CASE REPORT

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The curious case of a forehead metatypical basal cell carcinoma

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Abstract

The risk of developing basal cell carcinoma (BCC) during lifetime varies between 29–55%, while for squamous cell carcinoma (SCC) varies between 7–11%. Between them, considered to be a BCC, there is a particular histological type, named metatypical basal cell carcinoma (MTC) or basosquamous cell carcinoma (BSCC). In this paper, we presented a rare case of metatypical carcinoma of the forehead with an interesting history of unexpected recurrences, underlining the clinical, therapeutic and histological essential aspects that may come in use to other clinicians in managing this type of cancer. In this case, the last recurrent tumor invaded the external layer of the frontal bone and needed a temporo-parietal flap to cover the large defect, which was previously covered in 2014 using skin grafts. Using Hematoxylin–Eosin (HE) staining, the histological assessment revealed a basosquamous carcinoma (IDO-O 8094/3, according to *World Health Organization*). In addition to the histological aspects revealed using HE staining, in this case, diffused tumor cells were p63 nuclear positive, which according to Bircan *et al.* (2006), it is strongly and diffuse reactive in 82.1% differentiated, in 77.8% of superficial and in 72.3% of solid undifferentiated BCCs. The aggressive behavior was revealed by tumor's dimension, local invasion of the frontal bone with high mitotic rate as seen in the van Gieson and HE staining, also by the number of recurrences. The prognosis of this case is reserved due to the number of recurrent tumors, immunohistochemistry anomalies, involvement of the external layer of the frontal bone, tumor site, gender, poor remaining reconstructive procedures in case of a relapse, thus, close follow-up is to be recommended for a period of minimum five years. Recurrent tumors raise treatment difficulties regarding the reconstruction procedure of the defect after wide surgical excision. Therefore, the aggressive behavior of the MTC should be taken into consideration in clinical practice.

Keywords: basal cell carcinoma, metatypical basal cell carcinoma, p63, Ber-EP4.

Introduction

In western countries of Europe, more than 1.3 million of cases of skin cancer are identified and benefit from therapy annually, while in United States, more than 3.5 million are treated per year, proving the increase of its prevalence [1]. Ninety-six percent of the skin cancers are represented by basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), together being referred as non-melanoma skin cancer (NMSC) [1]. BCC develops usually in sun exposed areas, especially head and neck (70% of the cases), while the SCC is related to aging and UV exposure [2]. According to Miller & Weinstock, the risk of developing BCC during lifetime varies between 29–55%, while for SCC varies between 7–11% [3].

From the histological point of view, there are varied forms of BCC and SCC, some of them more common, other less or very rare. It is well known that BCCs are more locally invasive, slow developing and rarely metastasize, while SCC is more rare, aggressive, associated with large resection or amputation, and sometimes it metastasize in lymph nodes or other organs [4]. Between them, considered to be a BCC, there is a particular histological type, named metatypical basal cell carcinoma (MTC) or basosquamous cell carcinoma (BSCC). First reported by MacCormac, in 1910 [4], the histology of this tumors reveals features from both BCC and SCC, being considered a BCC from the clinical and morphological point of view, but with a more aggressive behavior, capable of metastasize, similar to SCC [5]. Some authors consider that this type should be treated as a separate type of tumor from BCC and SCC [4], other suggested that it is the metastatic BCC [5]. However, this form of BCC, due to its low incidence (less than 5% of NMSC) is poorly defined from the clinical and histological point of view [4]. In a recent study it has been investigated the role of p53, alpha-smooth muscle actin (α-SMA) and D2-40 immunohisto-chemistry, in order to differentiate various behaviors of BCC rare forms [6], while Webb *et al.* studied the role of antibodies *Ulex europaeus* agglutinin-1 (UEA-1),

Ber-EP4 and MOC-3 used for immunohistochemical staining in distinguishing MTC from basaloid squamous cell carcinoma [7]. It is generally accepted that surgical excision of this tumors may lead to healing, but there is an important risk of recurrence. It is not yet to be accepted that MTC may need larger surgical margins than common BCC, although some studies have revealed that larger surgical margins may decrease the recurrence rate [4, 8]. However, most of this BCC are located in the head and neck region, where skin reserves for covering are limited, therefore, skin grafts, local flaps or free transfer flaps may be required. In this case, other factors such as vascular diseases [9], hypertension [10], kidney disease associated with renal edemas [11], the integrity of the periosteum [12] may be taken into consideration regarding the survival of the flap or skin graft. In this paper, we presented a rare case of metatypical carcinoma of the forehead with an interesting history of unexpected recurrences, underlining the clinical, therapeutic and histological essential aspects that may come in use to other clinicians in managing this type of cancer. An accurate histological assessment may reveal the correct type of tumor, its behavior, its weaknesses, thus, helping the physician to adopt the best therapeutic attitude in order to deliver the best prognosis for the patient. More clinical studies are required in order to completely discover how this type of tumor should be efficiently managed.

Case presentation

In 2017, a 68-year-old male patient (P.I.) was admitted in the Department of Plastic Surgery and Reconstructive Microsurgery at the "Bagdasar–Arseni" Emergency Clinical Hospital, Bucharest, Romania (Chart No. 17286) for a left frontal ulcerated tumor (Figure 1).

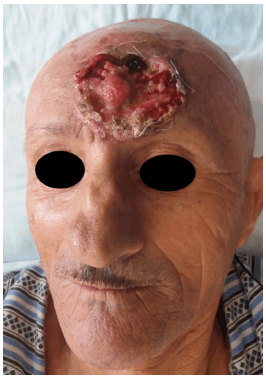

Figure 1 – ***Clinical aspect of an ulcerated tumor of the forehead.***

His medical history revealed previous lesions at the same site as follows. A papule measuring 2 mm that bleeds at friction was identified in 1993. Due to its growing, in the next five years, a topical treatment was applied for one year. After that, according to the patient, the lesion disappeared. At the same site, a lesion of 2 cm reappears after 15 years. A biopsy is performed revealing a BCC. In April 2014, he was first admitted in the Department of Plastic Surgery and Reconstructive Microsurgery of the "Bagdasar–Arseni" Emergency Clinical Hospital, Bucharest (Chart No. 7570) for a left frontal 2 cm nodular ulcerated tumor. Surgical large excision of the tumor until healthy tissue and covering of the defect using a split-thickness skin graft was performed. The histological assessment revealed common features of a nodular BCC [ICD-O 8097/3, according to *World Health Organization* (WHO)]. Using Hematoxylin–Eosin (HE) staining, tumor basal cell islets with peripheral palisades (Figure 2), large areas of central necrosis (Figure 3), a small infiltrative component at the dermal–epidermal junction, desmoplastic stroma and high mitotic rate were identified (Figures 4 and 5). The resection margins were free of tumor. Even though, after dismissal, the patient was referred to the regional oncological institute to continue treatment considering his medical history. The oncologist recommended six sessions of chemotherapy with Docetaxel and 5-Fluorouracil, in association with 25 sessions of local radiotherapy. Despite surgical and oncological treatment of the tumor, the patient underwent, in December 2015, at a regional emergency hospital another surgical procedure for the removal of a recurrence of the tumor. The histological assessment confirmed the presence of the BCC and also the complete removal of the tumor. Until February 2016, the follow-up revealed no signs of relapsing tumor. The patient stopped coming to periodic examinations until October 2017. At this point, the frontal tumor was ulcerated with central small and large nodules, measuring 5.5 cm in diameter, with irregular margins covered by crusts (Figure 1). A complete computed tomography (CT) revealed superficial thin osteolysis lesion of the external cortical layer of the frontal bone measuring 27 mm at the tumor site, with irregular contour, with no other secondary tumor sites or metastases. The routine blood test revealed hyperglycemia (146 mg/dL) and high levels of erythrocyte sedimentation rate (ESR – 60 mm/h) and fibrinogen (752 mg/dL). The patient was also known with untreated hypertension, benign prostatic hyperplasia and disabling hearing loss of the left ear. After a complete preoperative assessment was achieved, resection of the tumor with a 1.5 cm safety margin and the small area of radiodermatitis, near the lesion, was performed (Figure 6). The involved part of the calvaria was removed until healthy tissue, leaving the internal table intact. An extemporaneous exam was performed and recurrence of the tumor was confirmed. In order to cover the defect, a temporo-parietal fascio-cutaneous flap based on the left superficial temporal artery was performed (Figure 7). The secondary defect was covered using a split-thickness skin graft harvested from the ipsilateral thigh, using an electric dermatome. Two units of blood were administered during surgery. The outcome was good, with no postoperative complications registered (Figures 8 and 9) and the patient being was dismissed after 14 days from surgery, when the surgical site healed completely and the stitches were removed. Using HE staining, the histological assessment revealed a basosquamous carcinoma (IDO-O 8094/3, according to WHO, Figure 10). The basaloid tumor cells forming peripheral palisades were organized in micronodules (Figures 11 and 12). Among the basal tumor islets, an infiltrative architecture formed by proliferation of the tumor cells with abundant eosinophilic cytoplasm and high rate mitosis, some with distinct margins were identified as the squamoid component developing inside the tumor (Figures 13 and 14). Compared to the previous assessment in 2014, the necrosis areas were extremely reduced, but the tumor was much more invasive in the surrounding tissues, affecting the external cortical of the frontal bone,

as shown using van Gieson staining (Figure 15, a and b). The tumor fragments tested positive for p63 (clone 4A4, Santa Cruz Biotechnology®, 1:50 dilution; Figure 16, a and b) and negative for Ber-EP4 (clone Ber-EP4, BioLab International®, 1:400 dilution; Figure 17) immunohistochemistry.

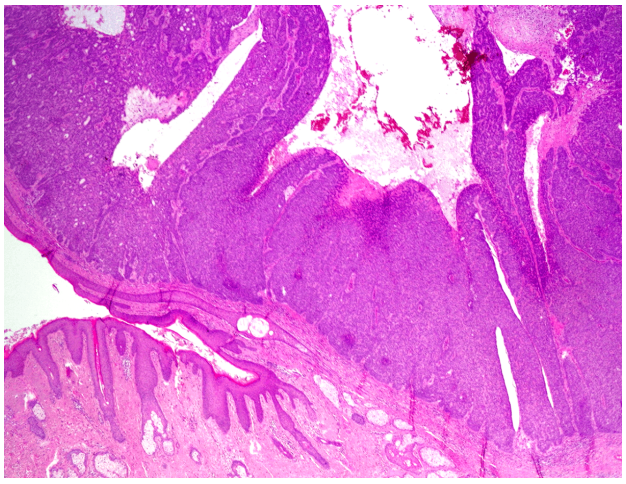

Figure 2 – ***Basaloid cell proliferation in well-demarked tumor lobules, with peripheral palisades (HE staining, ×25).***

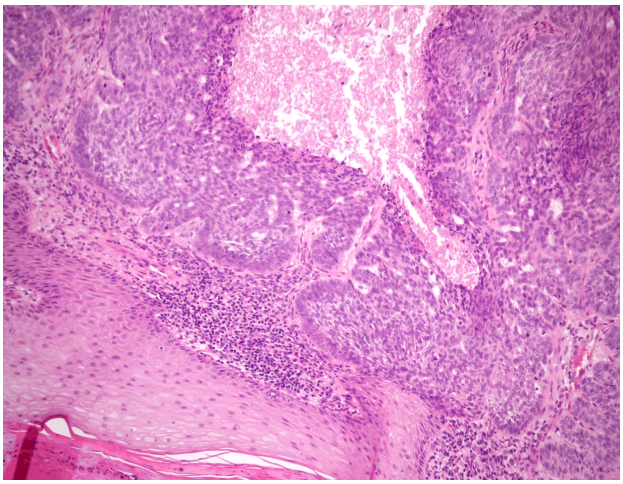

Figure 3 – ***Large areas of central necrosis (HE staining, ×20).***

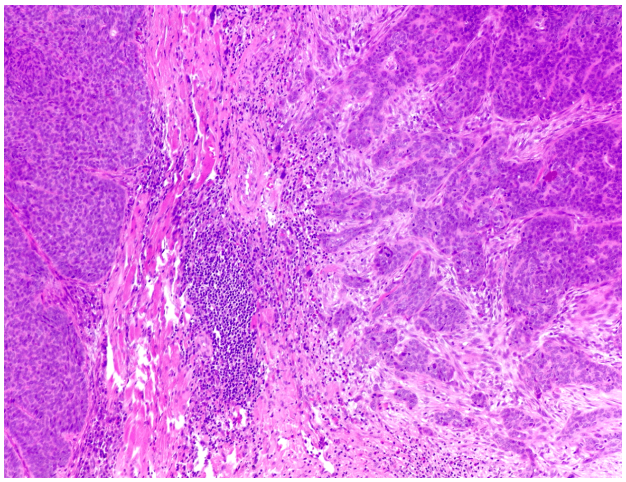

Figure 4 – ***Besides nodular tumor growth, a small infiltrative component at the dermal–epidermal junction, desmoplastic stroma and high mitotic rate is identified (HE staining, ×100).***

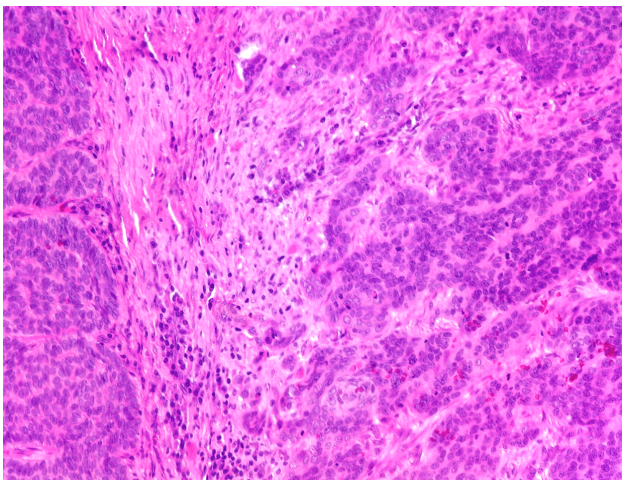

Figure 5 – ***Peripheral palisades of the basaloid cells (HE staining, ×200).***

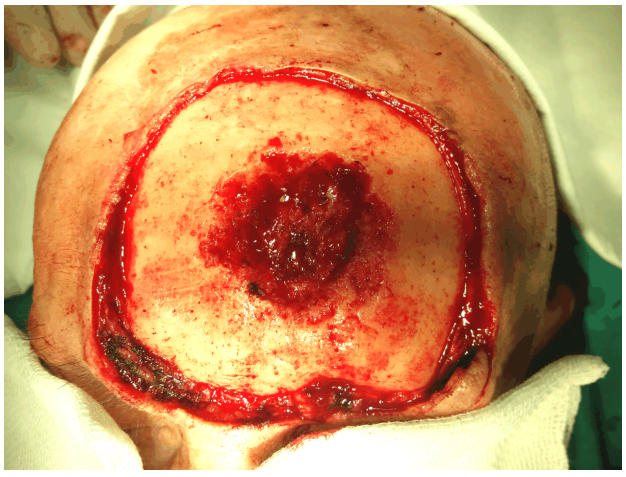

Figure 6 – ***Intraoperative aspect of a wide tumor surgical resection.***

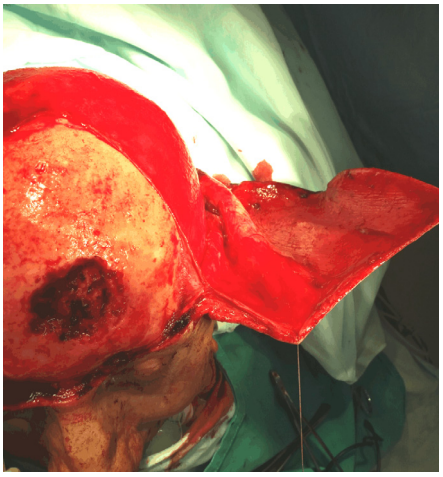

Figure 7 – ***Intraoperative aspect of the temporo-parietal fasciocutaneous raised flap.***

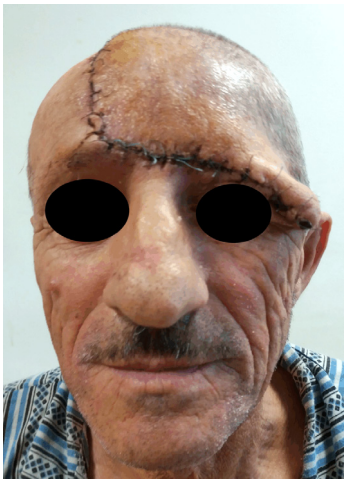

Figure 8 – ***Postoperative clinical aspect of the reconstructed soft tissue defect after forehead tumor removal.***

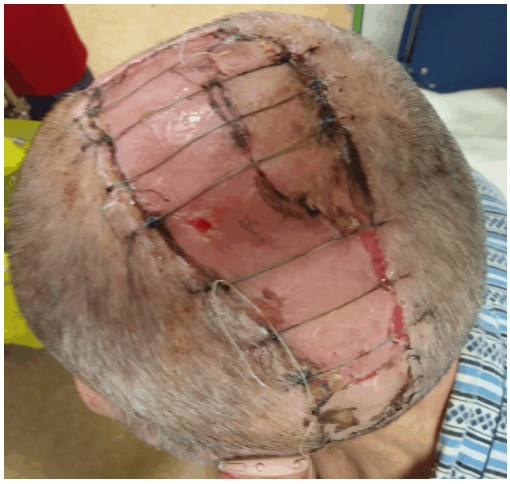

Figure 9 – ***Integrated split-thickness skin graft used to cover secondary defect resulted after harvesting the fasciocutaneous flap.***

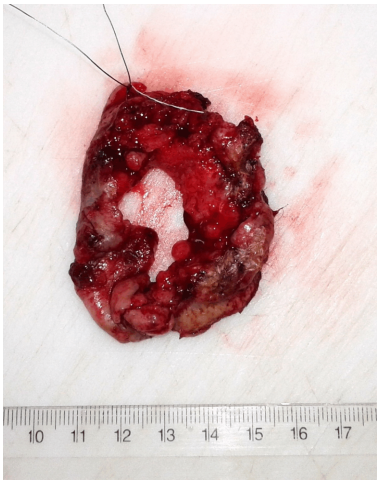

Figure 10 – ***Macroscopic aspect of the resected tumor.***

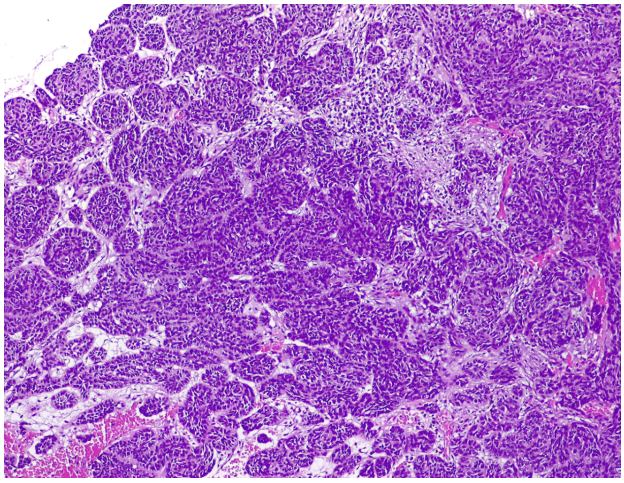

Figure 11 – ***The basaloid tumor cells forming peripheral palisades and organized in micronodules (HE staining, ×100).***

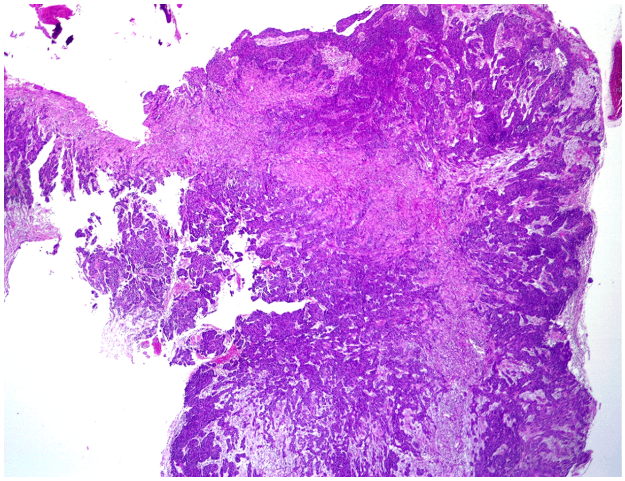

Figure 12 – ***Tumor fragment with infiltrative architecture proliferation (HE staining, ×25).***

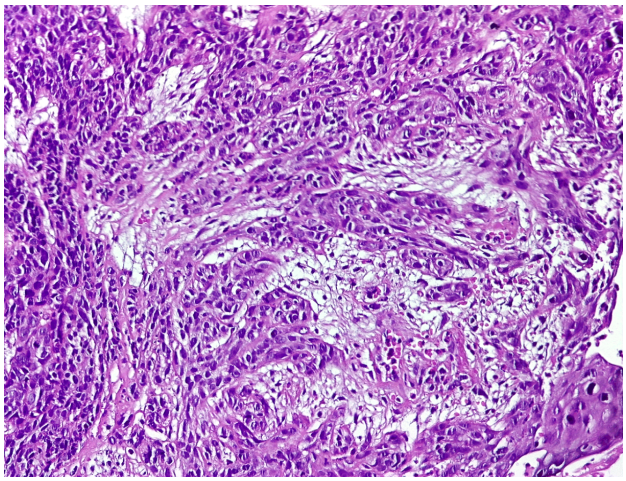

Figure 13 – ***Infiltrative architecture formed of tumor cells with abundant eosinophilic cytoplasm and high rate mitosis, some with distinct margins (HE staining, ×200).***

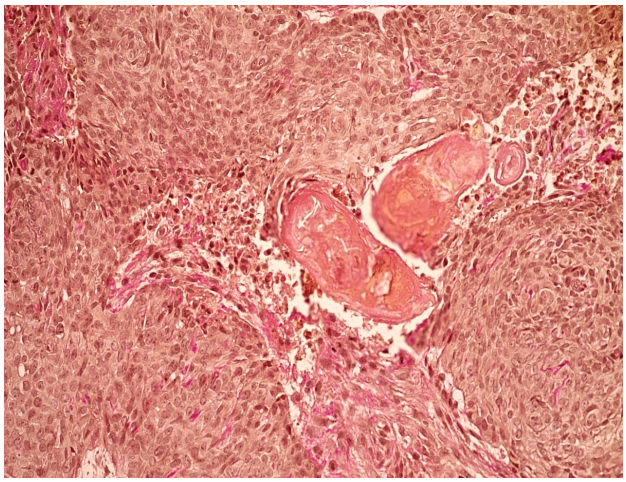

Figure 14 – ***Areas of squamous component of the recurrent tumor (van Gieson staining, ×40).***

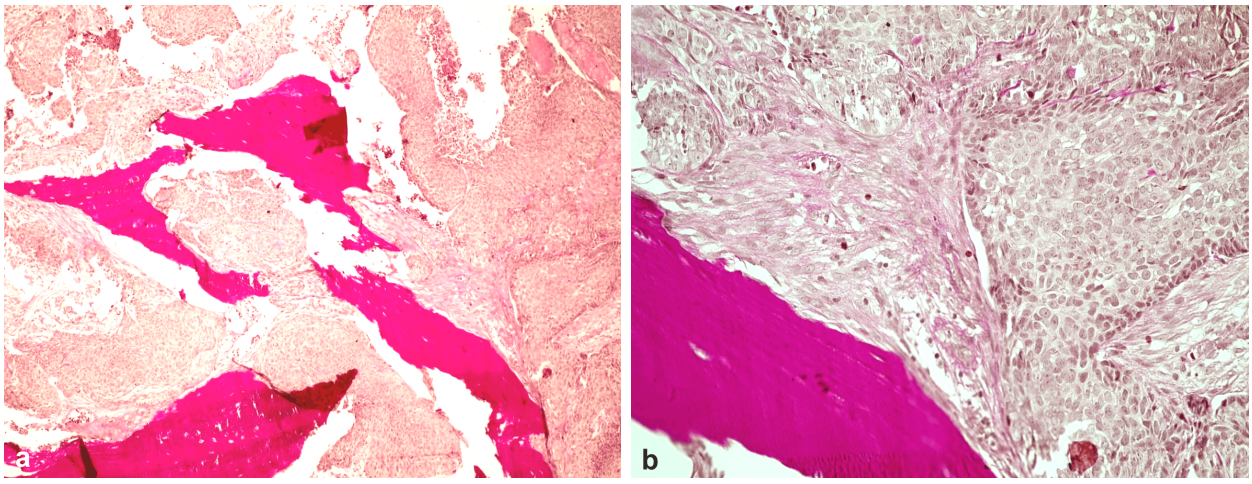

Figure 15 – *(a and b) Basal cell carcinoma invading the external layer of the frontal bone. Van Gieson staining: (a) ×10; (b) ×40.*

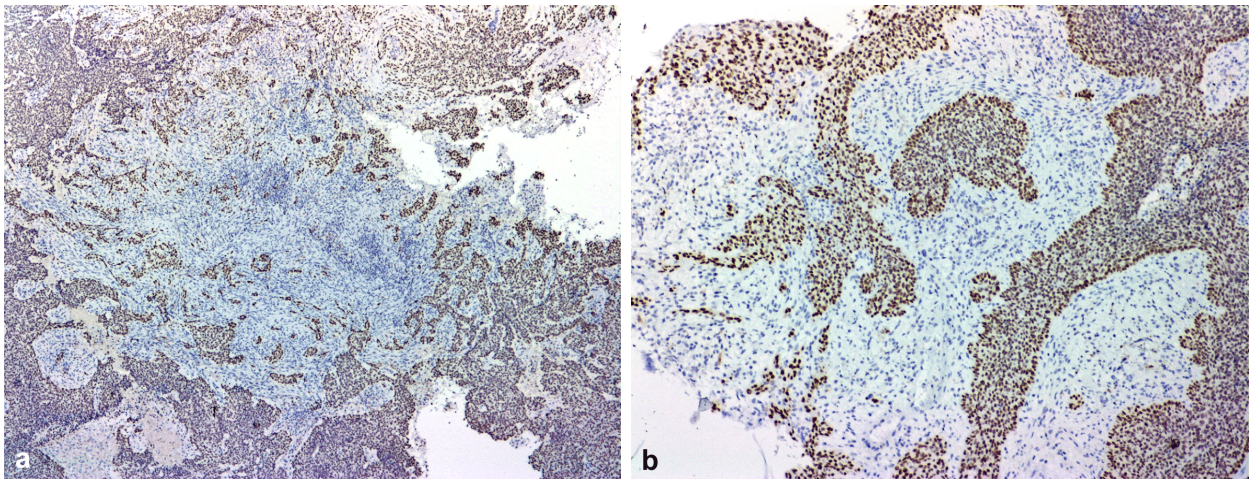

Figure 16 – *(a and b) Positive diffuse nuclear staining for p63 marker in tumor cells. Anti-p63 antibody immunostaining: (a) ×50; (b) ×100.*

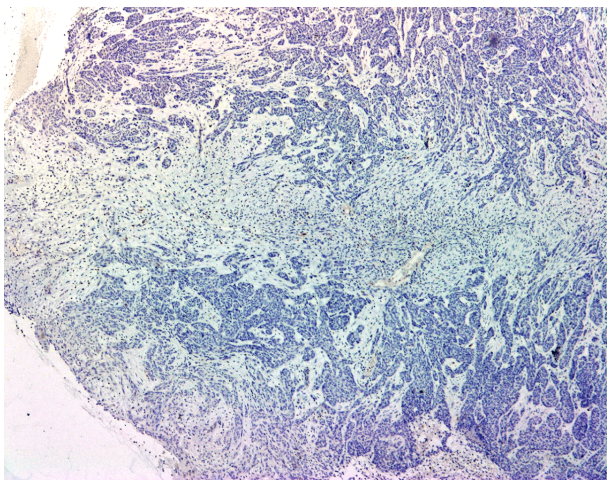

Figure 17 – *Negative staining for Ber-EP4 marker in tumor cells. Anti-Ber-EP4 antibody immunostaining, ×50.*

However, one week after surgery, the routine blood test revealed that the levels of glycemia, ESR and fibrinogen were higher than the ones at admission (147 mg/dL, 842 mg/dL, 88 mm/h). Also, the urea level was elevated (51 mg/dL). The follow-up revealed no local signs of recurrence. Due to previous experience with adjuvant therapy, the patient did not follow any other treatment. A secondary procedure was suggested in order to shape the pedicle of the flap for an improved aesthetic aspect. A five-year follow up was recommended in order to identify any other recurrence in due time.

Discussions

It is well known that BCC's usually develop slowly, but according to latest reports, the tumors emerged in the head and neck region have a tendency in becoming more aggressive and locally invasive, with increasing recurrence rates [6]. In Australia, the incidence of NMSC in this area, due to UV exposure, is between 1% to 2% per year [4]. In our case, the tumor developed on the forehead that was surgically removed in 2014, proved to be a nodular BCC. The second recurrent tumor was also a BCC, while the third proved to be MTC with a local aggressive behavior, invading the frontal bone. It is believed that MTC often occurs in recurrent lesions of BCC that were surgically removed and where radiotherapy was avoided, with a recurrence rate of 10–48% according to other studies [3, 4, 8]. However, in our case, despite 25 sessions of radiotherapy, the MTC managed to develop during a short period after this adjuvant therapy

was completed. It is not completely understood if local radiotherapy may have conditioned the developing of MTC.

Even if its incidence does not exceed 5% of all NMSC, the MTC has a risk of metastasis up to 7.4% as previous studies have reported [13, 14], compared to 0.55% in case of a BCC [14] and up to 16% in case of a SCC [15]. In order to reduce the risk of disease spreading, surgical excision should be performed as soon as possible. There is a controversy regarding the surgical margins. It is believed that 4 mm is associated with a good outcome in 96% of the BCC and in 97% of the SCC, while only 7% of BCC may infiltrate more than 1 mm from their clinical margins [16]. In our case, even if a large surgical margin was adopted during the first surgery and the histological assessment revealed the absence of the tumor, the BCC first relapsed after one year and then after two from the second removal. Therefore, obtaining clear morphological margins does not guarantee the absence of recurrence. As previous authors reported, even if Mohs' surgery or wide excision is performed, associated or not with complementary adjuvant therapy, it may not include discontinued subclinical tumor spreading, that may lead to recurrent tumor [16, 17].

Because in our case the first surgically removed tumor was also considered a recurrent tumor of the one diagnosed in 1993 and treated with local cream, adjuvant therapy was indicated. During chemotherapy, the patient accused nausea, hair loss, local itching and redness of the postoperative scar during therapy. It is cited in the literature that chemotherapy may be associated with renal diseases due to the excessive catabolic products that need to be eliminated, especially in patients with previous nephrology conditions [18–21]. In this case, the nocturia and polyuria were aggravated but no acute renal failure was encountered. Local radiotherapy may improve outcome after surgical removal of aggressive BCC or used as primary treatment in patients that are not candidates for surgery [22]. However, there are no certitudes of no local recurrent tumor, but instead it limits the reconstruction procedure in case of a larger tumor or wider excision, due to the irreversible anomalies it produces to the skin and local vascularization. Therefore, designing a flap in order to cover large defects after invasive BCC excision may prove to be a difficult challenge for the surgeon. There are other factors, such as autoimmune and other arteriopathies [9, 23], chronic kidney disease associated with erythropoietin deficit and secondary anemia [24], atherosclerosis [25], dialysis associate with decreased venous capacitance [11], transplant patients [10] immuno-suppression therapy or skin diseases that may affect elasticity or blood supply [20]. In our case, a large flap based on the superficial temporal artery was designed in order to cover the defect, which survived perfectly without any complications, despite the patient's history of local radiotherapy and untreated hypertension. In fact, a small area of radiodermatitis, which was next to the upper pole of the tumor, was included in the resected flap that contained the tumor. Along with the external layer of the frontal bone, the periosteum was also removed during surgical excision of the tumor in order to obtain safety margins. Therefore, its regenerative potential in bone healing and in neovascularization of the flap or skin grafts [12, 26, 27] could not be available in this case, which may had increase the chances of survival. Usually, when there is a risk of recurrence, defects are covered using the simplest method, direct suture or skin graft, as we proceeded during the first surgery, while for the second one due to the absence of vascular tissue that may integrate a skin graft, cortical bone involvement and wide excision, a local flap was needed, even though there are considerable chances of a recurrent tumor.

From the histological point of view, some authors consider that there are two subtypes of metatypical carcinoma: intermediate and mixed MTC [4, 8, 22]. The intermediate form is more often according to recent studies in two out of three cases of MTC [8] being defined by the presence of basaloid cells with abundant cytoplasm that form lobules or nest and become pale, while the mixed form is encountered in approximately 33% of MTC cases [8], being characterized by the coexistence of BCC features with foci of squamous cells and sometimes keratinization that forms squamous pearls [22]. In our case, there were discrete histological signs of an infiltrative pattern in 2014 and 2015, with isolated basaloid cells abundant with cytoplasm and high mitotic rate, but not enough to establish the diagnosis of MTC due to the fact that most of the cells were organized in lobules with peripheral palisades and central necrosis. In 2017, the histological assessment revealed basaloid cells that were forming micronodules with peripheral palisades, rare areas of necrosis and an infiltrative architectural proliferation of the tumor cells with abundant eosinophilic cytoplasm and high rate mitosis, some with distinct margins, identified as the squamoid component developing inside the tumor, suggesting the features of an intermediate subtype of MTC. NMSC may be clearly diagnosed regarding their form and, in some cases, their behavior using immunohisto-chemistry. In MTC, areas of BCC are positive for Ber-EP4 [an antibody which targets epithelial cell adhesion molecules (EpCAMs)] and for cytokeratin (CK) AE1/AE3, while areas of squamoid differentiation are CK AE1/AE3 positive and CK mouse monoclonal antibody – CAM 5.2 [22]. A decline of Ber-EP4 expression is seen in the transition zone [18]. Ber-EP4 is usually negative in epidermal keratinocytes and squamous epithelia [7]. A recent study revealed the importance of Ber-EP4 among MOC-31 and UEA-1 in differentiating BSCC from MTC [7]. According to Webb *et al.*, all the MTC cases included in the study tested positive for Ber-EP4, while only 16% of the BSCC were marked, 86% of the MTC tested positive for MOC-31, while only one case of BSCC was marked and only 21% of the MTC tested positive for UEA-1, while all of the BSCC proved to be reactive [7]. In our case, Ber-EP4 proved to be negative, which is more lightly to be encountered in SCC, but the HE staining revealed strong arguments for MTC, making this one of the few cases reported in the literature [28] of Ber-EP4 negative staining MTC. In addition to the histological aspects revealed using HE staining, in this case, diffused tumor cells were p63 nuclear positive, which according to Bircan *et al.* (2006) it is strongly and diffuse reactive in 82.1% differentiated, in 77.8% of superficial and in 72.3% of solid undifferentiated BCCs [29]. It is also used

to identify squamous differentiation [7]. Other markers, such as D2-40 (which is very reactive in aggressive MTC), p53 and α-SMA proved useful in revealing the most aggressive subtypes of BCC located in the facial region, and also may constitute valuable targets for new developed therapeutic agents [6]. Other studies revealed that Ki-67 expression may be related to the behavior of the tumor regarding surrounding tissues [30, 31]. However, in our case, the aggressive behavior was revealed by tumor's dimension, local invasion of the frontal bone with high mitotic rate as seen in the van Gieson and HE staining, also by the number of recurrences. Apart from the histological particularities, the increasing blood levels of ESR, glycemia and fibrinogen after surgical removal of the tumor remains unclear, therefore, it may have been related to the cancer as a systemic inflammatory response or to the medical background of the patient as seen in other cases of associated pathologies [32, 33]. Taking all of this into consideration, the prognosis of the case is reserved due to the number of recurrent tumors, immunohistochemistry anomalies, involvement of the external layer of the frontal bone, tumor site, gender, poor remaining reconstructive procedures in case of a relapse, thus, close follow-up is to be recommended for a period of minimum five years.

Conclusions

Recurrent tumors raise treatment difficulties regarding the reconstruction procedure of the defect after wide surgical excision. Therefore, the aggressive behavior of the MTC should be taken into consideration in clinical practice. Local radiotherapy may not lead to the desired effect in some cases of BCC. An accurate histological assessment may reveal the correct type of tumor, its behavior, its weaknesses, thus, helping the physician to adopt the best therapeutic attitude in order to deliver the best prognosis for the patient. More clinical studies are required in order to completely discover how this type of tumor should be efficiently managed.

Conflict of interests

The authors declare that they have no conflict of interests.

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