



Primary basosquamous carcinoma of the lower eyelid with ocular invasion

A case report

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Georgios Ouilson Papadopoulos*/**, Eleni Charitonidi***, Nikolaos Filippou***, Domna Fanidou****, Dimitrios Filippou**, Panagiotis Scandalakis**

*Department of Plastic Surgery, Evangelismos Hospital, Athens, Greece

**Department of Anatomy and Surgical Anatomy, Medical School, National and Kapodistrian University of Athens, Athens, Greece

***Department of Psychiatry, University Hospitals of Geneva, Geneva, Switzerland

****Department of Surgery, G. Gennimatas Hospital, Athens, Greece

Primary basosquamous carcinoma of the lower eyelid with ocular invasion. A case report.

INTRODUCTION: Ocular invasion is extremely rare for a primary eyelid Basosquamous Carcinoma (BSC). It can however occur in neglected cases if the clinical signs are overseen and the BSC is misdiagnosed for a less aggressive skin carcinoma.

MATERIALS AND METHODS: A 58-year-old man suffering from an inferior eyelid BSC that had been neglected for 7 years was referred to our clinic. A local infiltration of the maxillary sinus and the contents of the orbit by the tumor was discovered, and he was managed with a left orbital exenteration and resection of the involved orbital bone. A follow up was established.

DISCUSSION: BSC is a rare type of skin malignancy which as an entity rests between Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC), and its aggressive nature is often greater than that of the BCC and the SCC. Having no specific clinical features differentiating it from other BCC types, it can only be diagnosed by an adequate biopsy. Its early diagnosis is crucial in diminishing its recurrence rate and its metastatic potential. The standard therapeutical approach is the complete excision of the tumor, best performed by Mohs micrographic surgery. In cases of ocular infiltration, orbital exenteration is also usually necessary.

CONCLUSIONS: Suspect, rapidly growing skin lesions should alert clinicians and an adequate biopsy should be performed. Regarding BSC, prompt and complete excision along with systemic exclusion of metastases and a close follow up are necessary. Adjuvant radiotherapy and chemotherapy could be beneficial to the patients.

KEY WORDS: Basosquamous carcinoma (BSC), Basal cell carcinoma (BCC), Eyelid tumor, Ocular tissue invasion, Imiquimod, Maxillectomy, Metatypical basal cell carcinoma, Mohs micrographic surgery, Orbital exenteration, Orbit invasion, Squamous cell carcinoma (SCC), Vismodegib

Introduction

Basosquamous carcinoma (BSC, or metatypical basal cell carcinoma) is a rare type of skin malignancy which is described as an entity between basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) ¹. It represents 1-2% of all skin carcinomas and it is considered

as a more aggressive subtype of BCC ²⁻⁴. Basosquamous carcinoma can clinically be confused to a BCC which accounts for 80-90% of eyelid tumors ⁵⁻⁸. Thus, it is difficult to perform a differential diagnosis based on morphological and clinical features – therefore it is only possible by accurate histology ^{3,5,9-11}. Both the probability of metastasis as well as the recurrence tendency and the risk of orbital invasion is significantly higher in BSC than BCC ^{2-5,8,11-13}.

Considering the therapeutical approach, Mohs micrographic surgery is the standard treatment ^{3,5,14-18}. However, in the case of ocular infiltration, orbital exenteration is also performed, the goal being the complete excision of

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Correspondence to: Papadopoulos Georgios Ouilson, MD, Akronos 5, CP 11633, Athens, Greece, (e-mail: georgepapas1985@gmail.com)

the tumor ^{4,17,19}. To our knowledge, a primary BSC of the lower eyelid invading the ocular tissues has only been reported once by Malik and colleagues ⁸.

Here we report the case of a 58-year-old man suffering from an inferior eyelid BSC of 7 years' duration, who due to the infiltration of the maxillary sinus and the contents of the orbit, was managed with left orbital exenteration and resection of the involved orbital bone.

Case Report

A 58-year-old man was referred to our plastic surgery clinic for an inferior eyelid BSC, for which he had consulted a general surgeon only after 7 years of recurrent bleeding and ulceration. His medical history revealed a

positive history of smoking habits of 30 pack-years and a gastric bleeding before 30 years, treated successfully with proton pump inhibitors and with no current active disease. The primary excision, which had been performed by the general surgeon, showed the development of a BCC and positive surgical margins of excision, which prompted the referral of the patient to our clinic.

On examination, the patient presented a 1cm diameter, full thickness ulcer on his left lower eyelid where the initial excision was performed. On retinoscopy, there were no pathologic findings but during the general ophthalmic examination a diplopy due to a diminished action of the inferior rectus of the left eye was noticed. No regional lymph nodes were palpable. A second biopsy taken from the eyelid lesion revealed an extensive infiltration of the tissue with intermediate type BSC.



Fig. 1. CT scan showing a left inferior eyelid ulcer, extending from the medial to the lateral canthus.

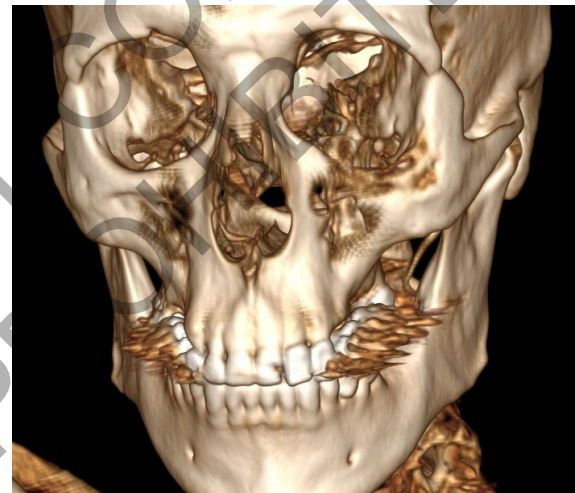
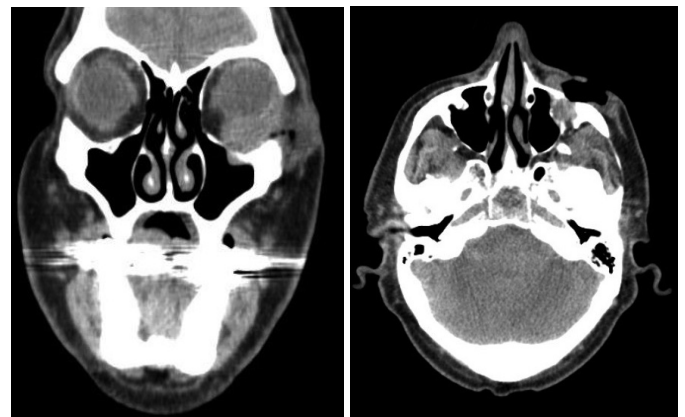


Fig. 3. CT scan showing infiltration of the floor of the orbit.



Fig. 2. CT scan showing infiltration of the soft tissues of the face under the eyelid with invasion of the orbit, the inferior rectus muscle and the inferior surface of the left eye's sclera.



Figs. 4 and 5. CT scan showing the tumor protruding into the left maxillary sinus.

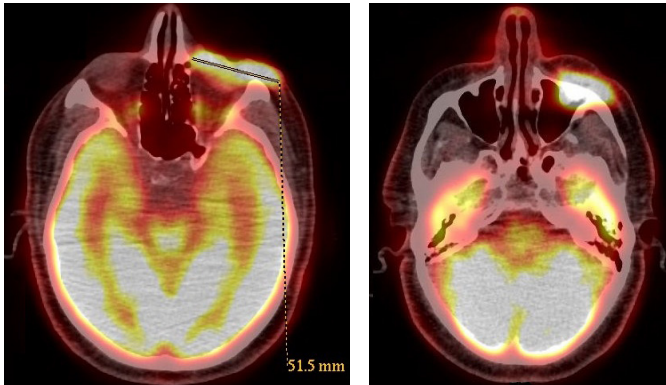


Fig. 6 and 7. PET-CT with 18-FDG showing the initial lesion's local infiltration.

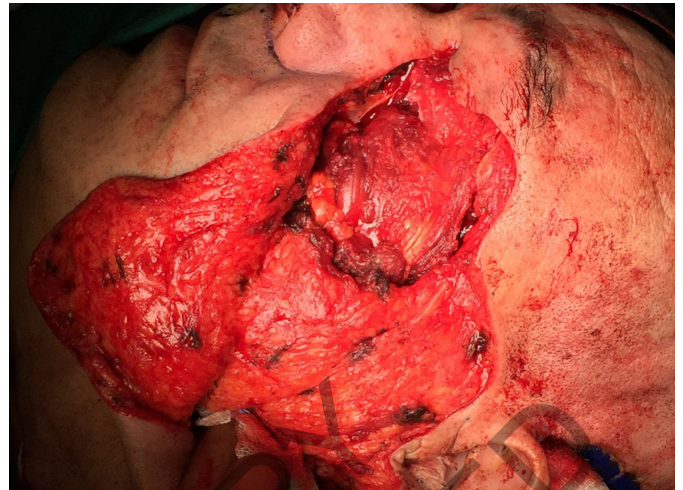


Fig. 10. Temporalis muscle flap fixated into the remaining orbit.

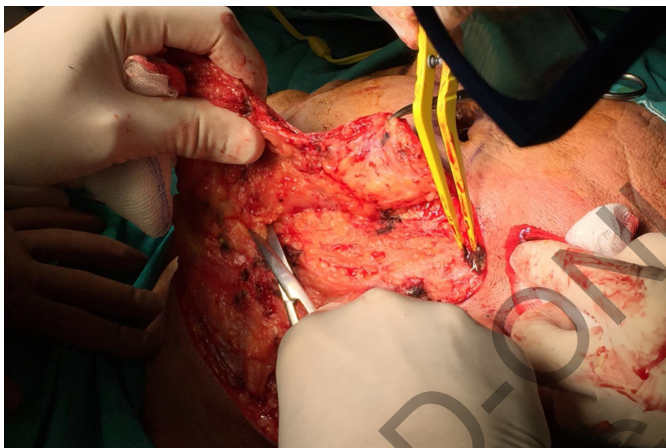


Fig. 8. Elevating the facial soft tissue and excising the lesion.



Fig. 11. The remaining healthy midface soft tissue ready to completely cover the orbit.



Fig. 9. Osteotomy of the lower part of the orbit down to the infra-orbital foramen.

A regional CT scan was immediately performed and showed a left inferior eyelid ulcer, extending from the medial to the lateral canthus (Fig. 1) and infiltrating the soft tissues of the face under the eyelid, invading the anterior part of the left orbit, the inferior rectus muscle and the inferior surface of the left eye's sclera (Fig. 2a). Inferior to these structures, it was also shown to infiltrate the floor of the orbit (Fig. 3) and protruding into the left maxillary sinus (Figs. 4, 5).

A full body CT scan showed a lymph node of 13 mm in the precarinal/sucarinal compartment of the mediastinum, but an additional PET-CT with 18-FDG confirmed only the initial lesion's local infiltration (Figs. 6, 7) and showed no distant metastasis or lymph node infiltration. A bronchoscopy was performed which also showed no endobronchial lesion, while the biopsies taken from the 13-mm mediastinal lymph node showed inflammatory processes without malignancy.

A modified superstructure maxillectomy was subsequently performed. A modified Blair incision extending from the tragus to the lateral canthus and an incomplete Weber-Ferguson incision down to the lateral nostril were made. After a medial and lateral canthotomy we elevated the facial soft tissue above the periosteum and we excised the lesion to the healthy margins (Fig. 8). Then a periosteal lifting inside the orbit, and an osteotomy of its lower part down to the infraorbital foramen were performed (Fig. 9). After an optical nerve neurotomy, the osteotomized orbit and its contents were removed en bloc. An intraoperative rapid biopsy showed infiltration of the mucosa of the roof of the maxillary sinus, thus an additional sinusectomy was performed. A temporalis flap was accessed through a hemicoronal skin incision of the same side. After an osteotomy of the zygomatic bone the muscle flap was fixated into the remaining orbit (Fig. 10) and covered completely with a cutaneous flap of the remaining healthy midface soft tissue (Fig. 11). There were no complications and there was excellent tissue healing.

Discussion

BSC is a rare skin malignancy with a reported incidence that ranges from 1 % to 2.7% of all skin malignancies^{5,8,9,20}. It presents the same epidemiological characteristics as BCC, located mainly on sun-exposed areas, with most of the cases involving the head and neck of white light skinned adults^{4,17,21-23}. Similar to BCC, BSC most often involves the lower eyelids^{2,24}. Our patient had a Fitzpatrick IV skin complexion but had frequent sun exposure in his everyday life, which in combination with his age and the recurrent bleeding, immediately alerted the general surgeon for the ulcer being malignant. The early diagnosis of a BSC is crucial in diminishing the recurrence rate and the metastatic potential, as the aggressive nature of this tumor is reportedly greater than that of the BCC and the SCC^{8,9,25}. In our case there was a delay of 7 years between the first appearance of the lesion and primary the consultation. Unfortunately, delayed consultation is common in lower socioeconomic status groups, due to the lack of information and means to this part of the population, and is associated to greater mortality and morbidity rates²⁶⁻²⁸. The same group exhibits a greater use of tobacco²⁹, which has been linked to an increased incidence of non-melanoma skin carcinomas³⁰⁻³⁶.

The clinical appearance of the BCC has no specific features differentiating it from other BCC types, thus the diagnosis is made only after a biopsy^{4,5,9,37,38}. Due to the controversies of the histological findings there is always the risk of misdiagnosis, confusing it with a BCC, especially at its early stages. Since the squamous differentiation might only be apparent on the deeper layers and in certain parts of the tumor, making a BSC appear

similar to a more benign lesion, an adequate biopsy is necessary^{4,9,39}. Nonetheless, its rapid growth should easily alert clinicians to an alternative diagnosis⁹. This was also our case since clinically the lesion was presumed to be a BSC and the initial biopsy was misleading, probably due to an insufficient depth of excision, as it was minimal in order to preserve the maximum tissue of the lower eyelid. Its immediate reappearance after the first excision however quickly raised a red flag to the patient's surgeon.

When BSC was first reported in 1910 by MacCormac, it was defined as a lesion where basal cell and squamous cell tumors coexist without any transition zone^{14,38}. Today there are several histologic definitions of BSC, from any BCC with evidence of keratinization to tumors with features of both of BCC and SCC, with or without a transition zone^{3,5,20}. There are 2 histological subtypes of BSC: The intermediate BSC, defined as basoid cell lobules that mature into paler cells with more cytoplasm, and the mixed BSC, which is a BCC mixed with grouped SCC cells, often exhibiting some focal keratinization^{3,11,20,38,40,41}. While the mixed type has a higher tendency to ulceration, it is the intermediate type that has shown to be more aggressive, including more frequent positive surgical margins and perineural invasions²². An intermediate BSC was also found in our second biopsy, and the regional CT results were congruent with the statistics, revealing extensive local invasion. Since a transitional zone is frequently discovered and taking into account the fact that the basal cell is a pluripotent cell and the SCC is the more aggressive tumor, it has been postulated the BSC derives from the differentiation of BCC into SCC^{8,9}, and it can be considered as a hybrid of BCC and SCC^{3,11,20,40,41}. Thus, any BSC should be treated as a rare and more aggressive form of BCC, with histological features of both BCC and SCC^{3-5,9,41}.

Currently, there is no standardized treatment protocol for BSC and further research is required to evaluate and optimize treatment for these tumors⁹. For the time being, surgical excision with tumor free margins is the gold standard of the treatment of a BSC, and it is suggested the margins should be wider than those for BCC^{2,3,9,14,20,42}. This was also the immediate decision of the tumor board for our patient. Where available, Mohs micrographic surgery should be the first option for the excision of a BSC, given the better cosmetic result and the lower recurrence rates compared to a simple excision^{3,5,14-18}. It is especially useful for locations such as the face and other sensitive areas, where preservation of skin tissue is most important^{3,15,43,44}. Due to the local infiltration of the orbit and its contents, micrographic surgery was excluded and we had to proceed to a more radical surgery. Orbital exenteration is the standard treatment of ocular tissue malignancies including any orbital invasive BSC^{17,19,45,46}. Exenteration could potentially be curative as it is in the cases of BCC or SCC¹⁹. While ocular

infiltration is very rare and mostly reported in recurrent BSC,⁸ a neglected or recurrent BSC can infiltrate the orbit, the eye, the nasal cavity and the maxillary sinuses or even the brain, leading to extensive morbidity^{4,47}. For orbital bone-adjacent tumors, bone resection is necessary, because tomography is not specific enough to rule out bone invasion^{17,19,46}.

A previous failed treatment of a skin malignancy and patient neglect have been reported to be the case in most of the patients needing exenteration⁴⁸⁻⁵⁰. The 7-year delay of treatment in our case was probably the most important factor in creating such an extended infiltration of the local tissues. The patient's left eye already showed functional impairment caused by the tumor, and the CT showed an affected rectus muscle and a sclera, in addition to the tumor extending into the bony structures. Thus, we considered an orbital exenteration with local osteotomy to be our first and best option.

The methods of reconstruction after an exenteration include a temporalis muscle flap, a midline forehead flaps, a dermal graft, a split thickness skin graft, a dermis fat graft and spontaneous granulation. There are some other options depending on the stage of the tumor, including a globe sparing exenteration and eyelid sparing techniques^{49,51-58}. Due to the extensive maxillary bone resection and thanks to the adequate mobilization of soft tissues we had already performed to achieve a safe resection, a temporalis muscle flap was our best option to cover the remaining cavity. This primary reconstruction method promotes faster healing with a good aesthetic result and allows for quicker return to activities for the patient. However a very meticulous follow up is required since the flap could potentially hide a recurrence.

There is not enough data concerning the use of adjuvant radiotherapy in BSC, however it has been postulated that BSC should be sensitive to radiotherapy like BCC and SCC²⁰. Although full excision with tumor-free margins is essentially the treatment of the BSC, depending on tumor stage and the risk of recurrence, adjuvant radiotherapy can be used as additional therapy to surgical treatment^{4,9,59}. Radiotherapy should also be considered for tumors where negative margins of excision cannot be achieved, and it could be combined with sentinel lymph node biopsy for high risk lesions, especially for larger tumors measuring more than 2 cm and those with lymphatic or perineural invasion²⁰. Since we managed to achieve negative surgical margins with our patient, we have decided to delay any plans for radiotherapy for the time being.

Concerning the role of chemotherapy, it has yet to be proved for the treatment of BSC⁵⁹. However, as is the case for other non-melanoma skin malignancies, some sensitivity is to be expected for chemotherapeutic agents such as topical chemotherapy with 5-Fluorouracil (5-FU), or systemic methotrexate, 5-mercaptopuracil, nitrogen mustard, actinomycin D, intravenous cisplatin or intrale-

sional bleomycin^{15,17,21,60}. In addition, Imiquimod, which is an immune system response modifier, has been shown to have a very good response in the treatment of BCC and SCC when applied locally, and it could be a possible treatment of superficial BSC smaller than 2 cm^{15,17,60-62}. Vismodegib, an inhibitor of the Hedgehog pathway, could be another alternative treatment for inoperable patients with BSC, as it has shown some results in treating cases of inoperable BCC^{3,63-65}. These alternatives have also been discussed as a secondary option in the case of an inoperable recurrence in our patient, however we have decided against using them as an initial adjuvant therapy.

We are however aware that while BSCs display a tissue invasion similar to that of BCC or SCC, they have a high metastatic and recurrence potential¹². The reported recurrence rates of BSC are between 10% and 51% for simple surgical excision and 4% for Mohs micrographic surgery and the metastatic incidence can be from 5% to 7.4%^{3,5,11,12,20,41,66}, which is much higher than these of the BCC^{2-5,12,41}. In a large series analysis by Martin and colleagues, significant factors predictive of recurrence ($P < 0.01$) were male gender (with the male-to-female recurrence ratio being 12:2.12), positive surgical resection margins, lymphatic invasion, and perineural invasion, while the size of the tumor size approached statistical significance with a $P = 0.076$ ²⁰. In another case series of 35 patients with periocular BSC by Karatas Siliestreli the rate of the recurrence and orbital invasion has been shown to be as high as 17%. The same study reported the following metastasis predicting factors: male gender, a positive surgical margins, a lymphatic invasion or a perineural invasion, a tumor size larger than 2 cm, and a local recurrence of the tumor^{2,67}. Our patient was a male with a tumor size larger than 2 cm but had negative surgical margins, and had neither a lymphatic invasion nor a perineural invasion. An eventual recurrence would further increase his risk of metastasis in the future. It has also been reported that the incidence of pulmonary metastasis of a BSC can be more frequent than that of the SCC¹², with a published case of a lung metastasis 9 years after the initial surgical treatment of an eyelid BSC²⁴. Thus, radiographic evaluation should be considered for every patient in order to fully investigate for metastases⁹. Although our patient had initially a medium risk of metastasis, once we discovered an enlarged lymph node in the mediastinum, we decided to definitely exclude a pulmonary metastasis with a bronchoscopy, while the PET scan further decreased any probability of a distant metastasis.

Close clinical and frequent follow-ups for 5 years is recommended in all cases, including those with complete tumor resection and negative surgical margins, due to a generally high risk of recurrence, local invasion, systemic metastasis and the aggressiveness of the BSC compared to other more benign lesions^{2,3,20,44,46,65}. For our patient, the proposed follow up is at 3-month intervals with clin-

ical exams including auscultation, skin and lymph node examinations, and a CT scanning at a 6-month interval for the first 2 years, followed by another 3 years of less frequent intervals with clinical exams every 6 months and a CT scan every 6 to 12 months. In the case of any suspect lesion a biopsy will be performed. A PET scan will be ordered in the suspicion of distant metastases. If any recurrence is confirmed a tumorboard will decide for the treatment options that will include the surgical, radiotherapy and chemotherapy protocols we have discussed.

Conclusions

Even though eyelids are the most common location of a BSC, ocular infiltration by a primary BSC, as discovered on our patient, represents a rare complication that has only been reported once by Malik and colleagues.

Due to the rarity of BSC and its clinical similarity to a BCC, we believe that it may be underreported and possibly confused with a BCC. This can lead to catastrophic complications, since a BSC is much more aggressive than BCC and in some cases even more aggressive than SCC. Although the BSC histology is characteristic, adequate biopsy depth is needed in order to see its distinguishing features. Thus, any rapidly growing or recurrent, suspicious looking lesion should be histologically examined. Complete excision to negative surgical margins either with Mohs micrographic surgery or a more radical operation, depending on the tumor size and its stage, is the current gold standard. Exclusion of distant metastases and a subsequent follow up at least on par with that of the SCC are necessary. Considering radiotherapy and chemotherapeutic agents against BSC, there is some potential and they should be discussed as an adjuvant or alternative therapy for certain cases where the surgical treatment might not be adequate or is contraindicated.

Our patient underwent a thorough series of exams including CT and PET scans along with a bronchoscopy in order to avoid missing a distant metastasis that could significantly deteriorate his prognosis. Once we determined the extent of the lesion, an exenteration and a modified superstructure maxillectomy were performed, while a temporalis flap covered the remaining orbit, along with a cutaneous flap of healthy midface skin. The aesthetic results were excellent and the patient is tumor free and has entered an intensive follow-up protocol for the first 5 years following the operation.

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