Quantitative study of Langerhans cells in basal cell carcinoma with higher or lower potential of local aggressiveness*

Estudo quantitativo das células de Langerhans em carcinomas basocelulares com maior e menor potencial de agressividade local

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Abstract: BACKGROUNDS - Basal cell carcinoma affects areas of the body that have been exposed to the sun, and this disorder has different clinical and histopathologic presentations. Some of these forms have a higher potential of local aggressiveness, while others have a lower potential. Langerhans cells actively participate in the skin immune system.
OBJECTIVES - To quantitatively evaluate the number of Langerhans cells on the epidermis of basal cell carcinoma with lower and higher potential of local aggressiveness and on adjacent normal epidermis.
METHODOLOGY - The authors divided the sample into two groups with 14 histological slides each: one with basal cell carcinoma with lower potential of local aggressiveness and the other with basal cell carcinoma with higher potential of local aggressiveness. Immunohistochemistry with S-100 protein was used in the identification of Langerhans Cells. Langerhans cells present in 7 microscopic fields were counted using optical microscopy (400X magnification) and Weibel's morphometric grade. The mean for each lamina was obtained. Wilcoxon's statistical test was employed.
RESULTS - In the group with lower potential of local aggressiveness, there was a significant increase in the number of Langerhans cells in the adjacent normal epidermis, as compared with the number of cells in the epidermis superposed to the basal cell carcinoma (pd 0.05). There was no significant statistical difference in the group with higher potential of local aggressiveness (p >0.05).
CONCLUSION - The higher number of Langerhans cells in the normal epidermis adjacent to the tumoral lesion with lower potential of local aggressiveness could indicate greater immunological resistance of the epidermis, thus limiting the aggressiveness of the neoplasm.
Keywords: Carcinoma, basal cell; Immunity; Immunohistochemistry; Langerhans cells; Medical oncology

Resumo: FUNDAMENTOS - O carcinoma basocelular localiza-se principalmente em áreas expostas ao sol, apresentando formas clínicas e histológicas diferentes, algumas com grande e outras com pequena agressividade local. Células de Langerhans participam ativamente do sistema imune da pele.
OBJETIVO - Avaliar quantitativamente as células de Langerhans sobrepostas aos carcinomas basocelulares de maior e menor potencial de agressividade local, assim como nas respectivas epidermes sãs adjacentes.
MÉTODOS - Dois grupos com 14 preparações histológicas cada. No primeiro, carcinoma basocelular de menor potencial de agressividade local e, no segundo, carcinoma basocelular de maior potencial. Empregou-se a imunoistoquímica com proteína S100 para identificação das células de Langerhans. Utilizando microscópio óptico em aumento de 400 vezes e a grade morfométrica de Weibel, foram contadas as células de Langerhans presentes em sete campos, obtendo-se a média em cada lâmina. Foi utilizado teste estatístico de Wilcoxon para análise estatística.
RESULTADOS - No grupo de menor potencial de agressividade local, na epiderme sã adjacente houve aumento significativo no número de células de Langerhans comparado ao da epiderme sobreposta ao carcinoma basocelular (p d 0,05). No grupo de maior potencial de agressividade local, não houve diferença com significado estatístico (p > 0,05).
CONCLUSÃO - O maior número de células de Langerhans na epiderme sã vizinha à lesão tumoral de menor potencial de agressividade local poderia representar uma maior resistência imunológica da epiderme, limitando a agressividade da neoplasia.
Palavras-chave: Carcinoma basocelular; Células de Langerhans; Imunidade; Imunoistoquímica; Oncologia

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INTRODUCTION

Basal cell carcinoma (BCC) is the skin neoplasm that affects humans more often. It is more common in areas of the body that are exposed to the sun and in leucodermic patients. It has a high incidence: of 205,869 patients examined between 1999 and 2005 in skin cancer prevention campaigns, 6.4% presented BCC[1]. According to Bandeira *et al*.[2], continuing sun exposure in tropical regions is one of most important factors in the pathogenesis of skin carcinoma.

Epidermal Langerhans cells (LC) are antigen-presenting cells. Therefore, it is their role to identify, process, and present newly formed antigens of tumor cells to the immune system. Once activated, the immune system will work towards the elimination of tumor cells.

Because BCC develops in the germinative cells of epidermal annexes, several factors influence the polymorphism of its clinical and histological presentations. Ackermam and Wade [3] draw attention to the cell proliferation and differentiation potential, in addition to the involvement of stroma in cellular response. Conjunctive tissue stroma proliferates with the tumor and is arranged in parallel bundles around the tumor mass, with a discreet lymphocytic infiltrate in the proximity. The arrangement, form, and relation of this tumor mass with the adjacent dermis originate several histological classifications of BCC.

In 1978, Kopf *et al.* [4] analyzed 3,531 BCC cases and classified them histologically into: Solid, Cystic, Adenoidal, Pigmented, Morpheiform, and Squamous basal. The last two are the most aggressive. Sexton *et al.* [5] created five larger groups in a histological study of 1,039 basal cell carcinoma cases: Nodular, Superficial, Micronodular, Infiltrative, and Morpheiform. Their objective was to study the surgical margins of these types of BCC. The authors concluded that the nodular and superficial types yield better results during surgical excision because they have a more compact architecture.

The histological aspect has a fundamental role in the prognosis of the disease, especially in relation to the potential of local aggressiveness, relapse, and chance of metastasis. Jacobs and Rippey [6] considered that the infiltrative type had potential of invasion of adjacent tissues in 86% of the cases, against 14% of the nodular type. Hendrix and Harry [7] compared the destructive potential of nodular BCC with micronodular BCC, and found that the latter has a higher potential. In 1998, Rippey [8] conducted an analysis of various histological classifications of BCC and considered the proposal by Sexton *et al*.[5] the most practical and didactic, as follows:

- Nodular > it has a well-defined structure, with precise contours and compact neoplastic mass limited by cells arranged in palisade. Mucine retraction is observed around the lesion, and the stroma tends to be thin around the tumor. It corresponds to 39% of the cases and it was considered a BCC with a low potential of local aggressiveness.
- Superficial > it is a tumor focus that extends from the epidermis to the papillary dermis, limited by well-defined cells in palisade. Peripheral retraction areas are found around the tumor. It corresponds to 17% of the cases and has a high potential of local aggressiveness.
- Micronodular > it is defined as small tumor nodules, often round, with not so well-defined cells in palisade in the periphery. A collagen-rich tissue, with little mucinous substance, is observed around the lesions. It represents 14% of the cases and was considered a BCC with a high potential of local aggressiveness.
- Infiltrative > it is a tumor of variable size and form, with few cells in palisade and dysmorphic nucleus. There is no evidence of adjacent tissue retraction. It corresponds to 8% of the cases and presented the highest potential of local aggressiveness.
- Morpheiform > tumor islands are small, elongated, with angular contours. There is no mucinous retraction and peripheral collagen is sclerotic. It represents 2% of the cases and its invasion potential and degree of local aggressiveness were considered very high.

The immunological system of the skin is composed by chemical substances, such as immunoglobulins, cytokines, immunocomplexes, and by cells. The cells that participate in this process are keratinocytes, lymphocytes, and antigen-presenting cells (APC), represented by Langerhans cells in the epidermis and macrophages in the dermis. [9] In order to obtain a immune response, the organism needs to be stimulated by an antigen, which activates APC, which in turn stimulate T lymphocytes (CD4+ cells) and B lymphocytes (CD8+ cells). Next, these cells release cytokines, interferon, and tumor necrosis factor, among others. [10]

This group of cells and substances that participate in the complex process of organic response to an antigen was denominated by Streilein[11], in 1983, SALT (Skin Associated Lymphoid Tissue). Later, Bos and Kapsemberg [12] suggested that every immunologically competent skin cell, such as mast cells, tissue macrophages, and granulocytes, associated with SALT, would constitute the Skin Immune System (SIS).

Paul Langerhans described the presence of dendritic cells in the human epidermis using an immunohistochemical process. It was later discovered that these cells originated in the bone marrow and they were named 'Langerhans cells' after him. These cells

are characterized by the presence of granules in the cytoplasm called Birbeck granules.[13,14] Silberg [15] showed that LC participated in the reaction of allergic contact dermatitis and recognized them as antigen-presenting cells. Patapova *et al.* [16] studied LC in the atopy involving immunomorphological aspects in the same way that Prignano *et al*. [17] did in psoriasis.

The process of skin oncogenesis, particularly of BCC, has been associated with the density, morphology, and physiologic response of LC. Studies by Gatter *et al*. [18], Chen *et al.* [19] and McArdle *et al.*[20] did not find significant statistical differences in the number of LC in the epidermis of BCC; however, they did observe that there was a higher number of these cells in the epidermis adjacent to the tumor. A significantly lowered density of LC in BCC and spinocellular carcinoma (ECC) was found in comparison with actinic keratoris (AK) and normal skin. [21,22] Vallcuende *et al.* [23] identified an increase in the number of LC in the surface of BCC and in the normal adjacent skin. Pereira *et al*. [24], comparing the number of LC in melanocytic nevus, MM, and normal kin, did not find a directly proportional difference between the number of LC and the malignancy of the melanocytic lesion.

Histological techniques have been performed to identify LC; however, the best results have been obtained with immunohistochemical studies. Chu *et al*. [25] used anti CD1 (BD, CA) markers to detect LC using electron microscopy, with superior results to those obtained with S100 protein and anti HLA-DR. A marker of LC, detected using optical microscopy, of general use and accessible cost is S100 Protein. Despite not being specific to LC, since it may mark other dendritic cells, it has been used in various works involving LC. [26,27,28,29,30]

METHODOLOGY

The registration books of histological preparations, from 1995 to 1999, of the Dermatology Center of Recife (CEDER) and Department of Pathology of the Pernambuco Cancer Hospital (HCP) were investigated.

A total of 120 cases diagnosed as basal cell carcinoma were selected. Of the total, 45 were of the micronodular, morpheiform, and infiltrative types (all considered BCC with a high potential of local aggressiveness), and 75 were of the nodular type (low potential of local aggressiveness). In all the cases, patients were aged 55-65 years, leucodermic, and had a single lesion in the face.

Laminas with sections stained with hematoxylin and eosin of the selected cases were reviewed and the following cases were excluded from the sample: cases that did not have free histological margins or basis and cases that did not show full epidermis in the area of the lesion or in the adjacent area. Based on these exclusion criteria, 28 cases were selected and divided into two groups with 14 laminas each.

Group 1 > BCC with lower potential of local aggressiveness (nodular type)(Figure 1).

Group 2 > BCC with higher potential of local aggressiveness (micronodular (figure 2), infiltrative, and morpheiform types).

Paraffin blocks with the histological material of the selected BCC cases were separated. Using a manual microtome, cuts of 5μ were performed and arranged in laminas previously immersed in a 3-aminopropyl-trietoxy-silane (APES) solution at 2% acetone. These laminas were then unparaffined and prepared for immunohistochemistry with S100 protein (Z 311, Dako Company; California; EEUU), using the peroxidase-antiperoxidase method (PAP) pioneered by Stemberger, in the Keizo Asami Immunopathology Laboratory (LIKA) of the Federal University of Pernambuco (UFPE).

A binocular optical microscope (Olympus) was used to count the number of LC, with 10x ocular and 40x objective, with consequent 400x magnification. Weibel's morphometric grade of 20 x 20 mm, totaling 400 points of 1 mm? each, was used in the ocular. Each point is called fundamental counting unit (FCU). With 400x magnification, LC were counted in 20 FCU in each one of the seven fields selected by lamina. The mean was then calculated. The cell was considered LC only when its nucleus was visualized, avoiding the duplicity of count due to the similarity between LC and their dendrites (Figures 3, 4).

The normal epidermis adjacent to the tumor lesion of BCC with lower potential of local aggressive-

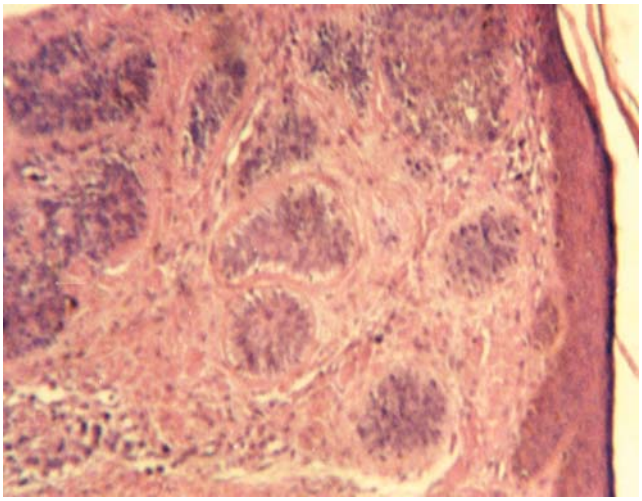

Figure 1: Nodular basal cell carcinoma, Hematoxylin and Eosin staining (10X)

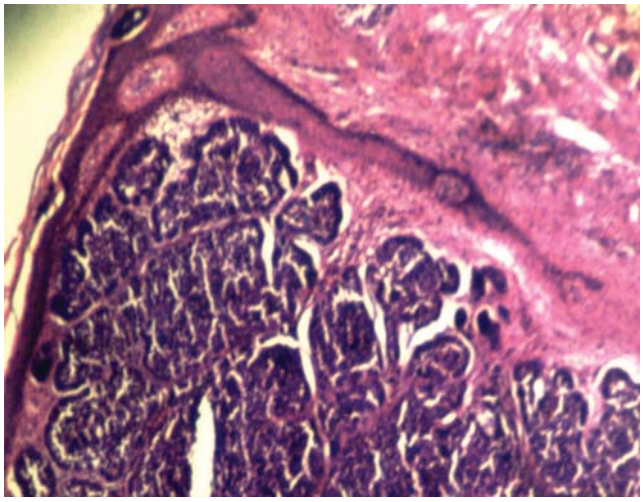

Figure 2: Micronodular basal cell carcinoma, Hematoxylin and Eosin staining (10X))

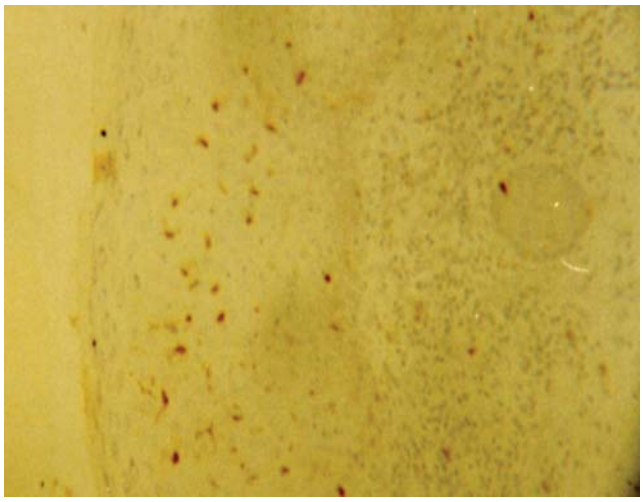

Figure 4: S-100 Protein staining of Langerhans cells of basal cell carcinoma; skin adjacent to tumor lesion of micronodular basal cell carcinoma - higher number of LC in the normal epidermis adjacent to the tumor

ness was called Normal Epidermis Adjacent to the BCC with low potential of local aggressiveness (NEALA). The normal epidermis adjacent to the BCC with higher potential of local aggressiveness was called Normal Epidermis Adjacent to the BCC with high potential of local aggressiveness (NEAHA). Regarding the area of the epidermis covering the tumor lesion, it was established that the epidermis superposed to the nodular BCC was called Tumoral Epidermis with Little Local Aggressiveness (TELA), and the epidermis superposed to the infiltrative, micronodular and morpheiform BCC was called Tumoral Epidermis with Higher Local Aggressiveness (TEHA).

Wilcoxon's statistical test was employed for the statistical analysis of the LC count present in the normal epidermis adjacent and superposed to the BCC lesion in the two groups studied.

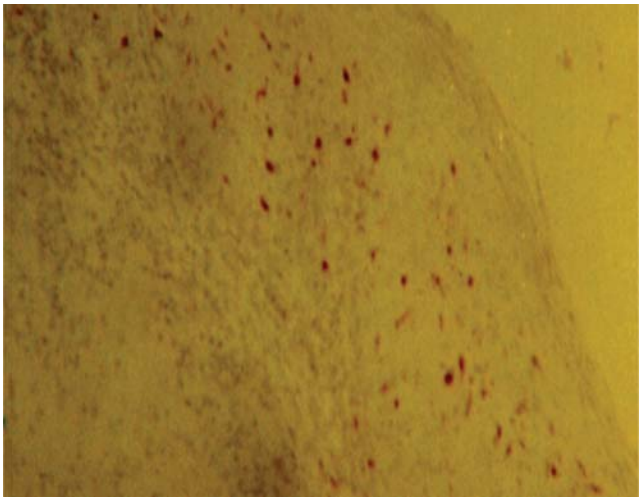

Figure 3: S-100 Protein staining of Langerhans cells of basal cell carcinoma; skin adjacent to tumor lesion of nodular basal cell carcinoma - great amount of Langerhans cells

RESULTS

The following results were obtained after a quantitative analysis of LC found on the epidermis superposed and adjacent to the BCC tumor with higher and lower potential of local aggressiveness using optical microscopy (Tables 1 and 2).

Of the total laminae with diagnosis of BCC with lower potential of local aggressiveness, a mean (X) of approximately 5.0 with standard deviation (δ) of 2.44 of LC by optical microscopic field in the epidermis superposed to the tumor lesion was obtained. The data correspond to a coefficient of variation (CV) around 53%. Apparently, this value indicates absence of symmetry and justifies the choice of median as a central tendency measure for the representation of data because it is not affected by extreme values. Based on this criterion, this punctual estimate yielded a value of 4.02, whereas the interquartil interval, as a dispersion or variability measure, yielded 1.29. Comparatively, we notice that the arithmetic mean of LC in the epidermis superposed to the BCC with lower potential of local aggressiveness is greater than the median. This fact confirms the absence of symmetry and indicates a curve slightly deviated to the left (negative asymmetry), where Mean < Median < Mode.

Conversely, in the normal epidermis adjacent to the tumor lesion, a mean of 6.7 with standard deviation of 2.7 was obtained. This yielded a coefficient of variation around 40%, that is, when the number of LC in the normal epidermis adjacent to the tumor lesion is considered, such cells are more concentrated than

Table 1: Relative number of LC in the epidermis above the BCC with lower potential of local aggressiveness (A) and relative number of LC in the normal adjacent epidermis (B)

Case	A	B
01	4,03	10,61
02	3,60	5,40
03	1,44	1,20
04	1,80	6,00
05	11,35	11,42
06	4,02	3,99
07	2,40	7,12
08	3,99	6,42
09	7,12	6,39
10	4,16	5,21
11	7,12	10,80
12	4,94	6,36
13	3,67	7,74
14	4,89	5,22
0	**4,61 ± 2,44**	**6,70 ± 2,68**

$p < 0,05$

Table 2: Relative number of LC in the epidermis above the BCC with higher potential of local aggressiveness (A) and relative number of LC in the normal adjacent epidermis (B)

Case	A	B
01	02,40	04,04
02	07,12	06,60
03	02,17	03,26
04	02,40	02,76
05	01,99	01,99
06	08,40	09,60
07	05,40	01,80
08	08,47	07,06
09	01,81	02,17
10	09,00	07,92
11	08,49	07,50
12	05,06	05,34
13	07,33	04,08
14	02,91	06,58
0	**5,21 ± 2,74**	**5,05 ± 2,38**

$p < 0,05$

when measured in the superposed epidermis with lower potential of local aggressiveness (Table 3).

When we analyze the results obtained through a quantitative analysis using optical microscopy of LC found in the superposed epidermis and in the normal epidermis adjacent to the tumor lesion of BCC with higher potential of local aggressiveness, the following punctual estimates were obtained (Table 4).

Comparatively, both the arithmetic mean and the median yielded very similar estimates, around 5.0, for the average number of LC in the epidermis superposed to the BCC with high potential of local aggressiveness and for the average number of LC in the normal epidermis adjacent to the tumor lesion. The standard deviation is approximately half of the interquartil interval (2.7/5.0). As a general practice, the arithmetic mean and the standard deviation in isolation should not serve as decision-making tools in the analysis of data. The coefficient of variation is a more thorough and reliable measurement because it is a measurement of relative dispersion. In both cases, there was high dispersion (52.6%:47.1%), which again indicates the absence of symmetry and, as a consequence, data not coming from a normal probability distribution.

DISCUSSION

Basal cell carcinoma is considered a low-malignancy tumor regarding the potential of dissemination. However, it has local destructive capacity and a tendency to relapse. There is still no consensus about its histopathological classification; still, some authors [5,6,7,8] consider the local aggressiveness of a tumor an objective concept to classify the extent of invasion of adjacent tissues. In this way, a group of BCC with lower local aggressiveness, such as the nodular type, is separated from a more aggressive and destructive group, such as the micronodular, infiltrative, and morpheiform types. This classification was suggested by Sexton *et al*. [5] after they studied 1,039 cases of BCC in detail.

In this work, LC were observed and counted in the epidermis above the lesion of BCC and in the normal epidermis adjacent to the tumor. The results obtained were statistically significant, and this indicates the quantitative deficit of LC as an important factor in the local aggressiveness of the tumor.

In malignant melanoma and spinocellular carcinoma there was a significant decrease in the number of LC when compared with a benign process such as actinic keratosis. Meissner *et al.*[21], in a quantitative analysis of 16 cases of BCC, SCC, AK, and normal skin, obtained results that confirmed a decrease in the number of LC in malignant lesions. Bergfelt *et al.* [22] compared malignant skin diseases (BCC and SCC) with non-malignant (AK) and normal skin of the face and trunk. There was no significant difference in the number of LC of malignant lesions in the face and trunk; however, in the normal skin and AK lesion, there was a slight difference between the number of LC of lesions in the face, an area of sun exposure, and trunk. There was a significant statistical difference between

Table 3: Punctual estimates relative to table 1 (relative number of LC in the epidermis above the BCC with low potential of local aggressiveness (A) and relative number of LC in the normal adjacent epidermis (B))

	A	B
X	4,61	6,7
δ	2,44	2,68
Cv	52,90%	40%
Md	4,02	6,37
Q1	3,60	5,22
Q2	4,02	6,37
Q3	4,89	7,12
Interquartil Int.	**1,29**	**1,97**

Table 4: Punctual estimates relative to table 2 (relative number of LC in the epidermis above the BCC with high potential of local aggressiveness (A) and relative number of LC in the normal adjacent epidermis (B))

	A	B
X	5,21	5,05
δ	2,74	2,38
Cv	52,60%	47,10%
Md	5,23	4,71
Q1	2,40	2,76
Q2	5,23	4,71
Q3	7,33	6,60
Interquartil Int.	**4,93**	**3,84**

the number of LC in AK lesions and normal skin and malignant pathologies. We can identify in these works the preoccupation to differentiate between malignant and non-malignant groups. Studies involving only BCC cases, such as those of Gatter *et al.* [18], Chen *et al.* [19], McArdle *et al.* [20], and Melo *et al.* [28] obtained very similar results. All of them identified a reduction of the number of LC in BCC compared to the normal adjacent skin.

To avoid variables that could interfere in the results, only patients in the age range of 55-65 years, leucodermic (phototypes I, II and III) and with a single lesion in the face participated in the study.

Other studies have investigated the number of LC in relation to various skin tumors; however, there hasn't been any attempt so far to associate the number of LC with the potential of local aggressiveness of BCC.

CONCLUSION

In the comparative analysis of the results, there was no significant statistical difference between the number of LC in the superposed epidermis and in the normal epidermis adjacent to the lesion of BCC with a high potential of local aggressiveness.

Nonetheless, a significant statistical difference was found between the number of LC in the normal epidermis adjacent to the tumor lesion of BCC with lower potential of local aggressiveness (more LC) and in the epidermis above the lesion.

These findings suggest that the higher number of LC found in the normal skin adjacent to the tumor lesion with lower potential of local aggressiveness may indicate a greater immunologic capacity of this area to limit the growth of the tumor, resulting in a more localized and restricted form of the disease.

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