Mixed (nodular and morpheic) upper eyelid basal cell carcinoma with orbital invasion – histological and clinical features

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Abstract
Basal cell carcinoma (BCC) is the most common type of cancer located in the periorificial area. We will present the clinical case of a 63-year-old male patient who was admitted to the 2nd Clinic of Neurosurgery, “Prof. Dr. Nicolae Oblu” Emergency Clinical Hospital, Iaşi, Romania, for an ulcerated tumor of about 0.8×0.7 cm in diameter with rolled edges and central necrosis in the upper eyelid with orbital invasion. According to the patient’s personal history, he also underwent Cortisone treatment for dermatomyositis. The magnetic resonance imaging (MRI) scan revealed behind the cutaneous flap, a lesion with 15/38/19 mm anteroposterior (AP)/transverse (T)/craniocaudal (CC) diameters. The surgeons made the excision of the tumor together with the eyelid remnants, and the left orbit exenteration defect. The histopathological exam of the surgical samples revealed an ulcerated epithelial tumor having its origin in the eyelid epidermis and invading all the thickness of the eyelid toward the palpebral conjunctiva, but also the orbital tissue. Immunohistochemical studies showed positive staining for cytokeratin (CK) AE1/AE3, CK5/6, and CK17, but not for CK7. The Ki-67 labeling index was 12%, suggesting a moderate proliferative activity. The final pathological diagnosis was mixed (nodular and morpheic) eyelid BCC infiltrative into the orbital tissue. Although BCC of the upper eyelid is a rare cancer and generally has a low recurrence risk, in the case of a patient undergoing Cortisone treatment for an autoimmune disease, the tumor may grow more rapidly by invading the neighboring tissues including orbit.

Keywords: mixed basal cell carcinoma, orbital invasion, chronic steroid treatment, dermatomyositis, immunohistochemistry.

Introduction
Skin cancer is the most common human malignancy [1]. Among skin cancers, basal cell carcinomas (BCCs), first described by Jacob, in 1827 [2], is the most frequent type, representing approximately 80% of all non-melanoma malignant skin tumors [3].

More than 80% of BCCs occur in the head and neck region [4, 5], followed by the trunk (15%) and extremities (only 5%) [1].

Of all BCCs located in the head and neck region, only 14% grow in the periocular area [5], half of them being encountered on the lower eyelid [6], and a quarter in the medial canthus [7]. The lateral canthus and upper lid are the least involved, with 6.67% each [7].

The etiology of BCCs is unknown, but there are reports that claim the causes include exposure to ultraviolet radiation, ionizing radiation, arsenic, and oral Methoxsalen (Psoralen), a fair complexion [1, 2], and iatrogenic or non-iatrogenic immunosuppression (rheumatoid arthritis, inflammatory bowel disease, organ transplantation, malignancies, skin infections, seborrheic dermatitis) [8] and some genetic disorders (e.g., Gorlin syndrome, xeroderma pigmentosum or albinism) [9].

We report the case of a patient with a mixed (nodular and morpheic) BCC of the left upper eyelid, which developed under chronic Cortisone treatment for dermatomyositis. The patient had tumor recurrence and orbital invasion two years after initial surgery and required exenteration and orbitoplasty with a free cutaneous graft. We underline the etiological significance of Cortisone treatment and the prognostic importance of the BCC histological type.

Case presentation
A 61-year-old man came to the Clinic of Neurosurgery, “Prof. Dr. Nicolae Oblu” Emergency Clinical Hospital, Iaşi, Romania, with a one-year history of a slowly growing and painful tumor involving his left upper eyelid and extended into the eyebrow area.

The clinical examination revealed obesity, particularly of the trunk and face, with “buffalo hump” and “moon face”, and an ulcerated tumor having 2×2 cm in diameter that affected two-thirds of patient’s left upper eyelid and his left supraorbital area. His medical history revealed third degree hypertension, with additional high risk, left anterior fascicular hemiblock, dermatomyositis treated with chronic corticosteroid medication for three years.

ISSN (print) 1220–0522      ISSN (online) 2066–8279
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/
Laboratory exams showed an eight-hour fasting blood glucose level of 128 mg/dL, interpreted as a glucocorticoid-induced diabetes mellitus. The cranio-cerebral computed tomography (CT) scan showed pathological contrast in the upper periorbital area, without orbital or intracranial invasion. Surgery was performed with the macroscopic total excision of the tumor and cosmetic correction of the residual defect, with a rotation-advancement frontal cutaneous flap. The histopathological (HP) exam of the resected lesion established the diagnosis of a mixed BCC (a combination of nodular and infiltrative types) involving the eyelid, with no histological clearance of surgical resection margins. The patient’s postoperative evolution was positive and he was discharged with the recommendation to return for periodic follow-up. The patient did not return for the recommended postoperative follow-ups and continued to take the Cortisone treatment prescribed for his previously diagnosed dermatomyositis. Two years later, the patient came to the Clinic of Neurosurgery again for tumor recurrence. The local exam showed a tumor on his left eyelid ulceration, 0.8×0.7 cm in its largest diameters, with a rolled border and central necrosis. The left eyeball was mobile with visual acuity 1.0 (Figure 1).

**Figure 1** – Clinical exam revealed an ulcerated lesion with an irregular, ill-defined margin, and palpable induration at the tissue edges, affecting the remaining left upper eyelid.

A head magnetic resonance imaging (MRI) scan (Figure 2, a–d) revealed moderate cortico-subcortical atrophy and left temporal angioma but did not reveal any cerebral tumor invasion. Also, there was a hypertrophy of bilateral inferior nasal conchae with quasi-complete obstruction of nasal cavities. In the left frontal area, posterior to the cutaneous flap, there was a lesion with hypersignal on T2 and low signal on T1-weighted imaging, with 15/38/19 mm anteroposterior (AP)/transverse (T)/craniocaudal (CC) diameters. The lesion came in contact but without a clear boundary with the anterior one-third of the right upper muscle of the eyeball and with the lachrymal gland. No signal changes were seen inside both eyeballs.

Due to tumor orbital invasion, a complex team of specialists, including a neurosurgeon, plastic surgeon and ophthalmologist, worked together and decided to perform the exenteration of the left orbit for which the patient gave his written consent. The surgeons made the excision of the tumor together with the eyelid remnants, and the left orbit exenteration, followed by cosmetic correction of the residual defect with a free cutaneous graft taken from the inguinal right fold (Figure 3, a and b). The HP exam of the surgical samples revealed an ulcerated epithelial tumor having its origin in the eyelid epidermis and invading all the thickness of the eyelid toward the palpebral conjunctiva, but also the orbital tissue. The tumor had a solid growth in its superficial layers, showing solid nests separated from the surrounding stroma by artefactual clefts (Figures 4 and 5). The solid nests were made of basaloid cells presenting typical peripheral palisading whereas the internal arrangement of the cells was rather chaotic (Figure 5).

**Figure 2** – (a–d) The cranio-cerebral and orbital MRI scan reveals moderate cortico-subcortical atrophy without tumor invasion into the cerebral parenchyma. There was hypertrophy of bilateral inferior nasal conchae with quasi-complete obstruction of nasal cavities. In the left frontal-palpebral area, behind the cutaneous flap, we noted tumor recurrence invading the left eye socket in its supero-external section. MRI: Magnetic resonance imaging.
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The tumor cells had a thin pale cytoplasm surrounding oval or round nuclei with a pattern of rough granulated chromatin. There were numerous atypical mitoses (2–4 mitoses/high power field). Some greater nodules showed central necrosis (Figure 6). The deepest part of the tumor showed an infiltrative pattern deeply penetrating into the orbital tissue. There were thin (one-to-two strands thick), linear, and branching strands of atypical basaloïd cells which were enmeshed in a densely collagenized stroma with many fibroblasts (Figure 7, a-d). Immunohistochemical (IHC) studies showed positive staining for cytokeratin (CK) AE1/AE3 (Figures 8 and 9), CK17 (Figures 10 and 11), and CK5/6 (Figure 12), but not for and CK7. The Ki-67 labeling index was 12% (Figure 13), suggesting a moderate proliferative activity.

The final pathological diagnosis was mixed (nodular and morpheic) eyelid BCC infiltrative into the orbital tissue.

The patient’s evolution after surgery was positive but he refused the aesthetic correction of his facial defect by orbital epithesis. The patient was discharged and redirected to the Department of Oncology.

Figure 3 – Surgical procedure for recurrent BCC: (a) Left orbital exenteration; (b) Cosmetic correction of the residual defect with a free cutaneous graft taken from the inguinal right fold. BCC: Basal cell carcinoma.

Figure 4 – Microphotograph of the surgical sample: BCC showing its characteristic histomorphological features (peripheral palisading, myxoid stroma, artefactual clefting) (HE staining, ×100). BCC: Basal cell carcinoma; HE: Hematoxylin–Eosin.

Figure 5 – The superficial part of the tumor was made up of solid nodules presenting typical peripheral palisading of the cells and chaotic arrangement of the cells in the central region. There were also some mitotic figures (HE staining, ×200). HE: Hematoxylin–Eosin.

Figure 6 – The tumor invaded all the depth of the eyelid toward the palpebral conjunctiva. Greater tumor nodules showed multiple and atypical mitoses and central necrosis (HE staining, ×200).
Figure 7 – (a–d) BCC invaded into the orbital tissues and presented thin strands of tumor cells and a dense fibrous stroma, thus creating a sclerosing pattern (HE staining, ×100). BCC: Basal cell carcinoma; HE: Hematoxylin–Eosin.

Figure 8 – BCC under the form of ulcerative lesion made up of proliferating nests of basaloid cells arising from epidermis and extending into the depth of the eyelid. All its cells showed immunopositivity for anti-CK AE1/AE3 antibody (×50). BCC: Basal cell carcinoma; CK: Cytokeratin.

Figure 9 – Higher magnification revealed that all tumor cells showed a brown coloration of their cytoplasm when immunostained with anti-CK AE1/AE3 antibody (×200). CK: Cytokeratin.
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Figure 10 – The ulcerative BCC was made up of tumor cells arranged in nests and strands containing tumor cells that exhibited intense immunopositivity for anti-CK17 antibody (×100). BCC: Basal cell carcinoma; CK: Cytokeratin.

Figure 11 – Higher magnification revealed that all tumor cells showed a brown coloration of their cytoplasm when immunostained with anti-CK17 antibody (×200). CK: Cytokeratin.

Figure 12 – Tumor cells arranged in small nests and thin strands included in a dense fibrous stroma showed immunopositivity for anti-CK5/6 antibody (×100). CK: Cytokeratin.

Figure 13 – Anti-Ki-67 antibody immunostaining showed nuclear positivity (×200).

Discussion

BCC arises from pluripotent cells located in the basal layer of the epidermis, and these cells can be differentiated into sweat and sebaceous glands or hair [3].

Slije et al. (2016) [10] have proven in vivo that facial BCC developed due to a long-term immunosuppression that formed an immunosuppressed niche in the facial skin, which represented a permissive microenvironment susceptible to skin cancer. Some studies reported a 10-fold higher incidence of BCC in renal-transplanted persons versus immunocompetent persons [11].

Our patient has long been treated with Cortisone for dermatomyositis, which may have been a risk factor for both the development of the primary tumor and for its progress, being locally invasive and with destructive growth.

The highest incidence is in 70- to 74-year-old patients, but the mean age at diagnosis is 60 years [5]. Our patient was also in his seventh decade of life.

The clinical appearance of BCC is polymorphic and ranges from an erythematous plaque with moderate desquamation to an ulcerated exophytic tumor with variable hyperpigmentation and the presence of small pearly lesions that constitute and delimit it clearly at its border [12].

Hematoxylin–Eosin (HE) staining of the surgical samples demonstrates tumor architecture and morphology. From a histological point of view, there is considerable variation in the HP type of growth among BCCs.

Traditionally, BCCs have been classified as solid (or undifferentiated) and with differentiation characteristics (i.e., to sebaceous, eccrine or other cell lines). Sexton et al. (1990) [13] reviewed 1039 cases of consecutive undifferentiated BCC, in order to define the histological pattern of this skin cancer. The authors found that the most common subtypes are mixed (38.6%), nodular (21%), superficial (17.4%), micronodular (14.5%), infiltrative (7%), and morpheic (1%).

The only proven histological prognostic factor of the biological behavior of BCCs, is the architectural growth pattern which is also an important determinant of the therapeutic approach. Undifferentiated BCCs are with
aggressive growth and with indolent growth. The aggressive growth tumors are infiltrative, sclerosing and morphoeform BCCs, while indolent growth tumors include nodular and superficial BCCs [14].

The histological classification of BCCs establishes a relationship between the patterns of growth and the clinical behavior of the tumor. Morpheaform, micronodular and infiltrative variants have high aggressive biological risk status, while superficial and nodular variants are less aggressive, being low-risk subtypes [15].

In 2014, The British Royal College of Pathologists [15] admitted that many BCCs contain both high-risk and low-risk patterns (so-called “composite” or “mixed” BCCs) and as such the overall clinical risk status of the tumor should be judged as having the behavior of the highest risk variants that is present, regardless of its location and percentage.

Sexton et al. (1990) [13] showed that superficial and nodular BCCs can be completely excised surgically in a high percentage of cases (96.4% and 93.6%, respectively), whereas morpheaform and infiltrative and micronodular BCCs have a higher incidence of positive tumor margins (33.3%, 26.5% and 18.6%, respectively) after surgical excision. If the tumor has a mixed pattern or an infiltrative type, its surgical removal may be incomplete.

Boulinguez et al. (2004) [16] analyzed histological sections of 33 recurrent BCCs and found that 24% of recurrent BCCs, located in the periorbital and perinasal areas and on the cheek, became histologically more aggressive. These authors also found that 20% of initial non-aggressive BCCs became aggressive at relapse and 31% of initial aggressive BCCs showed a more aggressive component during relapse. Therefore, they concluded that periorbital and perinasal areas, as well as the cheeks are areas with a poor prognosis for BCCs [16].

Our patient’s tumor reflected the same clinical behavior. His first resected periorbital tumor showed an incompletely excised, aggressive type (nodular and morphoeform) BCC that became more aggressive during recurrence, invading the whole depth of the eyelid, the cutaneous graft and the orbital tissue.

CKs are expressed specifically in the cytoplasm of epithelial cells. The use of cytokeratin immunostaining is justified in complex cases of BCC morphology. On IHC examination, the tumor cells of BCCs are CK AE1/AE3 positive [17, 18], CK5/6 positive [19], and CK17 positive [20], which have proved to be the most specific marker for BCC [21].

Both tumor samples excised from our patient showed the same IHC profile, i.e., positivity for antibodies that are specific for BCCs: anti-CK AE1/AE3, anti-CK5/6, and anti-CK19, demonstrating that both of them were BCCs.

BCC is a tumor of epithelial origin with local invasiveness. Surgical excision of an eyelid BCC remains the treatment of choice. BCCs have been excised with 3–4 mm tumor-free margins, in an attempt to ensure total clearance. However, even these margins are insufficient to guarantee complete excision of eyelid BCC and some authors reported that in up to 54% of the cases, histological clearance is not achieved [22]. When the initial resection margins are not free, there are necessary further resections until the resection margins are histologically assessed as tumor free.

There are many options for skin defect reconstruction [23], but we used rotation flap for the first surgery and free skin graft for the second. Relapses appeared after three or five years postoperatively in BCCs with morphoeform type [23]. Recurrence after surgery varies between 5% and 12%, over a two-year-period after surgery [5, 24], if the excision is incomplete.

It is generally believed that BCC has a low malignancy and its cure is usually achieved by excision, curettage, electrodesiccation, cryosurgery or irradiation [7].

Although metastasis usually occurs in less than one in 10 000 tumors [25], BCCs could infiltrate dermis and involve extradermal structures such as bone, muscle and cartilage [18].

The clinical course of disease may be rarely aggressive and regional or distant metastases can occur in patients with multiple local recurrences, necessitating exenteration for orbital invasion [7]. Orbital invasion of BCC is an uncommon event that can lead to increase of ocular morbidity and death. It has also been noted that autoimmune conditions may skin cancer development [26, 27].

Physicians need to be aware and alert to the possibility of high-risk tumors and consider appropriate and right imaging, since orbital invasion of BCC may be clinically silent [28].

Any neglected periorbital skin tumor can invade the orbit, with the risk of exenteration [29, 30]. Cooperation with the ophthalmologist and plastic surgeon is important, as intraorbital and ocular tumors require facial and orbital cavity reconstruction [31–34]. The incidence of orbital invasion is about 2% to 4% and the risk factors can be large size of the tumors, canthal areas, perineural spread, aggressive histology, multiple recurrences and age over 70 [35]. Orbital invasion may be clinically silent. Iuliano et al. (2012) [36] and Madge et al. (2010) [37] showed that the histologically morphoeform subtype is a risk factor for orbital invasion and requires exenteration in periorbital BCC.

Conclusions

Although BCC of the upper eyelid is a rare cancer and generally has a low recurrence risk, in the case of a patient undergoing cortisone treatment for an autoimmune disease, the tumor may grow more rapidly by invading the neighboring tissues including the eye socket. In addition, the identification of the morphoeform sclerosing subtype at the HP examination is a high aggressiveness indicator, the tumor being more destructive and more difficult to treat, requiring wider initial excision with significant aesthetic damage. Therefore, we recommend that the ophthalmologist should inform and educate their patients with BCCs, so that he or she should adhere to repeated medical follow-ups for early identification of any recurrence.

Conflict of interests

The authors declare that they have no conflict of interests.

References

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Received: March 12, 2018     Accepted: September 24, 2018