Axillary basal cell carcinoma – a rare form of a frequent kind of carcinoma

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Abstract
Basal cell carcinoma (BCC) is the most common cutaneous cancer. It seems that the most important prognostic factor is exposure to ultraviolet radiation (solar and artificial), correlated with other factors as well. In this article, we aimed to review basal cell carcinoma located in the axilla, referring to cases from our hospital. Axillary location of BCC is rare, with a very low number of cases quoted in the literature, compared to the high prevalence of basal cell carcinoma in the general population. During a period of two years, we detected only four cases of axillary basal cell carcinoma out of a total number of 921 cases diagnosed as BCC. We were interested in identifying certain factors involved in causing BCC, post-excision clinical evolution, histological type and aggressiveness of axillary basal cell carcinoma. Therefore, we quantified objectively the tumor and stromal expression of some immunological markers like: metalloproteinases MMP1, 3, 11, Ber-EP4 and Ki67. Histological types of tumors investigated here belong to the category of non-aggressive BCC, namely as nodular and superficial, although Ki67 index is greater than the average reported in the literature for this type of tumor. MMPs exhibited increased expression in tumors and stromal compartments, especially at the tumor invasion front, and was not associated with tumor ulceration or surrounding tissue remodeling-related changes. Our results confirm the literature data concerning the involvement of MMPs in BCC progression, whatever the tumor location is.

Keywords: axillary basal cell carcinoma, metalloproteinases, histopathology, immunohistochemistry.

Introduction
Basal cell carcinoma (BCC) is the most frequently encountered tumor of all cutaneous cancers, with an estimated annual rate of 750 000 new cases occurring worldwide [1, 2]. The majority of BCCs develop on sun-exposed areas, especially on the face and the neck, but approximately 9% of the new cases appear on covered areas (perianal area, groin, axillary region, areola or nipple) [3, 4].

The axilla is one of the areas with the least exposure to ultraviolet radiation. By thoroughly reviewing the dermatologic and surgical literature on this topic, we have found only a few reported cases of axillary BCC [5–16], with an average of one case per each reporting author. It is important to note that most authors have presented only one case of BCC within each article. Betti R et al. (2011) asserts that, up until March 2011, there were less than 35 cases reported in the entire specialty literature. By adding to these, the cases discovered by Betti R et al. after a research period of 14 years, the total number of cases in the literature barely reaches 60 [17].

In this article, we aimed to study the prevalence and also the clinical, histopathological and immunohistochemical aspects of this type of carcinoma with regard to the basal cell carcinomas (BCC) detected in a period of time between February 2010 and September 2012 in our clinic, considering the scarceness of the existence and detection of axillary BCC.

We assumed that the number of axillary BCC was actually higher in the global population, and the reduced number of reports may be a significant contributor to the low ratio of reported axillary BCCs towards the large number of de novo and recurrent BCCs observed in the medical literature available on this topic.

Patient and Methods
The starting case was a 76-year-old female patient with a brown, sharply margined patch, of slightly increased consistency, 1.6/1 cm in dimension, located in the left axilla. The first clinical examination did not prove the presence of axillary adenopathy. The anamnesis revealed that the lesion in cause had been evolving for almost four years, was painless and was not associated with any troublesome symptomatology. The patient had not abused of sun exposure during childhood or as an adult, had not worked in a toxic environment, had not applied any irritant substances in the axilla, had not been subjected to more than one thoracic X-ray during...
life, had not suffered any traumatism in the axilla and had no history of sunburn in this particular anatomic site. The clinical diagnosis was superficial type axillary basal cell carcinoma (Figure 1), a diagnosis which was subsequently confirmed both histologically and immunohistochemically. Surgical radical excision was the chosen therapeutic solution in this particular case. The patient did not present any sign of relapse, in a follow-up period of eight months after the intervention.

![Superficial basal cell carcinoma (76-year-old female patient).](image)

Starting from this particular case of atypical localization of basal cell carcinoma, we have studied all the BCC cases registered in the data basis of the Pathology Department between February 2010 and September 2012. Out of a total number of 921 BCCs, we have only detected four cases of axillary BCC; therefore, the percentage of axillary BCCs observed in our Department was 0.43% of all BCC.

The mean age of the four patients, at the time of detection of the axillary basal cell carcinoma, was 73.25 years. The time interval between the occurrence of the cutaneous neoplasm – as stated by our patients – and the definitive diagnosis established in our clinic was 4.2 years.

All patients were classified as Fitzpatrick type III skin phototype and were older than 60 years at admission.

Starting from these four cases of axillary BCC, we have tried to determine if there are any contributing factors favoring the location of these carcinomas in this area. Moreover, we have assessed the histological and clinical type of each of these BCCs and whether they are included or not in the category of aggressive type basal cell carcinomas (referring to NCCN 2011 Guidelines, “histopathological aggressive BCC means having morpheaform, sclerosing, mixed infiltrative or micronodular features in any portion of the tumor”).

All these axillary basal cell carcinomas have also been immunohistochemically investigated in order to see/objective the expression of MMP1, MMP3 and MMP11 matrix metalloproteinases, as well as for the Ber-EP4 and Ki67 markers, considering both tumor and stromal expression, in our pursuit to find out how aggressive these axillary basal cell carcinomas are.

The working protocol used for the immunohistochemical analysis of the four cases of axillary BCC is schematically presented in Table 1.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Company</th>
<th>Pre-treatment</th>
<th>Duration</th>
<th>Secondary antibody</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ber-EP4</td>
<td>Ber-EP4</td>
<td>Dako</td>
<td>Citrate</td>
<td>24 hours</td>
<td>Mouse</td>
<td>0.3/200</td>
</tr>
<tr>
<td>MMP1</td>
<td>Polyclonal</td>
<td>NeoMarkers</td>
<td>Without</td>
<td>24 hours</td>
<td>Rabbit</td>
<td>0.3/250</td>
</tr>
<tr>
<td>MMP2</td>
<td>CA-4001</td>
<td>NeoMarkers</td>
<td>Without</td>
<td>24 hours</td>
<td>Mouse</td>
<td>0.3/250</td>
</tr>
<tr>
<td>MMP3</td>
<td>None</td>
<td>NeoMarkers</td>
<td>Citrate</td>
<td>24 hours</td>
<td>Rabbit</td>
<td>2/200</td>
</tr>
<tr>
<td>MMP11</td>
<td>SL3.05</td>
<td>NeoMarkers</td>
<td>Without</td>
<td>24 hours</td>
<td>Mouse</td>
<td>0.3/200</td>
</tr>
<tr>
<td>Ki67</td>
<td>MM1</td>
<td>Novocastra</td>
<td>Citrate</td>
<td>24 hours</td>
<td>Mouse</td>
<td>0.5/200</td>
</tr>
</tbody>
</table>

**Results**

In all the four patients, the surgical treatment was chosen with complete excision of the tumor, confirmed by histopathological examination, deep and lateral margins were free of tumor. The mean macroscopic dimension of the axillary BCCs was 1.37/0.95/0.25 cm (counting for length/width/depth).

The distribution of patients by sex, age, phototype, evolution, histopathology type and tumor dimensions are presented in Table 2.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Age [years]</td>
<td>76</td>
<td>83</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>Phototype</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Evolution period [years] until detection</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Evolution at detection</td>
<td>de novo</td>
<td>de novo</td>
<td>de novo</td>
<td>de novo</td>
</tr>
<tr>
<td>Histological type</td>
<td>superficial nodular nodular ulcerated pigmented nodular ulcerated pigmented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor dimensions [cm]</td>
<td>1.6/1/0.1</td>
<td>2/1.4/0.2</td>
<td>1.2/1/0.5</td>
<td>0.7/0.4/0.2</td>
</tr>
</tbody>
</table>

The histopathological types of the four axillary basal cell carcinomas detected in our clinic were: three BCCs of nodular type and one ulcerated superficial carcinoma. (Figure 2).

All the basal cell carcinomas with axillary situation we have studied were de novo carcinomas, and all the four cases were encountered in women. None of the patients presented any other cutaneous cancers at the time of the examination. Also, the anamnesis revealed that this was the first time a cutaneous neoplasm was diagnosed and detected in all four patients.

Immunohistochemical analysis of the four axillary basal cell carcinomas ascertained the high positivity of MMPs (MMP1, MMP3 and MMP11) predominantly in the deeper tumor compartment, both intratumoral and stromal. A more pronounced positivity for MMP11 was also noticed at the invasion front of the tumor. Intense positivity was also shown in the superficial axillary type carcinoma (Figures 3 and 4).

First, we interpreted this in the context of the tumor ulceration and associated the expression of these MMPs with the surrounding tissue regeneration and remodeling, but the positivity in our cases was not related to tumor ulceration, as can be seen in the following images (Figures 5 and 6).
As already mentioned, we have also immunohistochemically analyzed the four cases of axillary BCC using Ber-EP4 markers (cytoplasmic marker for tumor cells) [18] and Ki67 (nuclear marker for the quantification of tumor proliferation) [19, 20]. In order to differentiate BCCs from squamous cell carcinomas and from benign basaloid tumors, the most frequently used and reliable marker remains Ber-EP4 [21, 22]. For the four axillary tumors, this marker was intense positive intratumorally, therefore certifying the diagnosis of BCC and ruled out diagnoses like trichoepithelioma, another kind of basaloid type tumor that BCC is frequent confused in this anatomic sites (Figure 7).
Ki67 presents a variable behavior [23] and its expression in the four studied cases was under 10%. However, Ki67 had a higher positivity in our cases than in the medical literature reports on this topic [20, 23] in respect to the mitotic index. In the invasion front of the tumor, the Ki67 index was predominantly increased, as compared to the center of the tumoral masses (Figure 8). The aggressivity of the tumors will also be assessed in time, concerning the future presence or the absence of the tumor recurrences in the clinical follow-up period. The aggressivity of the tumors will also be assessed in time, concerning the future presence or the absence of the tumor recurrences in the clinical follow-up period.

During the time period that has elapsed since the surgical excision and until this present moment, i.e. approximately one year, there have been no relapses of these cutaneous tumors in our patients.

**Discussion**

**Carcinogenesis and sun exposure**

Sun radiation, particularly UVB (280–315 nm), represent the most important factor involved in the carcinogenesis of BCCs. BCCs' incidence increases in an exponential manner and parallels the UV accumulation in the process of aging [24–27]. Judging by the current theories, basal cell carcinomas derive from incomplete differentiated, pluripotent, immature keratinocytes of epidermic or adnexal origin. Ultraviolet radiation exposure and chronic oxidative stress directly affect the DNA, resulting in mutations and chromosomal aberrations, all of these being encountered in basal cell carcinoma [28–31].

The biological effects of sun radiation on the skin can be classified as early, late and long-term repercussions [32]. Early phenomena are usually well tolerated and little harmful for the skin (caloric, antirachitic and anti-depressive action, immediate pigmentation). The late effects could be described as actinic erythema that occurs after a few hours post-exposure, late pigmentation (appears in approximately two days after exposure, with a maximum after three weeks), epidermal hyperplasia (thickening of the squamous layer) and effects on the immune system (moderate photoimmunosuppression). The long-term effects induced by sun exposure are skin ageing and photocarcinogenesis. Despite the fact that a direct connection between ultraviolet radiation exposure (solar or artificial) and BCC has been established, the appearance of basal cell carcinomas on unexposed areas suggests that there may be additional etiologic factors involved. These factors might include: genetic predisposition, local carcinogens, chronic ulcerations/inflammations, repeated trauma, or injuries (burns), immunosuppression, various genodermatoses, etc. The risk factors predisposing to basal cell carcinomas – according to Bolognia JL et al. [33] – are listed in the table below (Table 3).

<table>
<thead>
<tr>
<th>Table 3 – Risk factors involved in the development of basal cell carcinomas [33]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental exposure:</strong></td>
</tr>
<tr>
<td>• Cumulative/occupational sun exposure (early in childhood);</td>
</tr>
<tr>
<td>• Intermittent/recreational sun exposure;</td>
</tr>
<tr>
<td>• Exposure of various nature to UV light (PUVA, tanning beds);</td>
</tr>
<tr>
<td>• Ionizing radiation;</td>
</tr>
<tr>
<td>• Environmental exposure (hydrocarbons/pesticides).</td>
</tr>
<tr>
<td><strong>Pigmentary phenotype:</strong></td>
</tr>
<tr>
<td>• Fair skin;</td>
</tr>
<tr>
<td>• Presence of freckles;</td>
</tr>
<tr>
<td>• Red hair;</td>
</tr>
<tr>
<td>• Always burns, never tans.</td>
</tr>
<tr>
<td><strong>Genetic syndromes:</strong></td>
</tr>
<tr>
<td>• Xeroderma pigmentosum;</td>
</tr>
<tr>
<td>• Oculocutaneous albinism;</td>
</tr>
<tr>
<td>• Epidermodysplasia verruciformis;</td>
</tr>
<tr>
<td>• Dystrophic epidermolysis bullosa (primarily recessive);</td>
</tr>
<tr>
<td>• Ferguson–Smith’s syndrome.</td>
</tr>
<tr>
<td><strong>Predisposing clinical settings:</strong></td>
</tr>
<tr>
<td>• Chronic non-healing wounds.</td>
</tr>
<tr>
<td><strong>Immunosuppression:</strong></td>
</tr>
<tr>
<td>• Organ transplanation.</td>
</tr>
</tbody>
</table>

The carcinogenesis is a multistep process with intermediary stages, in which the activation of oncogenes, the disturbance of the “sonic hedgehog” signaling pathway, the deactivation of various tumor suppression genes such as p53 or the inhibition of immune mechanisms each play a role. UV exposure leads to epidermic cell DNA mutations, along with the suppression of the immune system. The involvement of sun exposure in the occurrence of basal cell carcinomas is obvious, as supported by the following:

- incidence of BCCs is directly related to the geographic latitude and the cumulated solar radiation dose;
- BCC development is frequently encountered in those dermatoses in which the role of the sun exposure is dominant (albinism, xeroderma pigmentosum);
- BCC occurs more frequently on sun exposed areas [25, 26, 32].

The carcinogenesis process starts even 40–60 years after sun exposure. However, exposure duration and the cumulative doses are less known than in squamous carcinomas, due to the lack of experimental animal models of BCC.

Besides UV, other carcinogenetic factors have also been incriminated, such as X-rays within therapeutic irradiation or thoracic radiographies. The latency period varies between a few weeks and 40–50 years and seems to be inversely proportional with the received dose [32]. UVA phototherapies increases BCC incidence, but in a lower manner than in the case of squamous cell carcinomas [34].

In rare cases, less frequent than in squamous cell
carcinomas, BCCs develop on areas of chronic ulcerations, burns or scars. BCC can also occur in organ grafts recipients requiring immunosuppressant medication, although the most frequently reported skin tumors in this particular instance are the squamous cell carcinomas [35].

In respect to the contributing/determining factors [7, 33, 35, 36] to the appearance of basal cell carcinomas, we did not detect any major and obvious causes that could have been involved in the occurrence of the axillary basal cell carcinomas. All patients denied sun exposure of the axillary region, came from the urban area, the nature of their work did not engage them in outdoor activities, had never used sun beds, had never had pathological conditions that would necessitate repeated pulmonary/thoracic X-rays and were not exposed to pesticides or aromatic hydrocarbons.

Given the above-mentioned risk factors involved in the development of BCC, we cannot state that the patients had abused of sun exposure or that a certain factor was obviously involved in the occurrence of axillary BCC; however, other authors reporting cases of axillary BCCs reached the same conclusion.

Studying the literature reports of authors who detected axillary basal cell carcinomas, we found that no certain histological type of basal cell carcinoma is more frequently encountered in these cases. In this respect, Park 3 et al. [37] described each of the four detected axillary carcinomas reported in his article as presenting a different histological type (nodular, adenoid, basosquamous and pigmented); on the contrary, Betti R et al. [17] recognized the preponderance of the superficial type in 64% and of the nodular type in 28% of the cases. Also, LeSueur BW et al. [11] in his study found the nodular type as occurring more frequently. In our cases, three out of four axillary basal cell carcinoma cases were nodular type BCCs, while only one case was superficial type BCC. Nodular and superficial BCCs, such as the ones found in these axillary BCCs, have the reputation of being less aggressive than the sclerodermiform type.

The mean age of our patients is higher than the values reported by the other authors: Kim SH et al. [9] – 56.4 years, Betti R et al. [17] – 64.96 years, LeSueur BW et al. [11] – 65.6 years and Mapelli ET et al. [13] – 70 years.

We were especially interested in observing through immunohistochemical methods if those axillary basal cell carcinomas are more aggressive or have a more increased invasive potential and therefore we objectified the expression of some metalloproteinases (MMP1, 3 and 11) and Ki67 markers, in the tumor and stromal compartments of the tumor.

Matrix metalloproteinases (MMPs) are proteolitic enzymes playing an important role in extracellular matrix remodeling. MMP type proteases are necessary for the scarring and regeneration of affected tissues and, depending on the substrate they act on, are classified as: collagenases, gelatinases, stromelysins, matrilysins and other MMPs. Also, MMPs are important in all phases of tumor progression, directly influencing the extracellular matrix by destroying the local architecture of the tissues and basal membranes, therefore favoring the tumoral invasion and metastasis. They also have an indirect action by creating a particular microclimate for the tumor, controlling the tumor angiogenesis.

In normal adult human skin, the MMPs are weakly expressed, but their level significantly increases in pathological conditions such as carcinogenesis, inflammation or in the scar formation process/wound healing.

The first finding regarding the importance of MMPs in tumor architecture was the correlation between the capacity of the cells to invade the surrounding tissue and the high levels of MMP in these areas. The high expression of MMPs in the invasion front of the tumor is well established; moreover, a few studies reveal the presence of MMPs in the very early stages of carcinogenesis. Metalloproteinases 1, 3 and 11 are well expressed in the stromal cells adjacent to the malignant epithelial cells in basal cell carcinomas. Cribier B et al. [38] show that MMP11 is intensely expressed in the aggressive types of BCC.

We tried to correlate our results with the ones reported so far in the medical literature pertaining to this subject. In our case, in the four axillary basal cell carcinomas we have presented, we ascertained the high positivity of metalloproteinases (MMP1, MMP3 and MMP11) predominantly in the deeper tumor compartment, especially at the tumor invasion front, both intratumorally and stromal. The expression of MMPs was not related to tumor ulceration or surrounding tissue remodeling-related changes, as can be seen in the following images (Figures 5 and 6). Our results confirm the literature data concerning the involvement of MMPs in BCC progression, even in this rare anatomotic location, i.e. the axillary region.

BCC rarity in the axillary region requires a histopathological and even immunohistochemical diagnosis in order to exclude with certainty another adnexal tumor or squamous cell carcinoma (CSC), especially a basaloid type of CSC, as clinical similarities contrasts with totally different biological potential and this is why we used Ber-EP4 confirmation.

Conclusions

Reported to the total number of histologically diagnosed carcinomas in our hospital, the percentage of axillary BCC is small (0.43%) and no particular etiological factor was detected. The clinical and histological types of these cases do not suggest an aggressive type of BCC, although Ki67 index is greater than the average reported in the literature for this type of tumor. These cases of axillary basal cell carcinomas belong to the regular type of basal cell carcinoma, but present an unusual anatomical location, unexplained by immunohistochemical markers. MMPs exhibited increased expression in tumors and stromal compartments, especially at the tumor invasion front, and were not associated with tumor ulceration or surrounding tissue remodeling-related changes.

References

Axillary basal cell carcinoma: additional 25 patient and considerations
tumor development
Accepted: September 12, 2013

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Received: April 20, 2013
Accepted: September 12, 2013

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