Histopathological aspects of some rare forms of facial basal cell carcinoma

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Abstract

Aim: The main objective of the study was to highlight the histopathological aspects of some rare forms of facial basal cell carcinomas. Patients, Materials and Methods: The 65 selected patients were diagnosed with head basal cell carcinoma (BCC), during 2011–2013, and they underwent surgery. The excised tumor tissue fragments were processed for paraffin embedding and stained with Hematoxylin–Eosin (HE), Masson's trichrome with Aniline Blue, and Alcian Blue–Periodic Acid Schiff (AB–PAS). Results: The youngest patient was 23 years old, while the oldest was 91 years. The facial BCC there was slightly higher prevalence in males of 34 out of 65 cases. Histopathologically, great varieties of morphological types have been identified in the 65 cases investigated. According to our data, by far the most common are nodular BCCs type, which represented 44.6% from the investigated cases, followed at some distance by morpheiform and superficial subtypes with 13.8% and 10.7%, respectively. The most rare cases of facial BCCs were: cystic, adenoid, fibroepithelial and basal with adnexal differentiation with in one single case each. Relatively rare were the following varieties: pigmented (four cases), combinations of several forms (four cases), metatypical (three cases), keratotic (three cases), and micronodular (two cases). Conclusions: Within the limits of this study, the data reported here shown that such a lesional pleomorphism very often requires to make a careful differential diagnosis with a number of other tumor or non-tumor entities.

Keywords: micronodular basal cell carcinoma, cystic basal cell carcinoma, adenoid basal cell carcinoma, fibroepithelial basal cell carcinoma, basal cell carcinoma with adnexal differentiation.

Introduction

Skin cancer is a malignant disease that has a much higher incidence than other forms of cancer localized to another organ or tissue. Over 3.5 million skin cancer cases are diagnosed annually in the US [1]. The incidence of skin cancer is on the rise by 5 to 7% per year, mainly as the result of ultraviolet (UV) exposure and aging [1, 2]. There are three basic anatomo-clinical forms of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM). BCC and SCC, called non-melanoma skin cancers (NMSCs) are the most common forms of skin cancer, accounting for about 96% [3, 4]. Skin cancer, including both melanoma and non-melanoma, is the most common type of malignancy in the Caucasian population [5]. The incidence of both MM and NMSC is on the rise, with an annual increase in MM of 0.6% among adults over 50 years [6].

Deviations in reported incidence rates exist and are attributed to varying risk factors amongst different populations, as well as discrepancies in national registration systems. Furthermore, the incidence of melanoma may be even higher than indicated, as the National Cancer Registries has reported an underestimation of its incidence in certain countries [7].

World Health Organization (WHO) has classified the surface epidermis tumors as follows [8]:

(a) Benign epithelial tumors: epidermal nevus; seborrheic keratosis; clear cell acanthoma; fibroepithelial polyp; Warty dyskeratoma; actinic keratosis; keratoacanthoma; benign lichenoid keratosis;

(b) Malignant epithelial tumors: basal cell carcinoma; nodular basal cell carcinoma; superficial basal cell carcinoma; micronodular basal cell carcinoma; fibroepithelial basal cell carcinoma; scleroderform basal cell carcinoma; basal cell carcinoma with adnexal differentiation; keratosis basal cell carcinoma; basal cell carcinoma with sebaceous differentiation; adenoid basal cell carcinoma; pigmented basal cell carcinoma; nevoid basal cell carcinoma syndrome; basosquamous carcinoma; squamous cell carcinoma; spindle cell squamous cell carcinoma; acantholytic squamous cell carcinoma; verrucous squamous cell carcinoma; squamous cell carcinoma with horny cyst; lymphoepithelial squamous cell carcinoma; Bowen’s disease; Bowenoid papulosis.
Major cutaneous malignant masses result from multifactorial causes such as environmental and host factors [9]. Some studies highlighted that facial region is one of the most common location of skin cancer [10]. The face, ear, pre- and post-auricular areas are the most high-risk anatomic locations for skin carcinoma [11]. The general predilection of cutaneous malignant mass for the head and neck sites is due to the many opportunities for these regions to be exposed to ultraviolet radiation [9, 12]. The main objective of the study was to highlight the histopathological aspects of some rare forms of facial basal cell carcinomas.

**Patients, Materials and Methods**

**Study patients**

The study patients were selected from those who came in the Department of Plastic Surgery within the Emergency County Hospital of Craiova (Romania), during 2011–2013. The 65 selected patients were diagnosed with head BCC and they underwent surgery.

The study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. The study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova and each patient was informed about the purpose and protocol of the study. Data were obtained from the medical records, surgical protocols and from the patients’ medical history. The following data were collected: patients’ gender, age, origin, tumor location and development. Data were processed only by descriptive statistics analysis.

**Sampling and preparation of tissue fragments**

For the purpose of our study, the excised tumor tissue fragments were washed in isotonic saline solution. They were fixed for 24 hours in 4% buffered paraformaldehyde and then routinely processed for paraffin embedding at the Laboratory of Pathology, Emergency County Hospital of Craiova.

For histological examination, the 3-μm thick cross-sections were stained with:

- Hematoxylin–Eosin (HE) for diagnostic reassessment according to WHO classification criteria of skin keratinocyte carcinomas [8];
- Masson’s trichrome with Aniline Blue to assess the degree of tumor fibrosis;
- Alcian Blue–Periodic Acid Schiff (AB–PAS) to assess the profile of mucins (neutral versus acidic) secreted by tumor cells.

Diagnostic slides were evaluated against the WHO diagnostic criteria of skin keratinocyte tumors [8].

**Results**

The analysis of data found in observation sheets allowed a distribution of investigated cases by age, shown by the table below (Table 1).

<table>
<thead>
<tr>
<th>Age group [years]</th>
<th>21–30</th>
<th>31–40</th>
<th>41–50</th>
<th>51–60</th>
<th>61–70</th>
<th>71–80</th>
<th>81–90</th>
<th>90–100</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>Percent</td>
<td>4.5%</td>
<td>7.7%</td>
<td>12.3%</td>
<td>17%</td>
<td>23.1%</td>
<td>18.5%</td>
<td>13.8%</td>
<td>3.1%</td>
<td>100%</td>
</tr>
</tbody>
</table>

According to data presented in Table 1, facial BCC in our study was widely found from the IIIrd to the Xth decade of life. The youngest patient was 23 while the oldest was 91. We encountered a peak incidence of 15 cases in the decade VII, representing 23.1% of all patients, followed by decades VIII, VI and IX, with percentages of 18.5%, 17% and 13.8%, respectively, from evaluated cases. The average age of occurrence for facial BCC on the studied cases was 62.23, while the median was 65. The gender distribution of the 65 BCCs is shown in Table 2.

By analyzing the data in Table 2, we found out that in cases of facial BCC, there was slightly higher prevalence in males of 34 out of 65 cases, representing 52.3% from the cases investigated with a gender ratio of 1:1.1 in favor of males. It was noticed a dominance of facial BCCs in males, especially for the Vth and the IXth decade of life, while the females were more frequently diagnosed during the VIIth decade of life. The average age for males was 60.8, while for females was 63.7. Median age for men was 61, while for women was 67.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>34</td>
<td>31</td>
<td>65</td>
</tr>
<tr>
<td>Percent</td>
<td>52.3%</td>
<td>47.7%</td>
<td>100%</td>
</tr>
</tbody>
</table>

The data assessment for lesional topography has been summarized in the table below (Table 3).

<table>
<thead>
<tr>
<th>Lesional topography</th>
<th>Forehead</th>
<th>Periorbital</th>
<th>Nose</th>
<th>Cheeks</th>
<th>Upper lip</th>
<th>Lower lip</th>
<th>Menton</th>
<th>Periauricular</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>9</td>
<td>7</td>
<td>18</td>
<td>13</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>Percent</td>
<td>13.85%</td>
<td>10.78%</td>
<td>27.7%</td>
<td>20%</td>
<td>7.7%</td>
<td>4.6%</td>
<td>6.15%</td>
<td>9.22%</td>
<td>100%</td>
</tr>
</tbody>
</table>

According to the above-mentioned table, the most common location of facial BCC was the nasal region with 18 (27.7%) cases, followed by the cheeks with 13 (20%) cases and the forehead with nine (13.8%) cases. This type of tumor has been encountered amongst our cases with a much lower frequency only three (4.6%) cases in the lower lip and four (6.15%) cases in the mental area of mandible, while periorbital, periauricular and upper lip were in a intermediate position with seven, six and five cases respectively. By gender, it was observed a higher rate of BCCs on periauricular and mandible mental areas in males, while in females, these tumors were found mostly...
in the cheeks and periorbital areas. Regarding age groups, we could not find any lesional topographic particularities among them.

Histopathologically, a great variety of morphological types have been identified in the 65 investigated cases, which were classified into the following subtypes: superficial, micronodular, nodular, morpheiform, cystic, adenoid, fibroepithelial, metatypical, keratotic, basal with adnexal differentiation, pigmented and associated forms. The table below shows the distribution of studied cases by the above-listed histopathological (HP) subtypes (Table 4).

<table>
<thead>
<tr>
<th>HP subtypes</th>
<th>Sup</th>
<th>M-nod</th>
<th>Nod</th>
<th>Morph</th>
<th>Cyst</th>
<th>Adn</th>
<th>FE</th>
<th>M</th>
<th>K</th>
<th>BAD</th>
<th>Pig</th>
<th>Asc</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>7</td>
<td>2</td>
<td>29</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>Percent</td>
<td>10.7%</td>
<td>3.1%</td>
<td>44.6%</td>
<td>13.8%</td>
<td>1.6%</td>
<td>1.6%</td>
<td>1.6%</td>
<td>4.6%</td>
<td>4.6%</td>
<td>1.6%</td>
<td>6.1%</td>
<td>6.1%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Sup: Superficial; M-nod: Micronodular; Nod: Nodular; Morph: Morpheiform; Cyst: Cystic; Adn: Adenoid; FE: Fibro-epithelial; M: Metatypical; K: Keratotic; BAD: Basal with adnexal differentiation; Pig: Pigmented; Asc: Associated forms.

According to data presented in the above table, by far the most common are nodular BCCs type, which represented 44.6% from the investigated cases, followed at some distance by morpheiform and superficial subtypes, with 13.8% and 10.7%, respectively. The most rare cases of facial BCC were: cystic, adenoid, fibroepithelial and basal with adnexal differentiation with in one single case each. Relatively rare were the following varieties: pigmented (four cases), combinations of several forms (four cases), metatypical (three cases), keratotic (three cases) and micronodular (two cases).

The histopathological aspects of rare forms of facial BCC will be presented next.

Micronodular BCC was diagnosed in only two new cases, representing 3.1% from the investigated cases. Both cases were males in older ages, one at the age of 75 and the other at 88. Topographically, in one case the tumor has developed in the back of the nose, and the other at the forehead.

Histopathologically, we have identified anastomosed basaloid cell chords with a fenestrated predominant pattern, which sometimes had a myxoid appearance. Micronodular proliferations have penetrated deeply into the deep dermis and/or subjacent adipose tissue (Figure 1d); in one case, there was an underlying muscle invasion (Figure 1e) and perineural invasion (Figure 1f).

Cystic BCC was found in one case, representing only 1.6% of all cases investigated. This type of tumor has grown in a male aged 75, in the right periorbital region.

Histopathological appearance of this tumor was similar to a nodular BCC type localized strictly into the thickness of dermis, consisting of aggregated large tumor with cystic spaces of various sizes within them (Figure 2a). Some of these structures can reach considerable size and their lumens contain homogeneous eosinophilic proteinaceous fluid, necrotic debris, red blood cells or mucins (Figure 2, b and c).

Tumor proliferation cases presented classical stromal retraction (Figure 2d) and peripheral palisade-like arrangement of basaloid carcinoma cells (Figure 2f). Among cells from the edge of cystic spaces, we have revealed the presence of mucin. Stroma from tumor proliferation cases was predominantly fibrous (Figure 2e).

Adenoid BCC was encountered in one case, representing only 1.6% of all investigated cases. The tumor has grown in a 61-aged male on the upper lip in adjacent nasal right wing area.

Histopathological examination of the tumors revealed that into their structure prevails thin cords of interconnected basal tumor cells, which give a reticular or glandular-like pattern (Figure 3, a and b). We noticed the presence of nodular compact aggregates with peripheral palisade-like arrangement and stromal retraction (Figure 3c). At the “mesh network tumor” and glandular-like spaces, we noticed the presence of a colloid or an amorphous granular material (Figure 3, b and c).

Some of glandular-like or tubular structures contained mucin into their lumen (Figure 3d). In addition, some of the basaloid cells that demarcate glandular-like structures had reversed polarity and subnuclear vacuolation, suggesting a secretory aspect. Tumoral stroma was of predominantly mucinous type, and in some places of fibrous type (Figure 3e). Tumor presented an invasive aspect into the deep dermis (Figure 3f) and perineural invasion.

Fibroepithelial BCC was diagnosed by us in only one case or 1.6% of all facial BCCs studied. This variety of carcinoma was found in a 78-year-old female, in the area of right nose wing.

Histopathologically, we have identified anastomosed basaloid cell chords with a fenestrated predominant pattern (Figure 4a), which extended from the epidermis to the deep dermis. In such a pattern, we did not notice the classical aspects of BCC with palisade pattern in the periphery and stromal retraction. In addition, the demarcation limit of stroma surrounding the tumor was clear (Figure 4b). Sometimes, we also reveal an adenoidal pattern type with adjacent stromal retractions of these proliferations (Figure 4c). The mesh network of basaloid carcinoma cells has revealed a predominantly fibrovascular (papillary-like) (Figure 4d) and fibrosis stroma (Figure 4e). In areas with intense fibrosis, we found the characteristic appearance of an actinic fibroelastosis (Figure 4f).

BCC with adnexal differentiation was diagnosed in one case, representing 1.6% of total facial BCCs investigated. The tumor developed in a 71-year-old woman on her upper lip.

Histological, the tumor consisted of carcinoma proliferation with nodular pattern, which showed sebaceous cell differentiation in the central zone (Figure 5a). Cellularity of these nodular proliferations is prevalent basaloid type with the cells having round-oval hyperchromatic nuclei.
and a high nucleo-cytoplasmic ratio. At the periphery, the cells exhibited the characteristic appearance of palisade while inside them there was a chaotic arrangement surrounding sebaceous cell groups (Figure 5, b and c). Stroma has been mainly fibrous with retractions in the vicinity carcinomatous proliferation (Figure 5, d and e). Carcinomatous proliferation was exclusively in the dermis without invasion of adjacent structures (Figure 5f).

**Figure 1** – Micronodular basal cell carcinoma: (a) Whole aspect of proliferative predominantly micronodular pattern; (b) Micronodular proliferation of invasive basaloid carcinoma into deep dermis; (c) Tumoral stroma predominantly fibrous; (d) Dermis and hypodermis invasive proliferation, invasion around eccrine sweat glands; (e) Subjacent skeletal muscle invasive proliferation; (f) Perineural invasive proliferation. HE staining: (a and b) ×40; (c–f) ×100.

**Figure 2** – Cystic basal cell carcinoma: (a) Basaloid carcinoma node with a cystic space cystic; (b) Wide cystic space with protein hematic content; (c) Wide cystic space containing mucin; (d) Artifactual space of stromal retraction; (e) Basaloid carcinoma cells with peripheral palisade-like arrangement; (f) Fibrous stroma character. HE staining: (a and b) ×40; (d and e) ×100. AB–PAS staining: (c) ×40. Massons’ trichrome staining: (f) ×40.
Figure 3 – Adenoid basal cell carcinoma: (a and b) Thin cords of interconnected basaloid tumor cells achieving a reticular pattern; (c) Basaloid nodular component associated with artifactual retraction of adjacent stroma; (d) Acid mucins predominantly found in the lumen of glandular-like structures; (e) Myxoid stroma and sometimes fibrous type; (f) Adenoid basal cell carcinoma invaded deep dermis. HE staining: (a and f) ×40; (b and c) ×100. AB–PAS staining: (d) ×100. Massons’ trichrome staining: (e) ×40.

Figure 4 – Fibroepithelial basal cell carcinoma: (a and b) Anastomosed basaloid cell cords showing a predominant fenestrated pattern; (c) Adenoid tumor type pattern associated with peritumoral artifactual retraction; (d) Predominantly fibrous vascular stroma (papillary-like); (e) Vascular fibrous (papillary-like) and fibrous stroma; (f) Actinic fibroelastosis area. HE staining: (a) ×40; (b) ×100; (c) ×200. Masson’s trichrome staining: (d and f) ×100; (e) ×40.
Discussion

Facial BCC accounted for about 88% of all BCCs of the head and neck investigated in this study. The peak incidence of cases was encountered in the VIIth decade, in which were 23.1% of total patients, their average age being 62.23 years. According to the study conducted by Janjua & Qureshi on 171 basal cell carcinomas located in head and neck region, the ages most often affected were decades VI and VII with a mean age of 61 years [13]. Aandani & Ganatra reported a maximum incidence in the decade V [14]. The incidence of this type of cancer tends to increase with age, more than 90% of BCCs developing in people over 60 [15].

Micronodular BCC was diagnosed in this study in only two cases. Its incidence varies widely from one study to another, from 1.6% [16], to 4% [17] and 19.4%, respectively [18], most likely due to different selection criteria of these cases [19].

Histologically, the characteristic appearance was micronodular pattern of growth and invasion in the deep dermis and/or subjacent adipose tissue. Kirihara et al. reported for this variant of BCC discontinuities of basement membrane around micronodular carcinoma proliferations, which would partly justify invasive behavior of these tumors [20]. A number of studies have shown that the micronodular BCC version has a great potential for relapse [21], showing a fairly high incidence of positive tumor margins of excision [22] and a high percentage of undetectable and clinically unapparent tumor extensions with poorly defined edges. Therefore, it is considered an aggressive tumor [23].

Cystic BCC was detected in only 1.6% of the cases studied. In the study conducted by Ben Simon et al., a caseload of 87 periocular BCCs, cystic variant was diagnosed in 7.8% of cases [24]. Specific histopathological aspect was the large tumor aggregates containing cystic spaces within them, of various sizes, with homogeneous eosinophilic proteinaceous fluid, necrotic debris, red blood cells or mucins. Other studies showed mucin between cells delineating cystic spaces [25]. Sometimes, the tumor may present differences of infundibular follicular type, so they must be distinguished from infundibulocystic variant of BCC, which, however, has cystic spaces filled with keratin material [26]. Other authors have described such tumors that clinically have imitated an epidermal cyst [27], a trichilemmal cyst or a trichofolliculoma one respectively [28], but histopathology refuted these diagnoses. There is also described a case of cystic BCC with hidrocystoma aspect where the cystic spaces are lined by one and two-layer epithelium, but without apocrine differences [29]. The differential diagnosis of these lesions may take into consideration inclusion cysts, oral mucocele and metastatic necrotic skin tumors. The formation mechanism of cystic spaces is considered to be a process of massive necrosis of the cells in the central area of the tumor due to rapid tumor growth [30]. If surrounding structures allow (e.g., genian location), neglected tumors can reach very large dimensions, literature describing cases of giant tumors [27].

In this study, adenoid BCC was diagnosed in the upper lip of a 61-year-old man. Histologically, the tumor was composed of thin cords of interconnected basaloid cells achieving a reticular or glandular-like pattern. Tumor presented an invasive character in the deep dermis and perineural invasion. In the study conducted by Hussain et al. on BCCs with eyelid location, adenoid variant accounted for 6.67% of all forms [31]. The differential diagnosis of these tumors includes: cystic adenoid carcinoma (proliferations carcinoma have no connection with the superjacent epidermis or annexes glands and perineural invasion is morphologically constantly met aspect in such tumors) and apocrine cribriform carcinoma.
(cellularity is much more pleomorphic, there is no connection with the epidermis, neither nuclear peripheral palisade pattern nor peritumoral stromal retractions are present) [32]. In some cases, the cells showed basolaid subnuclear reverse polarity and vacuolation suggesting a secretory aspect, and by positioning some cases in the adjacent dermis of tooth root imposed a differential diagnosis with peripheral ameloblastoma [33].

In general, adenoid variant is not considered an aggressive form of BCC. However, aggressive cases have been reported with invaded adjacent subcutaneous tissue, perivascular and perineural spaces [33].

The present study revealed a tumor of fibroepithelial basal cell carcinoma type in a 78-year-old woman in the nasal right wing region. Histologically, the tumor was composed of thin cords of anastomosed basolaid cells that have spread from the epidermis to the deep dermis. The nature of this tumor remains controversial, some authors considering it as a variant of BCC [34–36], while others consider it a fenestrated trichoblastoma, a benign tumor similar to basal cell carcinoma [37].

Histopathologically, Ackerman & Gottlieb take this entity close to basal cell carcinoma [38]. Some authors have described a Pinkus tumor variant with pleomorphic giant cell, which carry out a differential diagnosis of soft tissue tumors with giant cells [39]. The differential diagnosis of this entity includes as well: melanocytic dermal nevus, pedunculated fibroids, skin tag and seborrheic keratosis [40].

BCC with sebaceous differentiation type in this study had been diagnosed in a woman of 71, on her upper lip. Histologically, the tumor consisted of proliferation of carcinoma with nodular pattern that centrally showed sebaceous cytolgy differentiation type. The tumor was localized exclusively in the dermis without invasion of adjacent structures. Misago et al. investigating 1100 BCCs over 20 years of activity and found only one case showing definite sebaceous differentiation [41]. The degree of sebaceous differentiation in BCCs with such differentiation is not as prominent as in sebacea or sebaceous carcinoma. In fact, in the few reported cases of BCC with sebaceous differentiation, sebaceous component is reduced to a few scattered vacuolar sebocytes spreaded between the basolaid proliferations and to rare sebaceous duct-like structures [41]. To this day, there is no percentage of sebaceous differentiation content to guide subdivision in varieties of sebacea, sebaceous carcinoma and BCC with sebaceous differentiation. In literature, it has been reported cases of BCC, which had differences in composition concomitantly sebaceous and apocrine type [42].

Conclusions

Within the limits of this study, the data reported here shown that the facial BCC was encountered in the VIIth decade of life and in male. The most frequently topography of these types of tumors was the nasal region followed by the cheeks and the forehead. According to the gender, the facial BCCs were found mostly on periauricular and mandible mental areas in males and on cheeks and periorbital areas in females. Besides general characteristics, rare forms of facial BCC described in this study had pathological features, which led to a large lesional heterogeneity. Such a lesional pleomorphism very often requires to make a careful differential diagnosis with a number of other tumor or non-tumor entities.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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