles was used.

**Results:** The assessment was concluded with nine articles on the subject studied, eight of them of high quality and one of moderate quality. In all studies, the mast cells were identified both in AC and in SCC of lips and statistically significant differences, as to the increased density of these cells in AC and SCC, were identified when compared to normal mucosa. The location of mast cells in tissues was varied, but always related to the region of the only lamina, solar elastosis and stromal tumor.

**Conclusion:** There is evidence of the relationship between the presence of mast cells and events in the process of malignant transformation of AC in SCC of the lip.

## Introduction

Actinic cheilitis is a frequent lesion in the lower lip and is characterized by a chronic inflammatory process caused by excessive exposure of the lips to ultraviolet radiation<sup>1-4</sup>. It is considered a potentially malignant lesion in view of its possible transformation to a squamous cell carcinoma (SCC) of lips<sup>3</sup>.

Mast cells are connective tissue cells of mesenchymal origin whose chemical mediators act in the innate and acquired immune response, as well as in the degradation of extracellular matrix and activate the collagenase providing spaces for the neovascularization necessary to the recovery process<sup>5-6</sup>. The mast cell degranulation results in the release of specific substances, among them the tryptase, kinase, MMP, heparin, histamine, fibroblast growth factor, TNF- $\alpha$ , interleukins, chemokines and lipid mediator<sup>5</sup>. In the tumor microenvironment, mast cells are important effector cells of the deleterious effects of ultraviolet radiation, which can facilitate the process of carcinogenesis and metastase<sup>7</sup>. Studies show that the density of mast cells is increased in actinic cheilitis, and SCC of the lip<sup>8-9</sup>. Some authors claim that the accumulation of these cells is associated with the progression and prognosis of the tumor<sup>10-12</sup>.

Although several studies investigate the involvement of mast cells in photocarcinogenesis particularly skin and lip lesions<sup>9</sup>, the data are controversial and the real role of mast cells in the tumor microenvironment of these lesions is still unknown. The issue has aroused interest and requires more attention, therefore, it is proposed in this study to perform a systematic review aiming to analyze the literature concerning the presence of mast cells and their role in the pathogenesis of actinic cheilitis and its transformation to SCC of the lip.

## **Methodology**

### **Literature research**

To identify relevant literature on the role of mast cells in actinic cheilitis electronic search was conducted in the primary information bases Medline, Embase and Cochrane Central Clinical Trials, and it was limited to articles published retrospectively until August 2011. In the search strategy performed in MEDLINE (via PubMed) were used the following terms: mast cell and and actinic cheilitis and mast cell and lip cancer. We used the same keywords in English and in Portuguese for further research in Central and Embase. The search was limited to the titles of articles. From the results of initial screening, which was performed by independent evaluators, 29 journals that published relevant articles were identified (Fig. 1). Disagreements between reviewers were resolved by consensus.

### **Primary Outcome**

The primary outcome of interest in this study was the participation of mast cells in the process of progression of actinic cheilitis for squamous cell carcinoma of the lip. The Aspects: density, location and degranulation of mast cells were added to the primary outcome as indicators of change and cellular activity.

### **Eligibility criteria and screening process of the studies**

The articles identified by the initial search strategy were evaluated according to the following inclusion criteria: articles published in English, full text which were associated with the level of concentration of mast cells with epithelial changes produced in actinic cheilitis and / or cancers of the lip. Articles were excluded from the study of literature reviews, clinical case studies and studies that were related to mast cell tumors

(mastocytoma). The final screening assessment reports consisted of the full-text of selected articles.

### **Methodological quality assessment**

Two independent reviewers performed a comparative analysis of methodological quality using the scale NEWCASTLE-OTTAWA<sup>13</sup> for observational studies. This scale performs critical assessment where they are considered high-quality studies reach those who score  $\geq 6$ , a total of 9 points. We conducted an adaptation of the score being as follows: studies with score  $\geq 6$  (high quality) studies with a score of 3 to 5 (moderate quality) and studies with score  $<3$  (low quality). Following the sum of the number of points in the items assessed in each article.

### **Elements for the abstracts of the studies surveyed**

The basic elements of the abstract of each study were defined by one investigator and independently verified by another reviewer, is evaluated and resolved disagreements by consensus. In Table 1 are shown the elements of interest the articles evaluated in this study employed.

### **Results**

In the initial search by title the electronic search revealed 29 citations of which 20 articles were excluded because they are not related to the question, because they are repeated, referring to mast cell tumors, do not present the full text available in English or as they were reported case. Thus, after applying the eligibility criteria were selected for review nine relevant studies, which were qualified by the Newcastle-Ottawa scale, and obtained the following result: eight articles of high quality and one moderately (Figure 1).

In nine studies evaluated the samples were composed of paraffin embedded specimens of AC and / or lip SCC and controls consisting of normal labial mucosa. Most of the lesions studied in the samples was obtained from studies of men with white skin and with a mean age of 54.5 years.

In the study of the density of mast cells was observed that some authors compared lesions of actinic cheilitis and tissue normal<sup>14-16</sup>, while in others the comparison was between lesions of actinic cheilitis, lip cancer and tissue normal<sup>8,10,17-18</sup> or between injuries SCC the lip and tissue normal<sup>9,11</sup> (Table 2).

All studies identified mast cells both in AC lesions and SCC of the lip. The presence of inflammation was recorded in seven of these articles<sup>8,10,14-18</sup> and the presence of solar elastosis in six<sup>8,10,14,16-18</sup>. Moreover, the presence of mast cells was associated with neovascularization in tissue local<sup>9-11,14,16-18</sup>.

The location of mast cells in tissues was varied, but always related to the region for AC or SCC. In samples AC<sup>14-16</sup> mast cells were mainly located in the region of the lamina propria, along the surface epithelium and in the areas of solar elastosis. However, were also identified in the vicinity of areas of epithelial dysplasia, bordering the neoplastic islands<sup>8,10,17-18</sup>, or in the vicinity of neoplastic vessels<sup>9,11</sup>.

Some of the articles studied reported that mast cells when present were active and degranulated<sup>11,14,16</sup>. In cases related to AC<sup>14,16</sup> degranulation were associated with inflammation and areas of solar elastosis and in the case of squamous cell degranulation was related to increased number of blood vessels (neovascularization) around the area tumoral<sup>11</sup>.

In all studies of actinic cheilitis<sup>8,10,14-18</sup>, mild, moderate, and severe epithelial dysplasia was identified, always associated with mast cells in these areas. In the cases of SCC<sup>8-11,17-18</sup>, mast cells were always located in the region of the stroma tumor.

All studies reported a statistically significant difference between the increased density of mast cells in cases of lesions of actinic cheilitis and / or squamous cell carcinoma compared with normal mucosa; on the other hand there was no significant association between the presence of mast cells and differences in the degree of epithelial dysplasia, although the number of mast cells was increased compared with normal mucosa. Among the studies that assessed SCC was found in a significant difference between the increased density of mast cells and the degree of histological differentiation of the tumor<sup>17</sup>. The density of mast cells was increased in areas of high degradation of collagen<sup>10</sup>.

## Discussion

The activated mast cells release mediators or substances such as histamine, heparin, and proteoglycan enzymes (tryptase, chymase), growth factors and angiogenesis, leukotrienes, prostaglandins, among others, who are responsible for promoting inflammation, matrix destruction, tissue remodeling and angiogenesis<sup>19-21</sup>. The combined action of these chemical mediators can alter the microenvironment around the damaged epithelium by UV radiation - initiating agent, secondarily contributing to the process of malignant transformation of AC lesions and progression to SCC of the lip<sup>22</sup>.

In the context of chemical carcinogenesis, a strong intracellular oxidative stress with the generation of reactive oxygen species such as superoxide radicals and hydrogen peroxide, which is believed to be responsible for the formation of adducts in DNA<sup>23-25</sup>. In AC lesions, ultraviolet radiation is the physical agent initiating the process of carcinogenesis, being able to modify the structure of DNA molecules by both oxidative stress and by formation of DNA adducts (DNA adducts) resulting in mutations<sup>26-27</sup>. The inflammatory chemical mediators, which are released by mast cells near the damaged epithelium, can act as promoters of the

transformation process allowing the progression of the disease to a clinically detectable malignancy.

However, it is important to note that not all lesions and conditions with malignant potential, necessarily undergo transformation into a malignant neoplasia itself<sup>28-29</sup>. The probabilistic field involves genetic factors (ability to recover the damaged DNA), intermittent environmental exposures (cumulative effect), time and possibilities for early intervention in removing the cause.

One of the conditions necessary for tumor growth has something to do to angiogenesis<sup>30-31</sup>, responsible for not only nutrition, but also the metastasis of malignant neoplasias<sup>32</sup>. Mast cells identified in the peritumoral region, specifically near neoformados<sup>11</sup> vessels may be reinforcing the hypothesis that angiogenic chemicals mediators, when released, provide tumor growth. Remember that the action of metalloproteinases in the degradation of extracellular matrix favors the process of neoplastic growth.

## **Conclusion**

The concentration of mast cells often increased in areas of dysplastic epithelium and the tumor area, **as well as** its location always associated with epithelial most battered areas (solar elastosis and inflammatory infiltrate) **and** perivascular region suggest a strong relationship between mast cells and the process of malignant transformation of AC into SCC of lips.

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**Figure 1:** Number of studies according to the processes of searching, selection and evaluation of literature.

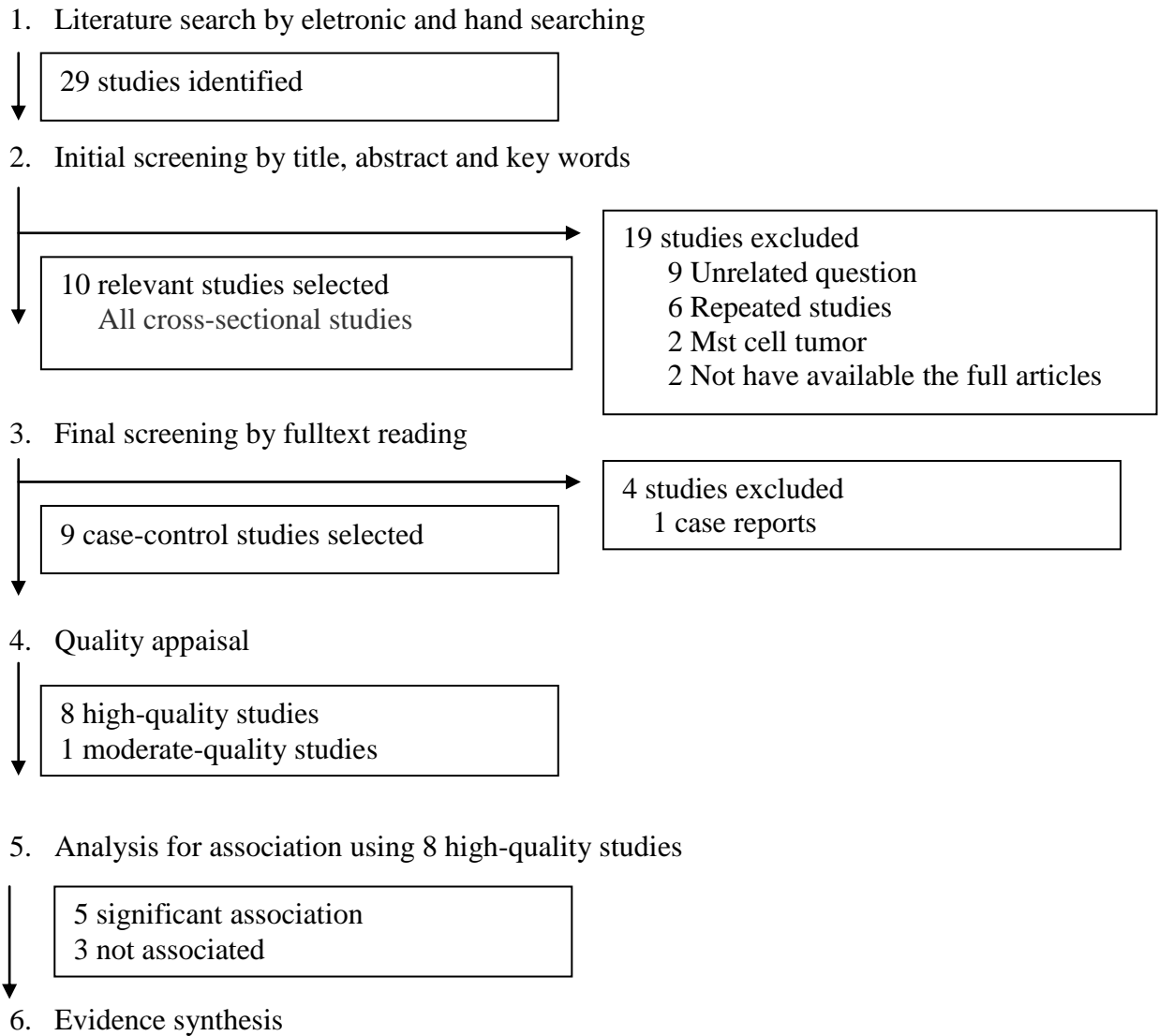


Table 1: Characteristics of the studies summarized researched the type of the study group and factor studied and type of association estimated.

First author, year	Rojas, 2004 Chile	Rojas, 2005 Chile	Gomes, 2008 Brazil	Rojas, 2009 Chile	Costa, 2009 Brazil	Araújo, 2010 Brazil	Souza, 2010 Brazil	Parizi, 2010 Brazil	Freitas, 2011 Brazil
Features									
Histopathological diagnosis (group sample types)	NOM/AC	NOM/SCC	NOM/AC/SCC	NOM/AC	NOM/AC/SCC	NOM/AC	NOM/AC/SCC	SCC	NOM/AC/SCC
Factor studied	Assess the contribution of mast cells in the degeneration of connective tissue in AC	Quantify and characterize subpopulations of mast cells in lip SCC	Compare the density of mast cells in NOM, degrees of dysplasia and SCC	Correlation cox2/triptase / PAR2 in progression AC	Investigate the population of MCs and their relation to microscopic parameters found	Investigate the presence of MCs in AC with different degrees of epithelial dysplasia	Determine the contribution of MCs in the process of carcinogenesis	Compare the concentration of MCs in SCC of the mouth and skin and assess whether there is correlation with the degree of differentiation of these tumors	Evaluate the density of migration and its association with MCs (MMP) 9 in SCC and AC
Association type estimate: statistical significance	MCs and their proteases were increased in AC compared with NOM *, which may contribute to the formation of elastosis favoring malignancy	MCs were increased in SCC compared with NOM * can contribute to the progression of SCC, stimulating angiogenesis, promoting extracellular matrix degradation and invasion	Increased density of MCs in AC and SCC compared with NOM *, suggesting an important role of these cells in the development of these lesions	MCs increased in AC compared with NOM, increased PAR2 and COX2 '	Increased angiogenesis and MCs * may reflect a change in the tumor microenvironment during photocarcinogenesis	Increased density of MCs in cases of mild and moderate dysplasia compared with NOM *, although no correlation existed between this increase and the degree of dysplasia	Increased density of MCs during carcinogenesis and these cells can be related to the stimulation of tumor angiogenesis	The concentration of MCs was lower in SCC of the mouth except when the tumor is located on the lip *.	Density of MCs increased in SCC compared with AC and NOM * and may promote the progression of SCC.

Factors studied in the articles and the type of association estimated.

NOM, normal oral mucosa; AC, actinic cheilitis; SCC, Squamous Cell Carcinoma of lip; MCs, mast cells, \* statistically significant ( $p < 0.05$ ).

Table 2: Characteristics of studies and evaluation of Newcastle-Ottawa Scale

First author, year and source	Typy of study	Sample size	Mean age (years)	Increased density of MCs	Degranulation of MCs	Location of MCs	NOS	
							Coding	Score
Rojas, 2004; Chile	Case-control AC/NOM	23	25-74	Y	Y	Near the area of solar elastosis and inflammation	10111111	7*
Rojas, 2005; Chile	Case-control SCC/NOM	29	25-84	Y	Y	Intratumoral and peritumoral stroma, around vessels	10111111	7*
Gomes, 2008; Brazil	Case-control AC/SCC/NOM	41	-----	Y	-----	-----	10111111	7*
Rojas, 2009; Chile	Case-control SCC/NOM	69	22-73	Y	-----	Lamina propria	10111111	7*
Costa, 2009; Brazil	Case-control AC/SCC/NOM	58	33-90	Y	-----	Scattered in the connective tissue and near the tumor cells	10111111	7*
Araújo, 2010; Brazil	Case-control AC/NOM	38	20-75	Y	Y	Lamina propria, solar elastosis and around of vessels	10111111	7*
Souza, 2010; Brazil	Case-control AC/SCC/NOM	71	20 +	Y	-----	Stroma adjacent to dysplastic tissue / neoplastic, near of vessels and nerves	10111111	7*
Parizi, 2010; Brazil	Case-control SCC	64	50 +	Y	----	----	10001111	5
Freitas, 2011; Brazil	Case-control AC/SCC/NOM	47	---	Y	-----	Stroma tumor, bordering the invasion of the epithelium and near the epithelium adjacent to tumor	10111111	7*

AC= actinic cheilitis, SCC= squamous cell carcinoma NOM= normal oral mucosa.

The studies were conducted in Brazil and Chile. The relationship question / answer was evaluated in nine case-control and eight articles were classified as high quality.

Y, Yes; + ages above \*evaluated for high-quality methodology by the modified Newcastle-Ottawa Scale (NOS). When a study presented all the criteria of NOS column appears as 11111111. Studies with scores of 6 or more, four or five, and three or fewer studies were classified as high, moderate and low quality, respectively.



Artigo em processo de envio para periódico Pathology and Oncology Research.

**Actinic cheilitis: histopathological evaluation of 44 cases.**

Rachel Reinaldo Arnaud\*, Maria Sueli Marques Soares\*\*, Marcos Antônio Farias de Paiva\*\*, Cláudia Roberta Leite Vieira de Figueiredo\*\*, Cláudia Cazal Lira\*\*, Francisco Diogo Carrilho de Oliveira Filho \*

\* Postgraduate student, Department of Clinical and Social Dentistry, School of Dentistry, Universidade Federal da Paraíba, João Pessoa, Brazil;

\*\* Adjunct Professor, Department of Clinical and Social Dentistry, School of Dentistry, Universidade Federal da Paraíba, João Pessoa, Brazil;

**Abstract**

*Objective:* The purpose of this study was to describe the histopathological findings in lesions of actinic cheilitis (AC). *Methods:* We conducted a retrospective study from cases with clinical diagnosis of AC recorded in the histopathology of the Service of Head and Neck Napoleon Laureano Hospital, PB, from 2000 to 2007. We selected 44 paraffin blocks that had histologic reevaluation of conditions through the construction of new laminas. These new sections were stained with hematoxylin and eosin (HE) and histopathological evaluation was performed by two independent examiners, and the changes classified according to OMS. We conducted a descriptive statistical analysis in SPSS for Windows version 13. *Results:* Of the total sample, 52.3% (23) cases were diagnosed in men and 47.7% (21) in women aged 27 to 92 years old. Most individuals (81.9%) were over 40 years old. Regarding the histologic features, 68.2% (30) of cases showed some degree of epithelial dysplasia, 36.3% (16) classified as mild dysplasia, 20.4% (9) moderate dysplasia and 11.3% (5) severe dysplasia. In 15.9% (7) was squamous cell carcinoma of lip (SCC). In epithelial tissue lining lips, the most frequent histologic findings identified were the presence of hydropic degeneration (79.5%) and hypergranulosis (56.8%). Inflammatory infiltrate was observed in 88.6% of cases and 86.4% in solar elastosis. *Conclusion:* Atypical cellular and transformation to SCC are common features in actinic cheilitis. We stress the importance of early diagnosis and the preservation patient with this injury.

**Key-words:** Cheilitis, Squamous Cell Carcinoma, Solar radiation, Carcinogenesis

## **Introduction**

Actinic cheilitis (AC) is a disease that affects mainly the lower lip of men over 60 years of age, of fair skin that are exposed chronically and overexposure to ultraviolet (UV) rays [7,12]. It has great clinical importance because it is a recognized lesion with malignant potential [25].

Clinically, it has two forms: acute and chronic. The acute form is characterized by mild edema and erythema, fissures and severe ulcers, and occurs when there is excessive sun exposure in a short time. Often, there is the resolution of these clinical changes without irreversible epithelial changes. The chronic form occurs when there is prolonged and cumulative exposure to ultraviolet rays and usually develops irreversible epithelial changes. The most common clinical presentation displays dry, cracked lips, slight volume increase and diffuse, limit loss of semi-labial mucosa and skin, and papules and / or patches leukoplakia [11,19].

Histologically, AC can make changes in epithelial tissues, including atrophy and decreased production of keratin, a common occurrence with mild to severe dysplasia [4,22]. In connective tissue there are inflammatory infiltrate and solar elastosis, which are characterized by the degeneration of collagen fibers, which will then display basophilia and amorphous appearance [15].

A large number of squamous cell carcinoma (SCC) of the lip is associated with the occurrence of a previous injury of actinic cheilitis [1,19]. The malignant process may not be visible to the eye at the time of clinical examination, although the histological level, epithelial dysplastic changes and the presence of inflammatory process in the examined tissue are predictive of malignant of the lesion [10,20].

Considering that AC is a frequent labial injury which may progress to SCC and it is important to conduct studies to discuss their histological changes, it is proposed in the present study to analyze a series of cases of such lesions histologically in order to describe the most common histological findings and contribute to the diffusion of knowledge among dentists.

## **Material and methods**

We conducted a retrospective laboratory study whose universe was represented by all cases with clinical diagnosis of AC recorded in the histopathology archive Service of Head and Neck Napoleon Laureano Hospital, João Pessoa, in the period 2000 to 2007. Eighty-nine paraffin blocks of biopsies of actinic cheilitis were initially separated from the files, and

among these, we selected those with pathological conditions for reevaluation by making new cuts. Thus, 44 blocks were cut into sections of 5µm and stained with HE and then evaluated by two independent observers using light microscopy. Differences between examiners were resolved by consensus.

To analyze the degree of epithelial atypia, we employed the criteria established by the World Health Organization, according to Barnes's considerations [4]. For each specimen, the grading of epithelial dysplasia was based on observation of the magnitude of changes involving the extension of the epithelium, considering: Absence of epithelial dysplasia when there was no change in the epithelium, epithelial mild dysplasia when only the lower 1 / 3 of the epithelium presented cellular atypia, moderate epithelial dysplasia, when even the middle 1 / 3 of the epithelium had dysplastic changes, severe epithelial dysplasia when changes reached more than 2 / 3 of the epithelium. It was characterized as carcinoma *in situ* who presented the specimen thickness atypia throughout the epithelium and invasive squamous cell carcinoma when there was disruption in the areas of basement membrane [12].

Other histological changes were also considered, including presence and type of keratin, hydropic degeneration, spongiosis, epithelial atrophy, epithelial hyperplasia and hypergranulosis in epithelial tissue. Moreover, the presence of solar elastosis and inflammatory infiltrate in the connective tissue were considered.

The data were processed using SPSS (Statistical Package for Social Sciences) for Windows version 13.0, where they performed a descriptive statistical analysis.

This study was approved by the Ethics Committee in Research of Hospital Universitário Lauro Wanderley CEP/ HULW / UFPB under protocol No. 448/10.

## Results

From the total sample it was observed that 52.2% (23) of the cases occurred in men and 47.7% (21) in women. In relation to the age of patients, it ranged from 27 to 92, being 81.8% (36) over 40 years old. As for the location of the lesions of actinic cheilitis, it was observed that 100% were in the lower lip.

Histological evaluation revealed that 68.2% (30) of the cases had some degree of epithelial dysplasia, and 36.3% (16) of mild dysplasia, 20.4% (9) of moderate dysplasia and 11.3% (5) of severe dysplasia. In 15.9% (7) SCC occurred, being 4.5% (2) carcinoma *in situ* and 11.3% (5) invasive carcinoma (Fig. 1).

Table 1 shows the distribution of the main findings of histological specimens, which shows that the most frequent were hidropic degeneration with 79.5% and 56.8% with hypergranulosis.

In the underlying connective tissue, we observed the presence of inflammatory infiltrate in 88.6% (39) of the cases, and solar elastosis (86%) (38) (Fig. 2).

## Discussion

In the Northeast region of Brazil warm climate prevails with high levels of solar radiation which makes it even more important to conduct studies of lesions such as actinic cheilitis [24]. According to Miranda, Ferrari, Calandro [17], the longer the exposure time, the greater the severity of AC lesions in subjects exposed to UV rays. Therefore, early diagnosis and proactive observation of the patient is of great importance to prevent disease progression.

The reasons for the increased susceptibility of the lips to changes caused by actinic cheilitis are various and includes a thinner keratin in the area, thin epithelial layer, a small amount of melanin and decreased secretion of sebaceous glands and sweat glands, ie, mechanisms normally involved in skin protection against radiation. Moreover, the AC lesions occur more frequently in the lower lip for this site is more directly exposed to sunlight [5,12]. Our study showed 100% of lesions in the lower lip, and this result is similar to Marcopoulos, Albanidou-Farmaki, Kayavis [15], however, Kaugars et al [12] and Pimentel et al [20] also found lesions in the upper lip in 3% of the cases.

The classic demographic profile of patients at high risk for QA reported in the literature is men over 50 years of age, fair skin and high solar exposure [6]. The results of this study are consistent with this profile of patients. Most of the patients found having the lesion was men [2,7,9,12,15,17,26], although the number of women has also been great, probably due to the nature of work of these patients. Cavalcante, Anbinder, Carvalho [7] claims that women may be less likely to suffer AC due to the use of lipstick, which can partially protect lips from the sun. In the present study, patients over 40 years old were most affected, confirming the study of Cavalcante, Anbinder, Carvalho [7] (75.86%), however, other studies observed prevalence from the fifth decade of life [2, 9,21,26].

The histopathological features of actinic cheilitis are important for diagnosis, prognosis and treatment of injury. The presence of epithelial dysplasia is a common finding and was observed in most lesions of the present study, this is corroborated by other studies [12,15], and differs from results of Cavalcante, Anbinder, Carvalho [7] in which all cases of actinic cheilitis evaluated had some degree of epithelial dysplasia. In this sample, in the cases

with dysplasia, it was observed a higher prevalence of mild dysplasia and moderate dysplasia in agreement with the results of other authors [2-3,12,15,20]. The highest percentage of mild dysplasia suggests that the degree of epithelial atypia alone does not indicate the malignant potential of AC [20]. On the other hand, the results of Cavalcante, Anbinder, Carvalho [7] showed higher percentages of moderate dysplasia or severe dysplasia in cases of AC. Besides the cases of epithelial dysplasia, it was observed high prevalence of SCC (15.5%) similar to the findings of Kaugars et al [12] and Markopoulos Albanidou-Farmaki, Kayavis [15]. These data underscore the potentially malignant lesions such as AC.

Our results showed that most lesions showed changes in epithelial thickness, ranging from hyperplastic to atrophic, a finding also described by Kaugars et al [12], whose AC lesions exhibited both hyperplasia and atrophy in 68.4% of their sample. In a smaller percentage, these same findings were reported by Pimentel et al [20] and Rojas [22], with a prevalence of 40.6% and 46.6%, respectively. .

The epithelial hyperplasia can occur in up to 100% of the samples of AC [16], as well as atrophy can occur in relatively high frequency [7,16]. Other epithelial alterations, frequently observed in this study, were hidropic degeneration, spongiosis and hypergranulosis. Markopoulos, Albanidou-Farmaki, Kayavis [15] observed a much higher percentage (75%) of spongiosis in relation to our study. The presence of ortoqueratina was more prevalent than paraqueratina, being the result similar to those of studies Kaugars et al [12] and Cavalcante, Anbinder Carvalho and [7].

Some studies indicate the solar elastosis as a histopathological more consistent and constant finding of actinic cheilitis [2,12,15-16,22-23,]. The solar elastosis reflects the sun damage to the tissue and may be an important factor in the development of AC without, however, being predictive of the development of AC to SCC [20]. In the present study, the solar elastosis was present in 86.36% of cases differing in some studies [7,15,22] that found solar elastosis in 100% of their samples.

The inflammatory process is recognized as a defensive mechanism of the body. However, there is evidence that the inflammatory reaction can act in the initiation, promotion and progression of tumors, since the mediators of inflammation contribute effectively to changes in the tumor microenvironment [13-14]. Several types of cancers arise at sites of infection, chronic irritation and inflammation [18]. However, this relationship is not yet fully known [8]. The results of this study showed that the inflammatory infiltrate occurred in 88.6% of the cases, being the moderate and severe inflammation the most frequent. Whereas in the studies of Cavalcante, Anbinder and Carvalho [7] and Rojas [22] inflammation occurred in

100% of the cases. In the study by Pimentel et al [20] this finding was strongly associated with the presence of epithelial dysplasia.

## Conclusion

Based on the results of the sample we can conclude that the cellular atypia and transformation to CCE are common features in actinic cheilitis. We stress the importance of early diagnosis and the preservation of the patient with this injury.

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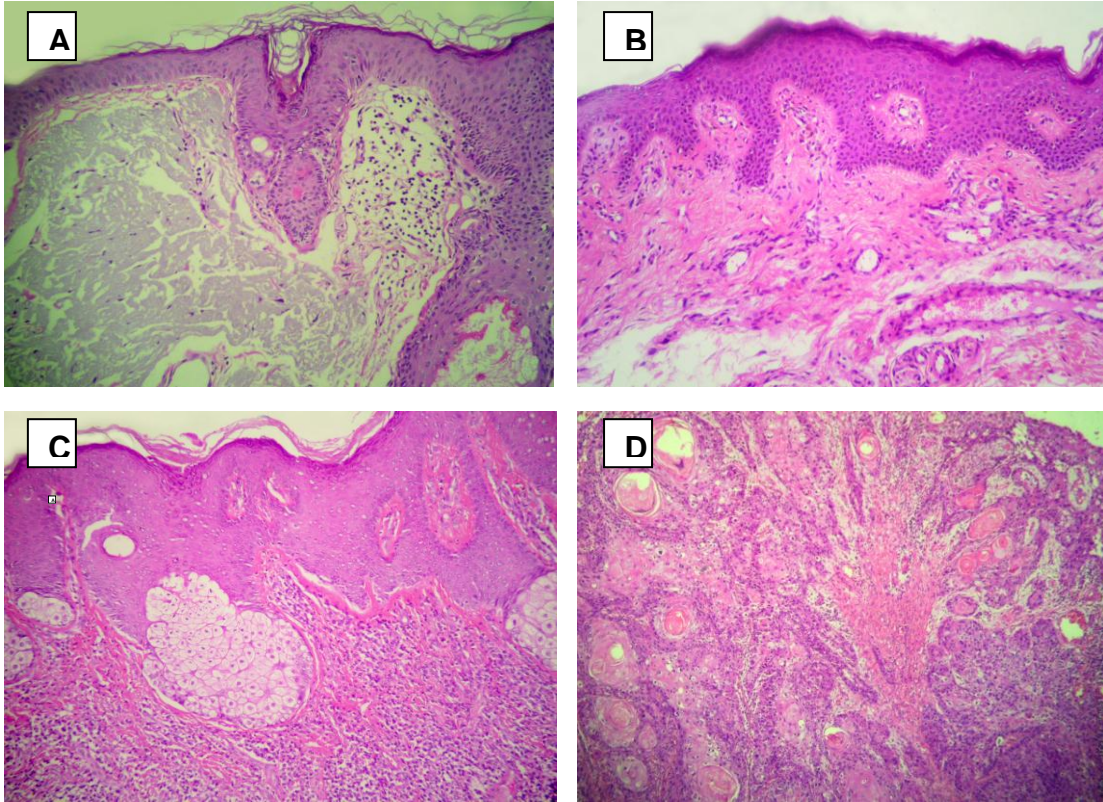
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**Table 1:** Distribution of the main histological characteristics of 44 specimens of actinic cheilitis.

<b>Histological Findings</b>		<b>n</b>	<b>%</b>
Parakeratosis		14	31,8
Orthokeratosis		35	79,5
Epithelial atrophy		13	29,5
Epithelial hyperplasia		17	38,6
Spongiosis		12	27,2
Hidropic degeneration		35	79,5
Hypergranulosis		25	56,8
Solar Elastosis		38	86,3
Inflammatory infiltrate	Mild	14	31,8
	Moderate	9	20,45
	Intense	16	36,36
Dysplasia	Mild	16	36,3
	Moderate	9	20,4
	Severe	5	11,3
Carcinoma <i>in situ</i>		2	4,5
Squamous cell carcinoma		5	11,36



**Figure 1:** Lesions of actinic cheilitis. **A** Presence of solar elastosis in injury AC with moderate dysplasia. **B** Lesions of AC without epithelial dysplasia. **C** Epithelium with mild dysplasia. **D** Squamous cell carcinoma exhibiting well-differentiated neoplastic islets. Hematoxylin-eosin, magnification 100X.



Artigo em processo de envio para periódico Archives of Dermatological Research.

**Density of mast cells in lesions of actinic cheilitis.**

Rachel Reinaldo Arnaud <sup>1</sup>  
Maria Sueli Marques Soares <sup>2</sup>  
Claudia Cazal Lira <sup>2</sup>

<sup>1</sup> Postgraduate student, Department of Clinical and Social Dentistry, School of Dentistry, Universidade Federal da Paraíba, João Pessoa, Brazil;

<sup>2</sup> Adjunct Professor, Department of Clinical and Social Dentistry, School of Dentistry, Universidade Federal da Paraíba, João Pessoa, Brazil;

## Abstract

The objective of this study was to analyze the density of mast cells in actinic cheilitis second the histological features of the lesion compared with normal mucosa. The sample comprised an experimental group of 33 cases with clinical diagnosed of actinic cheilitis. And a control group composed of nine blocks with specimens of normal oral mucosa. The paraffin blocks of the sample were cut and stained with hematoxylin and eosin and blue toluidine. The count of mast cells was performed 8 fields per case. The final reading was expressed with the average value of mast per case in cells /  $\mu\text{m}^2$ . In 57.6% of the cases there was some degree of epithelial dysplasia and 21.2% there was squamous cell carcinoma. The presence of inflammatory infiltrate and solar elastosis was observed in 84.9% and 81.8% of the cases, respectively. Mast cells were identified in 87.8% of the sample. The density of mast cells in the cases of actinic cheilitis was  $17.4 \pm 10.4$  cells /  $\mu\text{m}^2$ , and in normal tissue  $1.78 \pm 1.64$  cells /  $\mu\text{m}^2$ , with a significant difference ( $p < 0.001$ ). In addition, there was a statistically significant correlation between the density of mast cells with the processes of dysplasia ( $p = 0.004$ ) and inflammatory cell infiltration ( $p = 0.000$ ). The increased density of mast cells in actinic cheilitis lesions and its correlation with the processes of dysplasia and inflammation suggest involvement of these cells in disease progression to squamous cell carcinoma of the lip.

**Keywords:** Mast cells, actinic cheilitis, squamous cell carcinoma, carcinogenesis.

## Introduction

Actinic cheilitis (AC) is a potentially malignant lesion that can turn into squamous cell carcinoma (SCC) of the lip. It affects mainly the lower lip of fair-skinned people, who are 50 to 60 years old and exposed to excessive solar radiation [1-5].

Histologically, AC often reveals several epithelial changes, being common the occurrence of mild to severe dysplasia [6] and carcinoma *in situ* [7], and in the connective tissue, it is frequently observed solar elastosis and inflammatory infiltrate of variable degree [3-4,8].

Some authors claim that the inflammatory infiltrate tumor-associated contributes to squamous carcinogenesis [9-10]. Others believe that the mechanisms that result in malignization of actinic cheilitis may have the participation of components of the inflammatory process, like the mast cells, which are cells that proliferate after induction by ultraviolet radiation (UV) and that release potent mediators that act on inflammation, angiogenesis and degradation of the intercellular matrix [2,11-14]. Mast cells are present in greater amounts in lesions caused by UV radiation, such as the actinic cheilitis and squamous cell carcinoma of the lip. Some studies associate higher amount of mast cells to the development of actinic cheilitis [2,11].

In this context, this study aimed to determine the density of mast cells, the histopathologic features and qualify the inflammatory process in the lesions of actinic cheilitis, as well as the possible association between these variables, compared with normal tissue.

## Material and Methods

The study was approved by the Ethics Committee of Hospital Lauro Wanderley - CEP / HULW / UFPB under protocol number 448/10.

It was a case-control study where the experimental group was composed of 33 paraffin blocks of cases with clinical diagnosis of actinic cheilitis in subjects of both sexes, recorded in the Department of Head and Neck Dr. Napoleon Laureano Hospital, João Pessoa, PB, obtained in the period between the years 2000 to 2008. The control group consisted of nine blocks of paraffin embedded specimens of normal oral mucosa. To be included in the sample, the paraffin blocks should be able to be cut and stained again for histological analysis.

Each selected block was cut into 4  $\mu\text{m}$  thick sections to obtain two histological slides, one of them obtained by a staining routine technique with hematoxylin and eosin (H / E) and another slide stained with blue toluidine technique for identification of mast cells [11].

A histological evaluation was performed by two independent examiners in an optical microscope, where microscopic analysis of epithelial histology was conducted according to the criteria established by the World Health Organization (WHO). The dysplasia was classified according to WHO in mild dysplasia, moderate dysplasia and severe dysplasia [6]. The presence of solar elastosis and inflammatory infiltrate was also recorded, and the infiltration classified as mild, moderate or intense and in the selection of areas for analysis areas of ulceration were disregarded [15].

For the counting of mast cells, we used an optical microscope Motic BA 300  $\text{\textcircled{R}}$ , Canada, with a magnitude of 400x, attached to the computer with program Motic Images Plus 2.0. The reading was performed in 8 fields per slide, using a square reticulum (20x20), where each side of the field was 12 $\mu\text{m}$ , totaling an area of 144  $\mu\text{m}^2$  per field, the sum total of the eight fields equals to 1052  $\mu\text{m}^2$ . The average number of mast cells was obtained by reading the 8 fields and expressed as cells/ $\mu\text{m}^2$ .

Data were tabulated and statistical tests performed in SPSS (Statistical Package for Social Sciences) for Windows version 15.0. The procedures of statistical inference tests were performed by Mann-Whitney U, Kuskall-Wallis test, chi-square and Spearman coefficient, differences were considered statistically significant when  $p < 0.05$ .

## Results

Among the 33 specimens in the experimental group (AC), it was observed that 78.8% had epithelial changes ranging from mild dysplasia to SCC. In 57.6%(19) there was some degree of dysplasia, as well as 39.4%(13) mild, 15.2%(5) moderate and 3%(1) severe, and 21.2%(7) of cases occurred CCE. The inflammatory infiltration was observed in 84.9% of the sample, ranging from 39.4%(13) mild, 15.2%(5) moderate and 30.3%(10) intense. Solar elastosis was observed in 81.8% of the cases.

Mast cells were identified in 87.8%(29) of the cases (Fig. 1) and were located nearby the area of dysplastic epithelium (30.3%), in the lamina propria (24.2%), permeating the solar elastosis (15.5%), in the vicinity of vessels (9%), in the peritumoral region (18.8%) and submucosa (6%). In 15.2%(5) of the cases, mast cells were active, stage of degranulation, especially when close to the dysplastic area, tumor region, and vessels.

The average number of mast cells in specimens QA (experimental group) was  $17.4 \pm 10.4$  cells/ $\mu\text{m}^2$  ranging from 5.9 to 33 cells/ $\mu\text{m}^2$ , while in specimens of normal mucosa (control group) it was  $1.78 \pm 1.64$  cells/ $\mu\text{m}^2$ , ranging from 0.52 to 3.04 cells/ $\mu\text{m}^2$ . There was a statistically significant difference (Mann-Whitney U,  $p < 0.001$ ) when compared to the concentration of mast cells between the two groups. The average number of mast cells was  $27.57 \pm 5.94$  cells/ $\mu\text{m}^2$  in the cases of CCE, which was significantly greater (Kruskal-Wallis test,  $p = 0.001$ ) when compared with normal tissue and degrees of epithelial dysplasia (Graphic1).

There was a statistically significant correlation (Spearman coefficient,  $p = 0.004$ ) between the density of mast cells and the presence of epithelial dysplasia. Being observed a significant progressive increase (Kruskal-Wallis test,  $p = 0.001$ ) in the amount of mast cells, when there was an increase of the severity of the degrees of dysplasia.

The inflammatory infiltrate showed a statistically significant correlation with the density of mast cells (Spearman coefficient,  $p = 0.000$ ) and the number of mast cells increased depending on the degree of inflammation (Kruskal-Wallis test,  $p = 0.003$ ) (Table 1).

It was also observed statistically significant correlation between epithelial dysplasia and inflammatory infiltration (Spearman coefficient,  $p = 0.002$ ). However, while checking if the degree of dysplasia was associated with the degree of inflammation, there was no significant association (Shi-Square,  $p = 0.398$ ).

By analyzing the density of mast cells in the presence / absence of solar elastosis, it was observed that there was no statistically significant difference (Mann-Whitney U,  $p = 0.05$ ).

## **Discussion**

Mast cells are inflammatory cells that have been recognized as important effector of the deleterious effects of solar radiation on the skin [16-17]. Recent studies show that these cells are significantly increased in lip lesions induced by radiation as actinic cheilitis [2,18-19] and squamous cell carcinoma of the lip [11,15,20-25]. In the present study we observed an increase in the number of mast cells in AC lesions compared to normal tissue intraoral, corroborating the results of Araújo et al. (2010), Costa et al. [15] and Gomes et al. [11].

On the other hand, in the present study, we found a significant association between the density of mast cells and different degrees of dysplasia, confirming the results of Gomes et al. [11] and Ch'ng et al. [26]. These authors noted a close correlation between the activation of mast cells and the different phases of hyperkeratosis, dysplasia, carcinoma *in situ* and invasive oral carcinoma. For these authors, during the process of carcinogenesis there is a sequential infiltration and degranulation of mast cells in CCE. It is noteworthy that the changes in the cytoskeleton epithelial in potentially malignant lesions may precede structural changes, as probably observed by Santos et al. [27] who identified changes in the pattern of differentiation of keratin in AC. Supposedly these changes depend on the stage the process of transformation is, as well as on the continuity of the action of the etiologic agent on the tissue.

The relationship between the density of mast cells and the different degrees of dysplasia are not found frequently diverging in our results [15,18-19].

The location of mast cells was related to peritumoral region, around vessels, near the area of inflammation, epithelial dysplasia and solar elastosis. These findings were similar to those of other authors [2,11,18-20,22-23] reinforcing the hypothesis that mast cells could participate in the process of malignant transformation of actinic cheilitis.

As the results of Rojas et al. [20], Rojas et al. [28] and Grimbaldston, Finlay-Jones, Hart [29] the density of mast cells was correlated with the presence of local inflammation. There is evidence that the inflammatory response, in that region tissue may be contributing to the progression of the benign process to a malignant one [14].

The migration of mast cells to the tumor site and its activation may be a necessary condition for its effect promoter on the tumor. Since the failure of this process may be responsible for the decline of these cells in lesions with malignant potential and malignant lesions of the oral cavity [30].

The consistent presence of mast cells in AC lesions in our sample may have been mediated by mechanism explained by Huang et al. [31]. In this process, in the presence of inflammation, the release of chemical mediator SCF (factor derived from tumor stem cells) is responsible for activation of c-kit receptor on mast cells resulting in differentiation, migration, maturation and survival of these cells in the tumor microenvironment.

It is worth mentioning that the above experiment involved lesions controlled with transgenic animals and an artificially controlled tumor microenvironment, which requires reservations for extrapolation of its results for actinic cheilitis in the lip of humans.

## Conclusion

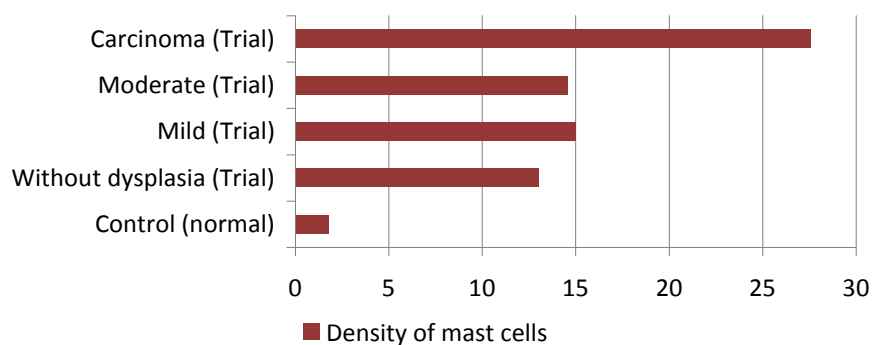
The increase of the density of mast cells in AC lesions and its correlation with the process of dysplasia and inflammation suggests their involvement in the disease progression to SCC of the lip.

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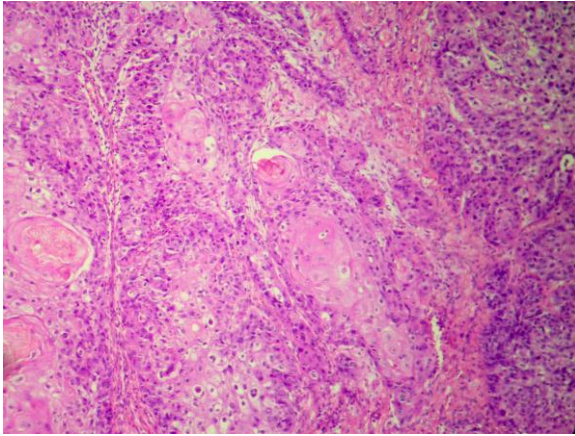
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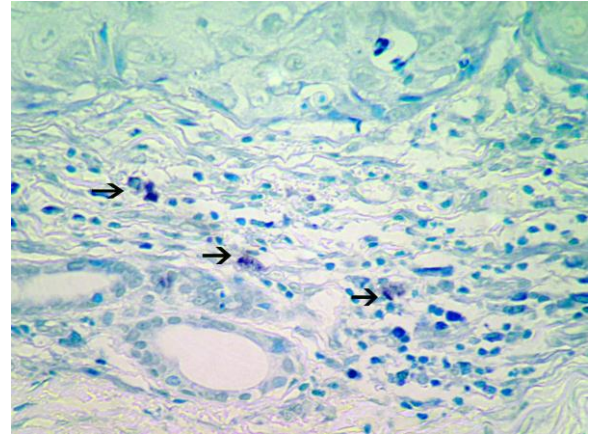
**Graphic 1:** Density of mast cells according to the degree of dysplasia and carcinoma in the experimental group and control.

**Table 1:** Evaluation of the density of mast cells according to the degree of inflammation.

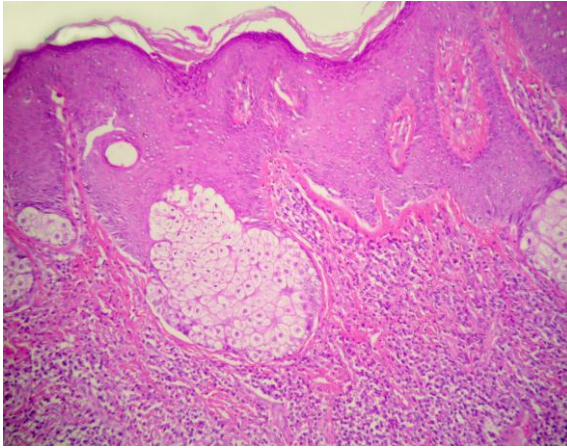
Average of the mast ±Standard deviation	Inflammatory Infiltrate	Values Inferential
3,80±7,43	Absent	<b>p=0,003*</b>
16,85±8,64	Mild	
17,00±11,51	Moderate	
25,20±5,75	Severe	



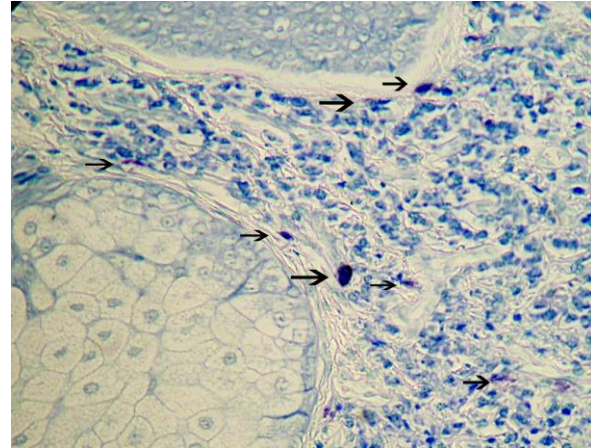
A



B



C



D

**Figure 1:** In **A** photomicrograph of well-differentiated SCC showing neoplastic islets and numerous pearls corneas. Fibrovascular stroma can observe an intense inflammatory infiltrate (HE, 40X). In **B** photomicrograph of previous injury stained with toluidine blue. The arrows identify mast cells present in the stroma of lesions surrounding the neoplastic islet (400X). In **C** photomicrograph of QA lesion of the lower lip vermilion where we observe pseudostratified epithelium exhibiting acanthosis and hyperorthokeratosis. Some projections epithelial show gland metaplasia. The region of the lamina propria exhibits intense inflammatory infiltrate. (HE, 100X) In **D** Higher magnification of the previous cut stained with Toluidine blue displaying numerous mast cells active (arrows) in interspersed among the inflammatory cells and in proximity to the epithelial tissue (AT, 400X).

## **4 DISCUSSÃO GERAL**

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As lesões de QA despertam interesse entre os pesquisadores por ser uma doença com potencial de transformação maligna em CCE de lábio e por possuir grande frequência em regiões de alta incidência solar. Portanto, estudos sobre os eventos que ocorrem nessa lesão são de grande importância pela possibilidade de contribuir para o conhecimento do potencial carcinogênico e eventos histopatológicos envolvidos com essa patologia bucal.

A amostra estudada no capítulo 3 revelou algumas das características clínicas já identificadas em indivíduos portadores de QA, ou seja, ocorrem predominantemente no lábio inferior de homens de pele clara, com mais de 50 anos e que se expõem excessivamente a radiação solar. No entanto, Pinera-Marques et al. (2010) estudaram lesões de QA em pescadores e não encontraram correlação entre a idade e o tempo de exposição ao sol e o diagnóstico histopatológico de displasia ou malignidade. Isso pode refletir a dificuldade em prever a transformação maligna das lesões cancerizáveis, mesmo com fatores etiológicos bem definidos.

Nos capítulos 2 e 3 do presente estudo ficou evidenciado que a atipia celular e transformação para CCE de lábio são características histopatológicas comuns em lesões de queilite actínica. Portanto, é de grande importância a realização de um diagnóstico precoce e a preservação do paciente com esta lesão labial.

Uma relação significativa entre os processos de displasia epitelial e a presença de inflamação foi identificada, entretanto, sem relação com a intensidade do processo inflamatório presente no tecido. Estudos anteriores observaram uma estreita relação entre displasia epitelial e inflamação, sugerindo a participação ativa do processo inflamatório na desorganização epitelial em lesões de queilite actínica e ceratose actínica (KAUGARS et al., 1999; BERHANE et al., 2002). A intensidade do processo inflamatório na QA representou, no estudo de Pimentel et al. (2006), a

única característica histológica associada com o grau de atipia epitelial e com a presença de CCE.

Componentes do processo inflamatório, como os mastócitos, estiveram consistentemente presentes e em maior quantidade nos casos de QA de nossa amostra quando comparados com a mucosa oral normal. A localização dos mastócitos foi frequentemente observada em regiões próximas ao epitélio displásico, permeando a elastose solar, proximidade de vasos e região peritumoral, sendo esses achados semelhantes aos de outros autores (ROJAS et al., 2004; ROJAS et al., 2005; GAJE et al., 2007; GOMES et al., 2008; ARAÚJO et al., 2010; SOUZA et al., 2010; FREITAS et al., 2011).

Além da presença, foi verificada correlação significativa entre a densidade destas células em QA com displasia e CCE quando comparados à mucosa oral sem alterações displásicas. Tais achados mostram-se similares aos encontrados em estudos anteriormente publicados (IAMAROON et al., 2003; ROJAS et al., 2004; ROJAS et al., 2005; GAJE et al., 2007; GOMES et al., 2008; ROJAS et al., 2009; SHARMA et al., 2010; SOUZA et al., 2010; FREITAS et al., 2011. Pode ocorrer um número similar de mastócitos em lesões de QA e CCE, embora tenha sido sempre maior quando comparado com tecido normal (COSTA et al., 2009; MICHAILIDOU, MARKOPOULOS, ANTONIADES, 2008; ARAÚJO et al., 2010).

A relação entre a densidade dos mastócitos e os processos de displasia epitelial identificada no presente estudo corrobora os achados de Gomes et al. (2008) e Ch'ng et al. (2006) cujos relatos permitiram afirmar que durante o processo de carcinogênese há uma infiltração sequencial e degranulação de mastócitos. Entretanto, essa relação não foi observada em outros estudos (ARAÚJO et al., 2010; SOUZA et al., 2010).

O aumento da densidade dos mastócitos esteve também relacionado com a presença de inflamação (ROJAS et al., 2005; GRIMBALDESTON, FINLAY-JONES, HART, 2006; ROJAS et al., 2009). Tal fato demonstra que os mastócitos são recrutados para os locais de inflamação e essenciais na promoção da resposta inflamatória (KINET, 2007). Além disso, o microambiente inflamatório modula a migração e invasão celular facilitando a proliferação de células alteradas e contribui para formação e progressão do câncer (LIN, KARIN, 2007). Essa ação seria decorrente da produção de radicais de oxigênio ativo, o qual resultaria na mutação gênica celular. Por outro lado, Gaje et al. (2007) afirmam que a densidade dos mastócitos é independente do infiltrado inflamatório. Outros autores afirmam ainda, que a inflamação observada na região peritumoral não está associada com as células mastócitos (COUSSENS et al., 1999; HERMES et al., 2001).

Neste contexto, alguns autores afirmam que os mastócitos podem contribuir para tumorigênese através de quatro diferentes mecanismos: supressão do sistema imune celular induzido pela radiação UV, o aumento da angiogênese, degradação da matriz extracelular e promoção de mitoses de células tumorais (CH'NG et al., 2006; GRIMBALDESTON, FINLAY-JONES, HART, 2006). Os mastócitos são em grande parte responsáveis pela manutenção e mediação da resposta imune, no entanto, a exposição à radiação UV pode alterar diretamente a função dessas células resultando na supressão do sistema imune. A angiogênese tem sido reconhecida por está associada com a progressão, agressividade e metástases de vários tumores malignos incluindo o CCE (IAMAROON et al., 2003; SHARMA et al., 2010) por ser essencial para o crescimento e sobrevivência das células tumorais (FREITAS et al., 2011). Através das suas próprias proteases e, indiretamente, pela interação com outras células e ativação das metaloproteinases, os mastócitos

participam da degradação da matriz, que é necessária para propagação do tumor (CH'NG et al., 2006; FREITAS et al., 2011). Além disso, há evidências de que os mastócitos estão envolvidos na progressão do tumor pela estimulação mitogênica direta das células neoplásicas pelos seus mediadores incluindo o FGF-2 (fator de crescimento fibroblático-2) e IL-8 (CH'NG et al., 2006).

## **5 CONCLUSÃO GERAL**

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Os indícios histopatológicos sugerem participação dos mastócitos no processo de transformação maligna do epitélio labial com queilite actínica.

Os mastócitos estiveram presentes na maioria das lesões de queilite actínica, estando sua densidade aumentada, quando comparada a mucosa normal. Além disso, esteve relacionada com a presença de inflamação e os diversos graus de displasia epitelial.

As células foram localizadas nas regiões próximas a área de epitélio displásico, na lâmina própria, permeando a elastose solar, na proximidade de vasos, na região peritumoral e submucosa.

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## **APÊNDICE**

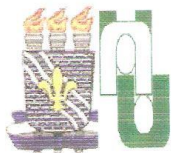
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**ANEXOS**

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## ANEXO A



UNIVERSIDADE FEDERAL DA PARAIBA - UFPB  
 HOSPITAL UNIVERSITÁRIO LAURO WANDERLEY - HULW  
**COMITÊ DE ÉTICA EM PESQUISA COM SERES  
 HUMANOS - CEP**

**CERTIDÃO**

Com base na Resolução nº 196/96 do CNS/MS que regulamenta a ética da pesquisa em seres humanos, o Comitê de Ética em Pesquisa do Hospital Universitário Lauro Wanderley - CEP/HULW, da Universidade Federal da Paraíba, em sua sessão realizada no dia 31/08/2010, após análise do parecer do relator, resolveu considerar **APROVADO** o projeto de pesquisa intitulado **AVALIAÇÃO DA CORRELAÇÃO ENTRE DENSIDADE DOS MASTÓCITOS, GRAU DE DISPLASIA EPITELIAL E INFILTRADO INFLAMATÓRIO EM LESÕES DE QUEILITE ACTÍNICA**. Protocolo CEP/HULW nº. 448/10, Folha de Rosto nº 363172, CAAE Nº 0367.0.126.000-10 da pesquisadora RACHEL REINALDO ARNAUD.

Ao final da pesquisa, solicitamos enviar ao CEP/HULW, uma cópia desta certidão e da pesquisa, em CD, para emissão da certidão para publicação científica.


João Pessoa, 22 de setembro de 2010.

Iaponira Cortez Costa de Oliveira  
 Coordenadora do Comitê de Ética  
 em Pesquisa - CEP/HULW


**Profª Drª Iaponira Cortez Costa de Oliveira**  
 Coordenadora do Comitê de Ética em Pesquisa-HULW

## ANEXO B

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Title: Mast cell participation on malignant transformation of Actinic Chelitis: A systematic review.

Soares, Maria Sueli

Authors: Arnaud, Rachel  
Lira, Cláudia

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## ANEXO C

Hotmail - rrarnaud@hotmail.com - Windows Live

Página 1 de 1

Windows Live™ Hotmail (39) Messenger (2) SkyDrive | MSN

## Hotmail

Novo | Responder Responder a todos Encaminhar | Excluir Lixo Eletrônico Limpa

## Caixa de Entra...

## Pastas

## Lixo (51)

Rascunhos (17)

Enviados

Excluídos

Nova pasta

## Visualizações rápid...

Sinalizadas (1)

## Fotos (6)

## Documentos do Office...

## Messenger (2)

1 convite

Pesquise contatos

Fernandinho

Hortensia

Sair do Messenger

Início

Contatos

Calendário



## Submission Confirmation Voltar para mensagens |

**Jeyel Tecson** Adicionar a contatos 19:51  
Para Rachel Reinaldo Arnaud Responder ▾

Os anexos, as imagens e os links desta mensagem foram bloqueados para sua segurança.  
Mostrar conteúdo | Sempre mostrar conteúdo para jeyel.tecson@springer.com

Dear Dr. Rachel Reinaldo Arnaud,

Thank you for submitting your manuscript, "Actinic cheilitis: histopathological evaluation of 44 cases.", to Pathology & Oncology Research

During the review process, you can keep track of the status of your manuscript by accessing the following web site:

<http://pore.edmgr.com/>

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20/11/2011

## ANEXO D

Mensagem de Impressão do Windows Live Hotmail

Página 1 de 1

**AODR: Submission Confirmation for Density of mast cells in lesions of actinic cheilitis.**

De: **em.aodr.0.273484.3dbdd14a@editorialmanager.com** em nome de **Editorial Office ADR**  
(adr@dermatology.uni-kiel.de)

Enviada: domingo, 20 de novembro de 2011 23:57:42

Para: Rachel Reinaldo Arnaud (rrarnaud@hotmail.com)

Dear Dr. Arnaud,

Your submission entitled "Density of mast cells in lesions of actinic cheilitis." has been received by Archives of Dermatological Research

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is <http://aodr.edmgr.com/>.

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to our journal.

Kind regards,

Editorial Office  
Archives of Dermatological Research