CASE REPORT

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Basal cell carcinoma and basosquamous carcinoma, two faces of the same condition?

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Abstract

Basal cell carcinoma (BCC) is the most common locally invasive malignant epidermal neoplasm. It is generally a tumor that runs a slow progressive course and can usually be cured by surgery. Basosquamous carcinoma is considered by some authors a rare subtype of BCC, while others describe it as independent tumor with different evolution from BCC. The aim of the study was to present a very interesting case of initially otherwise ordinary BCC that during its repeated and extensive relapses changed its histopathology in a basosquamous carcinoma, despite the free surgical margins and leading to major surgeries with loss of right eye. We present a case of 75-year-old male diagnosed in 2008 with a tumor located in the right naso-orbital region. The patient underwent surgical treatment, the histopathology being consistent with BCC. He presented recurrences of the tumor in 2009 and 2010 that were excised at approximately 9 and 16 months, respectively, from the first intervention. In 2010, the surgical procedure was radical, with removal of the tumor and the entire right superior eyelid. This approach proved to have negative side effects over the right eye in time. Therefore, after two months, a complete exenteration of the right orbit was necessary. The tumor recurred again for three times, after 20, 30 and 42 months from the first intervention and every time surgical treatment was applied. The microscopic inspection of the biopsies showed similarities between recurrences and initial tumor. In 2013, after 57 months from the first intervention, the patient was readmitted with a lesion in the same region that was excised but that time the histopathology differed from the previous, the tumor being composed of sheets of achromic epithelioid cells, with vesicular nuclei and prominent, eosinophilic nucleoli. The tumor cells were positive for pan-cytokeratin AE1/AE3 and negative for S100 protein, human melanoma black 45 (HMB45) and vimentin that sustained the diagnosis of basosquamous carcinoma. The paper presented an interesting case with different histopathological features from a recurrence to other, with important implication in diagnosis and prognosis. The transformation of BCC into basosquamous carcinoma sustain that the basosquamous carcinoma is better a rare, aggressive variant of BCC, than an individual lesion.

Keywords: basal cell carcinoma, basosquamous carcinoma, achromic melanoma, basosquamous carcinoma, immunohistochemistry.

Introduction

Basal cell carcinoma (BCC) is the most common locally invasive non-melanocytic malignant epidermal neoplasm predominantly affecting Caucasians [1]. The incidence of BCC increases every year in USA, Canada and most European countries and the highest rate seems to be in Australia. In Europe, the incidence is around 150/100 000 residents, with large variations due to geographic areas [2–7]. In Romania, the incidence of BCC is not known exactly [8].

The factors that increase the risk of BCC include: UV radiation – directly through sun exposure or tanning beds; age – usually BCCs occur in people age 50 or older; gender – men are more likely to develop BCC then women are; environmental and occupational factors; skin type – BCC occur more often in people with light skin and is very rare in black people; history of skin lesions – if one has a personal or a family history of BCC or other form of skin cancer, then it has an increased risk of developing this type of lesions [9–12]. About 80% of this type of lesions is located on the sun-exposed skin of the head and neck, and of those, 30% are found on and around the nose [13].

The histopathology shows three major subtypes: nodular, superficial, and infiltrative (morpheaform). Rare subtypes have mixed histopathology as basosquamous (metatypical) carcinoma that shares features of BCC and squamous cell carcinoma (SCC).

In most cases, BCC generally runs a slow progressive course. Untreated, the tumor invade and destroy the surrounding tissues, leading to severe mutilation when located in the face and neck region [14]. BCC rarely metastasize with a medium rate of 0.0028% to 0.5%. This rate increases proportionally with the dimensions of the tumor to 50% for tumors larger the 10 cm in diameter [15]. On the other hand, basosquamous carcinoma has a more aggressive, different behavior, with a high tendency to recur locally and spread to lymph nodes or other organs.

In most of the BCC cases, the treatment is surgery or radiotherapy, with surgery showing the best results [16, 17]. The goal of the treatment is to eradicate the tumor with acceptable functional and esthetic outcome [16]. Recurrent BCC is more difficult to cure than primary lesions [14]. The treatment of basosquamous carcinoma requires extensive surgery with negative margins, but even so, the risk of local recurrences is between 15% and 50%. Mohs surgery reduces the risk at 5%.

The aim of the study was to present a very interesting case of initially otherwise ordinary BCC that during its repeated and extensive relapses changed its histopathology in a basosquamous carcinoma, despite the free surgical margins and leading to major surgeries with loss of right eye. Moreover, the article highlighted the importance of immunohistochemistry (IHC) in the differential diagnosis of an achromic tumor in the head and neck area.

Patient, Materials and Methods

The paper presents a case of 75-year-old Caucasian male, non-smoker, admitted in the Department of Maxillo-facial Surgery, Emergency City Hospital, Timişoara, Romania, for five times between 2008 and 2013, for multiple recurrences of a tumor in the right naso-orbital region.

The main occupation of the patient was agriculture, fact which would imply long-term sun exposure. The family medical history showed no instance of skin cancer or other significant diseases. The patient was known with hypertension under medication and the general condition was satisfactory. Routine blood tests were normal, except the erythrocyte sedimentation rate (ESR) that was slightly increased. The chest radiograph showed no pathological alterations.

For the first time, the patient was admitted in November 2008, for a lesion that appeared approximately six months before the medical examination and was at first smaller but it slowly increased in dimensions without the tendency of spontaneous heal. The lesion was painless, with hemorrhagic tendency when traumatized. On clinical examination, a 2/1 cm skin ulceration situated in the right naso-orbital-region was seen. The patient underwent surgical treatment, consisting in radical excision of the tumor and a full thickness skin graft was used to cover the resulted defect.

The surgical specimens excised were fixed in 4% (*v/v*) buffered formalin, sent to the Service of Pathology and embedded in paraffin. Four μm-thick sections were cut using a semi-automated Leica RM2235 rotary microtome, displayed on Super Frost microscope slides and stained with Hematoxylin and Eosin (HE). The histopathology showed a nodular tumor composed of large islands of monotonous cells, with scant pale blue cytoplasm, and small nuclei. Around tumor islands, retraction artifact was noted. The lesion was ulcerated and covered by necrotic debris. These features were consistent with ulcerated nodular BCC, excised in normal tissues (Figure 1, a–c).

In August 2009, after nine months from the first intervention, the patient was readmitted with a recurrence on the nasal side of the surgical scar. The lesion was excised with clinical oncological margins. This time, the resulted defect was not covered and the wound healed *per secundam*. The microscopic examination of the excised material, showed similar aspects as first biopsy, with variable sized nests of basaloid cells surrounded by slit-like retraction artifacts and myxoid stroma, some of them centered by keratotic plugs that imposed the diagnosis of nodular BCC with keratotic differentiation (Figure 2, a–e). The tumor was excised in unaffected tissue.

In March 2010, the patient presented another recurrence consisting in an ulceration including the skin of the right dorsal side of the nose, the medial canthus of the right eye and a portion of the superior right eyelid. We decided for surgery and, after 16 months from the first intervention, a radical excision of the tumor and of the entire superior and inferior eyelid were performed (Figure 3, a–c). On HE staining (Figure 4, a–c), the tumor showed two components, one nodular composed of large and small rounded nests of basaloid cells with retraction artifact, disposed in the superficial dermis, and a more aggressive component infiltrating the reticular dermis and the subcutis with irregular tongues of basaloid cells delineated by fibrotic stroma. Between fibroblasts, fibrocytes and myo-fibroblasts, there were observed few melanophages. The surgical margins were free of disease. The features were consistent with nodular BCC with micro- and macro-nodular pattern associated with infiltrative, morpheaform BCC.

Because reconstructive surgery of the right eyelids was not performed, negative side effects over the right eye appeared. Therefore, after one month, a complete exenteration of the right orbit was necessary. After *per secundam* epithelialization of the resulted orbital defect, the patient received a right orbit epithesis attached to glasses in order to restore the esthetic function (Figure 5, a–c).

The tumor recurred again for the three times, after 20, 30 and 42 months from the first intervention. In all the situations, the lesion was located on the right dorsal side of the nose and surgical treatment was applied (Figure 6, a–c). On HE slides, at 20 months after initial diagnosis, the tumor was disposed in dermis and subcutis, being composed of large islands of basaloid cells, features consistent with nodular BCC (Figure 7a). At 30 months after initial diagnosis, the tumor tongues that invaded the subcutis were centered by keratotic plugs that sustained the diagnosis of nodular BCC with macro-nodular pattern and keratotic differentiation and infiltrative, morpheaform BCC (Figure 7b). At 42 months after the first diagnosis, the tumor cells were disposed in small and large islands, surrounded by slit-like artefactual retraction clefts, pathognomonic aspects for nodular BCC with micro- and macro-nodular pattern (Figure 7c). In all the situations, the tumors were excised in normal tissues.

In August 2013, after 57 months from the first intervention, the patient was readmitted with another lesion in the right dorsal side of the nose that was excised (Figure 8, a and b).

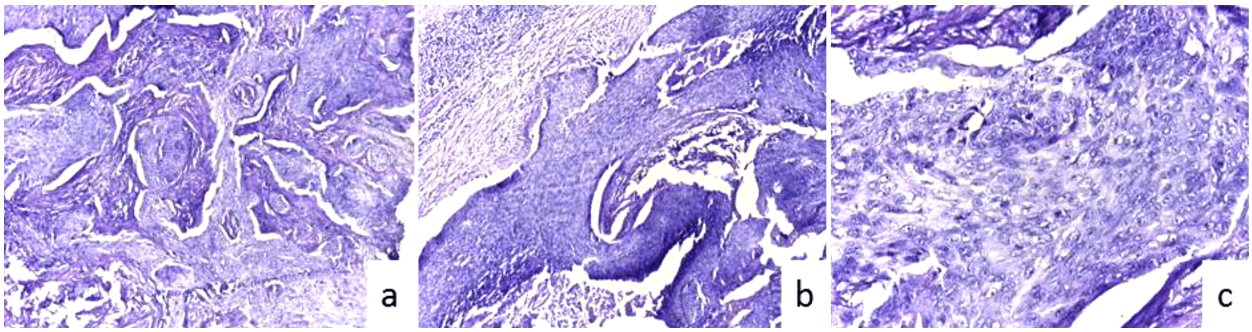

Figure 1 – ***Histopathology of the excised tumor showed islands of tumor cells with retraction artifact, consistent with nodular basal cell carcinoma. HE staining: (a) ×40; (b) ×100; (c) ×400.***

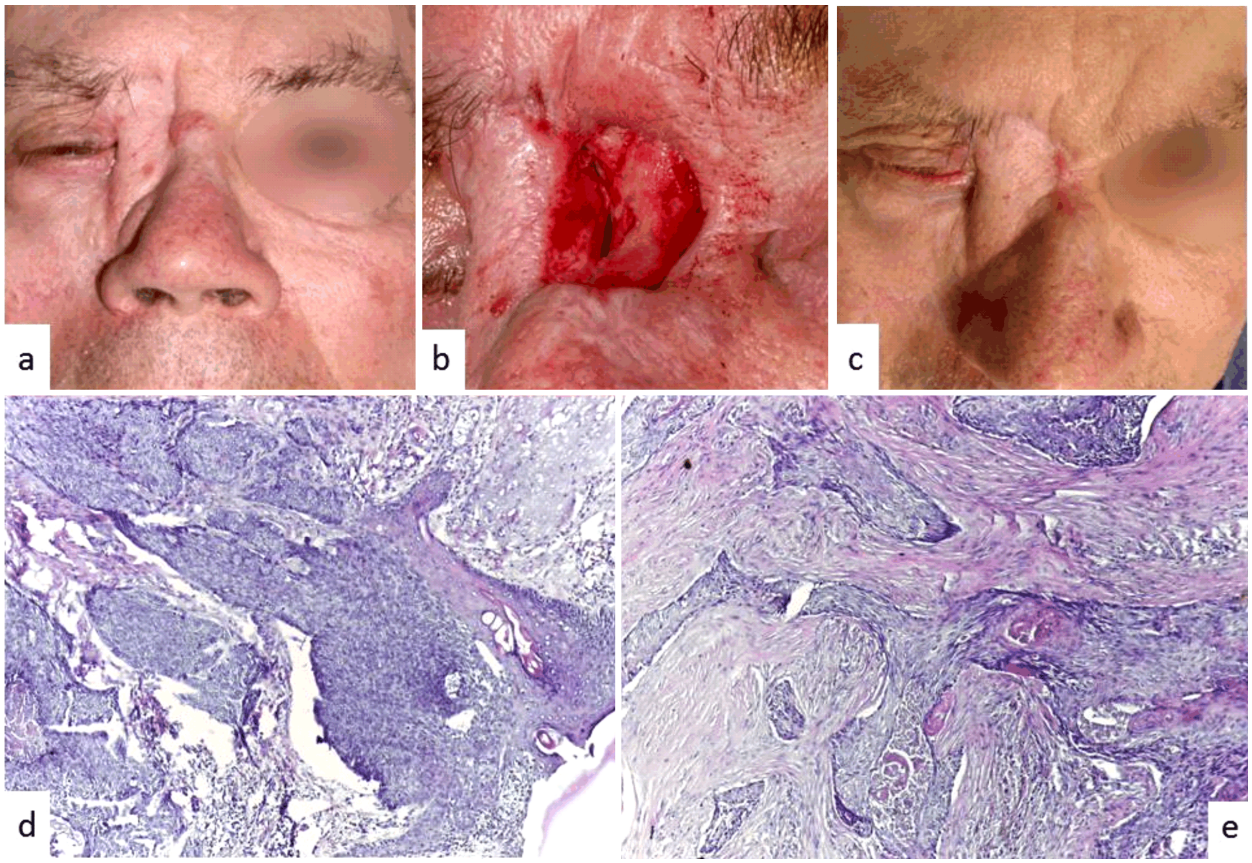

Figure 2 – ***Recurrence in 2009, after nine months from the first intervention: (a) Clinical aspects of the tumor on the nasal side of the surgical scar; (b) Intraoperative aspects; (c) Postoperative aspects; Histopathological aspects with large nests of basaloid cells (d), some of them centered by keratotic plugs (e) (HE staining, ×100).***

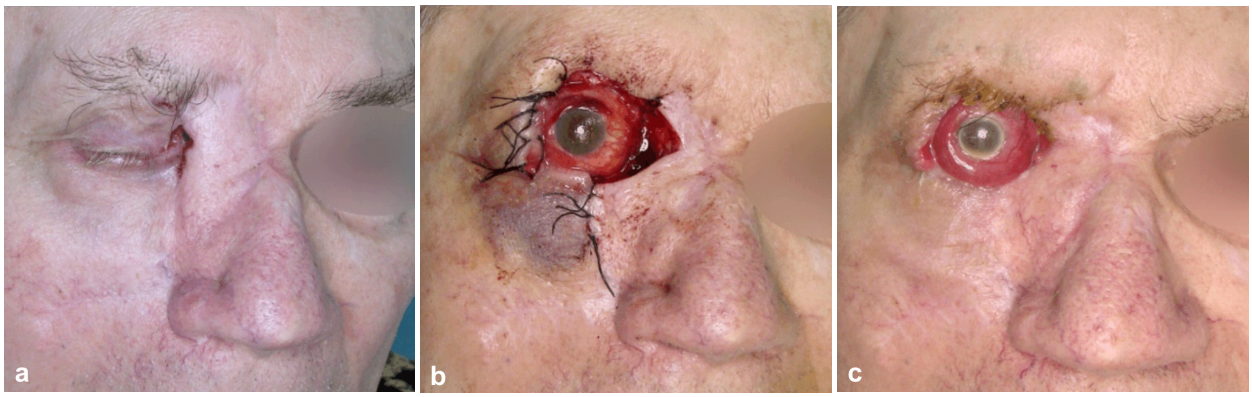

Figure 3 – ***(a–c) Clinical aspect in 2010, after 16 months from the first intervention, with a recurrence including the skin of the right dorsal side of the nose, the medial canthus of the right eye and a portion of the superior right eyelid. The tumor was excised with negative side effects over the right eye.***

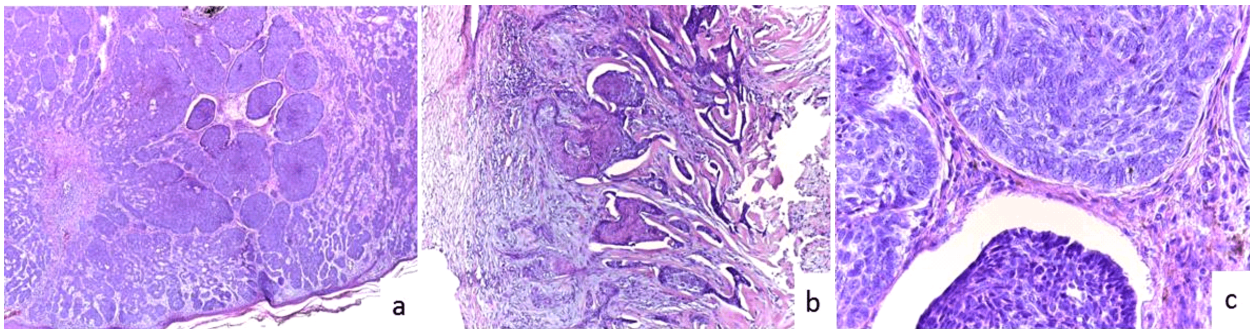

Figure 4 – ***Histopathological examination of 2010's recurrence: (a) Tumor composed of small and large islands of basaloid cells, some of them surrounded by retraction artifact; (b) Infiltrative component of the tumor with tongue of basaloid cells in a desmoplastic stroma; (c) Zoom-in of tumor basaloid cells and surrounded stroma containing some melanophages. HE staining: (a and b) ×40; (c) ×400.***

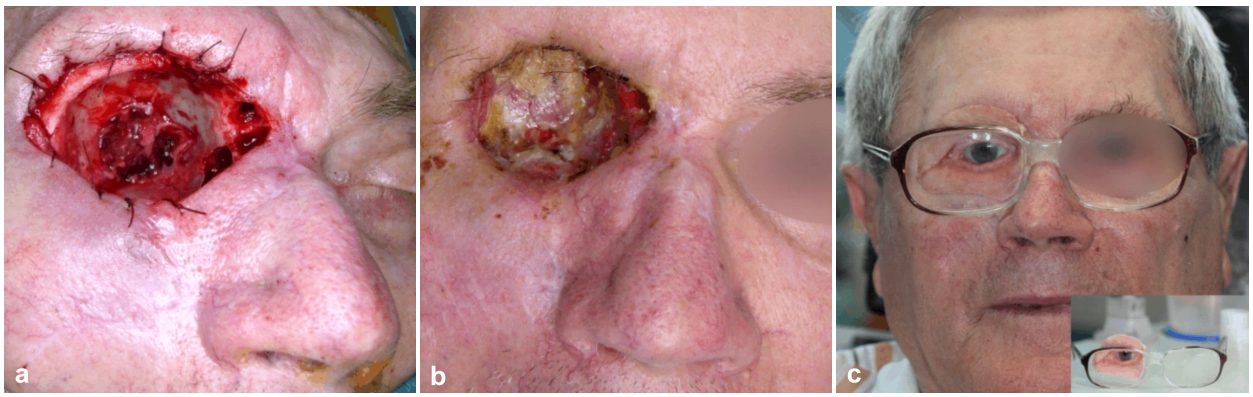

Figure 5 – ***(a–c) Considering the irreversible damage of the right eye, a complete exenteration of the right orbit was performed. The patient received a right orbit epithesis attached to glasses.***

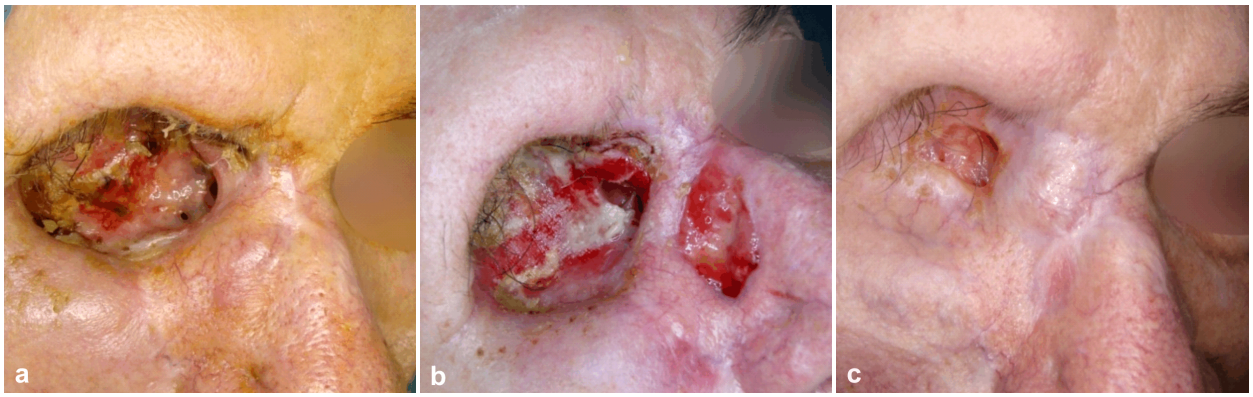

Figure 6 – ***(a–c) The tumor recurred again for three times, after 20, 30 and 42 months from the first intervention and surgical treatment was applied.***

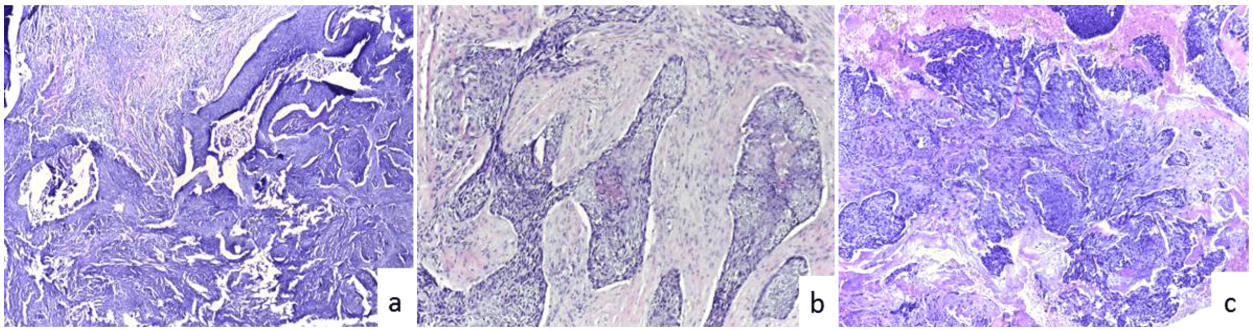

Figure 7 – ***(a) After 20 months from the first diagnosis, the tumor was composed of large sheets of basaloid cells surrounded by retraction artifact in a collagenous stroma; (b) At 30 months from the first diagnosis, the tumor excised was composed by tongues of monotonous basaloid cells, some of them centered by keratotic plugs; (c) Small and large islands of tumor cells composed the lesion excised after 42 months from the diagnosis. HE staining: (a and c) ×40; (b) ×100.***

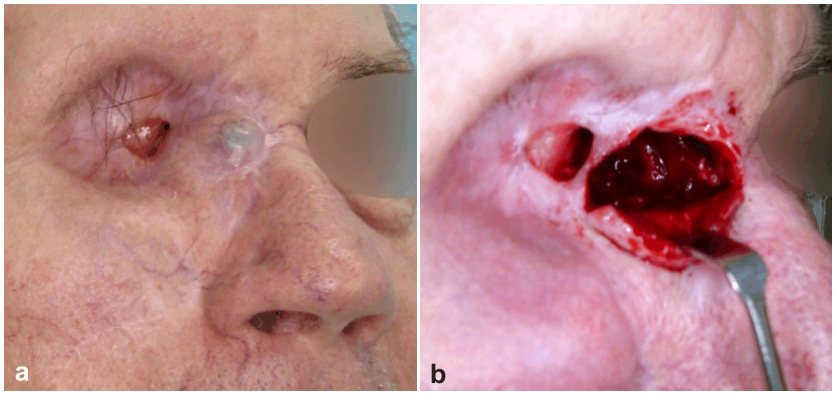

Figure 8 – *(a and b) In 2013, after 57 months from the first intervention, the tumor recurred in the right dorsal side of the nose and was excised.*

On HE slides, the recurrence of 2013 showed a different histopathology from the previous. The tumor was disposed in dermis and subcutis being composed by two components. One component (Figure 9, a and b) presented cells with eosinophilic cytoplasm and vesicular nuclei, with inconstant nucleoli. Some of the cells presented eosinophilic macronucleoli. No pigment was observed in the cytoplasm of the tumor cells, but few melanophages were noted between tumor islands. The second component (Figure 9, c and d) was composed by large islands of monotonous basaloid cells, surrounded by retraction artifact. On morphological-stained slides, the differentials included achromic melanoma, SCC or basosquamous carcinoma.

For differential diagnosis of the last recurrence, IHC was used. For IHC, the slides were dewaxed in toluene and rehydrated in baths with decreasing concentration of ethanol. Antigen retrieval, if necessary, was performed as stated on the antibody datasheet. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide solution (Peroxidase Block Solution, Novocastra, Newcastle upon Tyne, United Kingdom). Sections were treated with 0.4% casein in phosphate-buffered saline, with stabilizers, surfactant, and 0.2% Bronidox L as a preservative (Novocastra), in order to block unspecific binding and then were incubated with the primary antibodies [S100 protein, human melanoma black 45 (HMB45), vimentin, Ki67 and pan-cytokeratin (CK) AE1/AE3]. All the antibodies were obtained from Novocastra, and dilutions, incubation time, and antigen retrieval solutions were resumed in Table 1. The antibodies diluent and the antigen retrieval solutions were supplied by Novocastra (Table 1). The detection system used was Novolink Polymer Detection System (Novocastra). The antigen–antibodies complexes were visualized by 3,3'-diaminobenzidine (DAB) tetrahydrochloride (Novocastra). The nuclei were counterstained with Hematoxylin. The slides were observed using a Leica DM500 microscope and the pictures were captured through a Leica DMshare system.

Table 1 – *Antibodies used in differential diagnosis*

Antibody	Clone	Dilution	Antigen retrieval	Incubation time
S100 protein	Not applicable	1:200	Not recommended	30 minutes
HMB45	HMB45	1:60	Proteinase K	30 minutes
Ki67	MM1	1:200	Heat-induced epitope retrieval, pH 6	30 minutes
Vimentin	V9	1:800	Heat-induced epitope retrieval, pH 6	30 minutes
Pan-CK AE1/AE3	AE1:AE3, 20:1 ratio	1:100	Heat-induced epitope retrieval, pH 6	60 minutes

HMB45: Human melanoma black 45; CK: Cytokeratin.

The tumor cells were intense and diffuse positive for pan-CK AE1/AE3 (Figure 9e) and negative for vimentin (Figure 9f), HMB45 (Figure 9g) and S100 protein (Figure 9h). Ki67 proliferative index was around 30% (Figure 9i).

The morphological and immunohistochemical data sustain the diagnosis of basosquamous carcinoma.

All the clinical data and histopathological features were noted in Table 2.

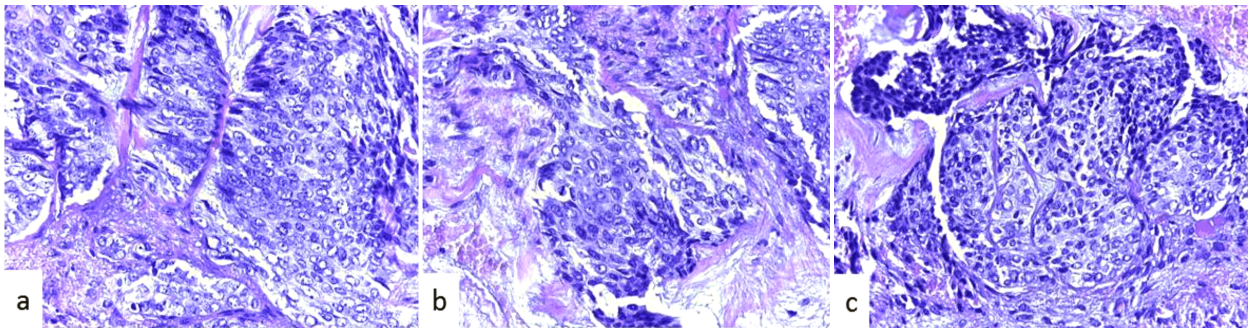

Figure 9 – *The last recurrence from 2013, presented two different components (HE staining, ×100): squamoid cells with eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli (a and b) and basaloid cells with monomorphous appearance, scanty, basophilic cytoplasm and small nuclei (c).*

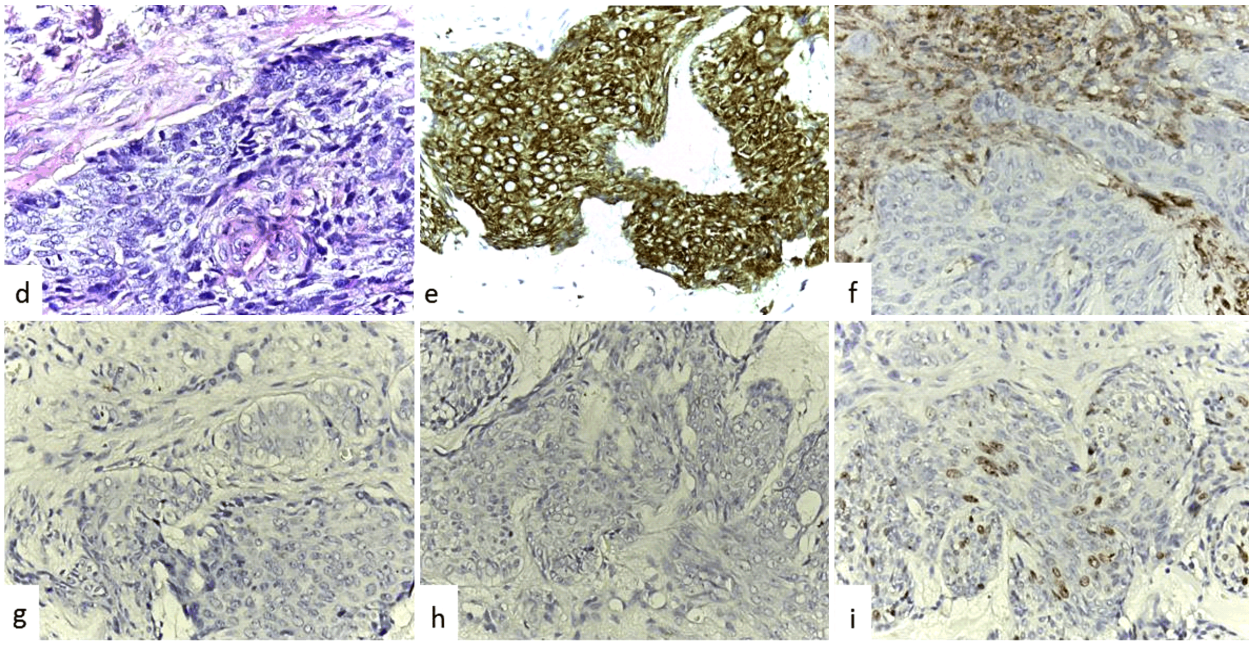

Figure 9 (continued) – ***The last recurrence from 2013, presented basaloid cells with monomorphous appearance, scanty, basophilic cytoplasm and small nuclei (d – HE staining, ×100). The cells were positive for pan-cytokeratin AE1/AE3 (e, ×100) and negative for vimentin (f, ×100), HMB45 (g, ×100) and S100 protein (h, ×100). Ki67 proliferative index was high (i, ×100).***

Table 2 – ***Clinical data and histopathological features***

Relevant past medical history and interventions			
▪ 75-year-old Caucasian male, non-smoker; ▪ family medical history showed no instance of skin cancer or other significant diseases; ▪ the patient was known with hypertension under medication, general condition was satisfactory; ▪ routine blood tests were normal except the ESR that was slightly increased, the chest radiograph showed no pathological alterations.			
Date (month/year), Patient File No.	***Signs and symptoms***	***Treatment***	***Histological findings***
11/2008, 34522	▪ skin tumor in the right naso-orbital region, 2/1 cm in dimensions with large ulcerated surface; ▪ painless with hemorrhagic tendency; ▪ evolution in approximately six months.	▪ surgical treatment consisting in radical excision of the tumor; ▪ a full thickness skin graft was used to cover the resulted defect.	▪ ulcerated nodular BCC
08/2009 (after nine months), 27755	▪ recurrence on the nasal side of the surgical scar	▪ the lesion was excised with clinical oncological margins; ▪ the resulted defect was not covered and the wound healed *per secundam.*	▪ nodular BCC with keratotic differentiation
03/2010 (after 16 months), 6917	▪ recurrence consisting in an ulceration including the skin of the right dorsal side of the nose, the medial canthus of the right eye and a portion of the superior right eyelid	▪ radical excision of the tumor and of the entire superior and inferior eyelid were performed; ▪ reconstructive surgery of the right eyelids was not performed.	▪ nodular BCC with micro- and macro-nodular pattern associated with infiltrative, morpheaform BCC
04/2010 (after 17 months), 13596	▪ due to the fact that reconstructive surgery of the right eyelids was not performed negative side effects over the right eye appeared	▪ complete exenteration of the right orbit was performed; ▪ after *per secundam* epithelialization of the resulted orbital defect, the patient received a right orbit epithesis attached to glasses in order to restore the esthetic function.	NA
07/2010 (after 20 months), 22205	▪ recurrence on the right dorsal side of the nose	▪ radical surgical treatment	▪ nodular BCC
05/2011 (after 30 months), 15034	▪ recurrence on the right dorsal side of the nose	▪ radical surgical treatment	▪ nodular BCC with macro-nodular pattern and keratotic differentiation and infiltrative, morpheaform BCC
05/2012 (after 42 months), 18676	▪ recurrence	▪ radical surgical treatment	▪ nodular BCC with micro- and macro-nodular pattern
08/2013 (after 57 months), 34292	▪ skin lesion on the right on the right dorsal side of the nose	▪ radical surgical treatment	▪ basosquamous carcinoma

ESR: Erythrocyte sedimentation rate; BCC: Basal cell carcinoma; NA: Not applicable.

Discussions

A correct diagnosis of BCC is, in most of the cases, easy to made, the tumor showing pathognomonic histological aspects, as palisading of tumor cells at tumor islands periphery and retraction artifact.

The literature do not offer a generally accepted classification of BCC but most authors divide them in low-risk lesions, including nodular type and high-risk lesions, including infiltrating or morpheaform BCC and BCC with mixed histopathology, as basosquamous carcinoma [18]. Nodular BCC seems to be the most common subtype, being composed of small or large cell islands that classify the tumor in micro- or macro-nodular pattern [19]. Similar to data presented in the literature, the most common type diagnosed in this case was nodular BCC. Few cases could present keratotic differentiation that imposed the differential diagnosis with SCC.

In few cases, with complex histological features, supplementary IHC reactions are necessary in order to differentiate BCC from other lesions as carcinoma, melanoma or soft tissue tumors [20–31]. As in our case, even if the initial lesion and the recurrences presented features characteristic for BCC, the recurrence from 2013 showed a different histopathological aspect, being composed by two components, one with large islands of epithelioid cells with moderate pleomorphism and many typical and atypical mitosis and another with smaller cells, with basophilic cytoplasm, surrounded by slit-like retraction artifacts. The presence of a tumor with high pleomorphism imposed the use of IHC in order to correct differentiation between BCC and other tumors.

Moreover, the change of cell phenotype was seen in different tumors of solid organs. In these cases, the tumor stromal myofibroblasts have an important role in the epithelial mesenchymal transition [32]. As in the case presented, after many recurrences with similar histopathology, the tumor changed in basosquamous carcinoma.

There are several factors that influence the prognosis of BCC increasing the risk of recurrence: size of the tumor, location in the central region of the face around the nose area, poorly defined margins, histological subtype, perineural or perivascular involvement, failure of the previous treatment and, in some cases, immunosuppression [33–35]. Even if, in the presented case, all the specimens were removed in unaffected tissue, the tumor recurred for many times. It was demonstrated that in BCC, as in other epithelial or non-epithelial tumors, the tumor cells present different mutations of oncogenic genes that promote tumorigenesis [36]. In acral melanoma, at several centimeters from the last tumor cell, the melanocytes can present pro-oncogenic mutations. Similar to this, the presence of cells with pro-oncogenic mutation in follicular epithelia of otherwise normal skin, can explain the development of several recurrences even if the lesions were removed in normal tissue.

The prognostic factors should help the clinician to characterize the lesion as low or high risk and to predict the possibility of recurrence after treatment; thereby, the presence or absence of these factors can influence the treatment option [14]. In case of a low-risk BCC, there are some treatment techniques that can be used, like cryosurgery, curettage, radiotherapy, all having the main disadvantage of not allowing histological examination. Surgery with intraoperative or postoperative histological examination can be used to treat both low and high-risk tumors and is considered to have the best results [17]. In case of primary BCC, the tumor is excised with a peripheral margin of clinically healthy tissue of 3–5 mm [37]. Recurrent BCC is more difficult to treat and cure than primary BCC and require wider peripheral surgical margins of 5–10 mm [14].

Although has a slow progressive course, BCC can produce sever deformity due to the invasion of the surrounding tissues or after treatment. This kind of mutilation appears especially in the face and neck region.

The treatment option with the lowest rate of failure is surgery. Regardless of the technique, the aim of the treatment is to eradicate the tumor with satisfactory esthetic and functional results. In some cases, surgery may be inappropriate due to the small percentage of cure or because of substantial deformity resulted.

Primary BCC has a very low rate of recurrence, while recurred BCC is more difficult to cure and has a much higher rate of recurrence. The risk of recurrence depends on the tumor characteristics and the treatment option and technique.

Moreover, the particularity of this case was represented by the different histological aspects of biopsied specimens.

Conclusions

The article presented an interesting case of BCC that developed many recurrences even if all the lesions were removed in normal tissues. The identification of the cell of recurrences origin needs further molecular investigation. Moreover, the case changed its histopathology during the recurrences, from a BCC to a basosquamous carcinoma. Also, the article highlighted the importance of IHC in the differential diagnosis of achromic tumors.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Horaţiu Constantin Urechescu, Nicolae Constantin Balica and Cristian Andrei Sarău equally contributed to the manuscript.

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