

Basal cell carcinoma-not always the ‘good guy’: Case report of a life-threatening basosquamous carcinoma and review of the literature

CORNEL ADRIAN PETREANU^{1,2}, ELENA-DANIELA ȘERBAN³,
MARIA-MAGDALENA CONSTANTIN^{3,4}, CORNEL SAVU^{1,2}, ALEXANDRU VICTOR ZARIOSU²,
OANA CLAUDIA DELEANU^{5,6}, STEFANA BUCUR^{3,4} and TRAIAN CONSTANTIN^{7,8}

¹Department of Thoracic Surgery, ‘Carol Davila’ University of Medicine and Pharmacy, 050474 Bucharest;

²1st Department of Thoracic Surgery, ‘Prof. Dr. Marius Nasta’ Institute of Pneumophthysiology, 050159 Bucharest;

³2nd Department of Dermatology, ‘Colentina’ Clinical Hospital, 020125 Bucharest; Departments of ⁴Dermatology
and ⁵Pneumophthysiology, ‘Carol Davila’ University of Medicine and Pharmacy, 050474 Bucharest;

⁶2nd Department of Pneumophthysiology, ‘Prof. Dr. Marius Nasta’ Institute of Pneumophthysiology, 050159 Bucharest;

⁷Department of Urology, ‘Carol Davila’ University of Medicine and Pharmacy, 050474 Bucharest;

⁸Department of Urology, ‘Prof. Dr. Th. Burghel’ Hospital, 050659 Bucharest, Romania

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Abstract. Cutaneous basosquamous carcinoma is a variant of basal cell carcinoma that is characterized by histopathological features of both basal and squamous cell carcinoma. Due to its local invasiveness, high frequency of recurrence, and its metastatic potential, it is considered to be one of the most aggressive subtypes of basal cell carcinoma. We present the case of an 81-year-old male who was admitted to the hospital with incessant hemorrhage arising from a cutaneous tumor that later proved to be a basosquamous carcinoma. Due to the COVID-19 pandemic at the time, the patient did not seek medical attention as soon as the bleeding was observed, although he did present when the symptom increased in intensity and became incessant. To our knowledge, this is the first case report of a cutaneous basosquamous carcinoma that presents with a massive life-threatening hemorrhage tumor, thus endangering the patient's life. The clinical and histopathological features, the behavior and the treatment of cutaneous basosquamous carcinoma are further reviewed in this article.

Introduction

Basosquamous carcinoma (BSC), also called metatypical basal cell carcinoma, is a subtype of basal cell carcinoma (BCC), displaying histological features of both BCC and squamous cell carcinoma (SCC) (1). This tumor may have a more aggressive behavior that resembles more an SCC than a BCC in terms of invasiveness and poor prognosis, with a greater likelihood of recurrence and metastasis (2).

As with any other BCC, it presents as a plaque, papule, or nodule with an ulcerating potential. Elderly, fair-skinned white men are the most affected, especially on the head and neck area (3). Dermoscopy shows polymorphous vascular structures typical of BCC combined with scaling, ulceration, white circles and white structureless areas (4,5). Histopathologically, it is characterized by islands of basoid cells mixed with atypical squamous cells (1). According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, BSC is included in the high-risk BCC category (2). This is due to the higher metastatic rate when compared with conventional BCC (5-8.4 vs. <0.1%) (6). These metastases occur especially in regional lymph nodes and lungs (7). There is also a higher risk of local recurrence, estimated at 4.5% (8). This leads to a median survival rate of 6.5 years and an overall 5-year survival rate of 54% in the cases of metastatic disease (9). First-line treatment for high-risk BCC, therefore BSC, is Mohs micrographic surgery (MMS) (2,10,11). Other surgical methods include standard surgical excision with postoperative margin assessment (2,10) and staged excision with circumferential margin assessment (10,12). External beam radiotherapy (RT) is recommended for patients who cannot tolerate surgery (10,13).

Correspondence to: Dr Elena-Daniela Șerban or Dr Maria-Magdalena Constantin, 2nd Department of Dermatology, ‘Colentina’ Clinical Hospital, 19-21 Stefan cel Mare Boulevard, 020125 Bucharest, Romania
E-mail: elenadaniela.serbann@gmail.com
E-mail: drmagdadinu@yahoo.com

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Case presentation

An 81-year-old male presented with a hemorrhagic tumor located in the suprasternal notch. He had chronic atrial fibrillation and was under chronic anticoagulation treatment with apixaban. There was no personal clinical history and family history for other tumors, skin or otherwise. The tumor had appeared approximately 12 years ago and had a rapid growth during the previous year, but the patient did not seek medical care due to the COVID-19 pandemic crisis at the moment. Physical examination revealed a bleeding vegetating tumor (Fig. 1A), measuring 14x12 cm. The perilesional skin appeared erythematous and edematous. Clinically, there was no evidence of lymphadenopathy. The clinical differential diagnosis included SCC, BCC, Merkel cell carcinoma, amelanotic melanoma, or cutaneous metastasis of unknown origin. The patient was controlled using mechanical hemostatic methods such as direct pressure and gauze pack and local hemostatic agents, while also stopping the anticoagulant. To further plan the surgical excision, especially in consideration of the tumor's great size, a whole-body computed tomography (CT) scan was performed which did not reveal any metastasis or neoplastic infiltration of the muscle fascia. Therefore, standard surgical excision with 2-cm margins was performed with the immediate repair of the surgical defect using adjacent tissue flaps (Fig. 1B). The histopathology examination revealed a large ulcerated eso-endophytic lesion invading the dermis and the subcutis composed of atypical basaloid strands and islands commingled with islands of polygonal atypical squamous cells with abundant eosinophilic cytoplasm, embedded in a cellular fibrotic stroma and chronic inflammatory infiltrate. Lymphovascular invasion was present. No perineural invasion was observed. Circumferential, peripheral and deep margin assessment was negative. At immunohistochemistry, there was diffuse positivity for cytokeratin 34betaE12. The basaloid component stained positive for Ber-EP4 with loss of immunoreactivity of Ber-EP4 in areas showing squamous differentiation, whereas epithelial membrane antigen (EMA) and p53 were partially immunoreactive only in the squamous differentiated areas (Fig. 2). The Ki-67 immunoreactivity was about 60-70%. Based on the data gathered, a diagnosis of basal cell carcinoma, basosquamous subtype, was made. The TNM according to the Eighth Edition of the American Joint Committee on Cancer Classification (AJCC) was pT3Nx (14). Since there was no sign of residual disease, no further treatment was indicated and follow-up was recommended.

At six-month follow-up, there was no clinical sign of local recurrence or metastasis.

Discussion

Non-melanoma skin cancer (NMSC) is the most common group of cutaneous neoplasms in the Caucasian population with basal cell carcinoma (BCC) being the prevalent entity, although precise epidemiologic data are limited, as in most countries there are no cancer registries that collect data regarding it (15-17).

However, the NMSC incidence rate is on a steady increase in the USA, most European countries, and Australia, with the latter registering the highest growth (15). These trends could

be explained in regards to the inverse association of BCC with the country's geographic latitude and the Fitzpatrick skin phototype of its inhabitants (16).

Literature indicates that BCC is a heterogeneous entity and that specific histological variants can arise in particular areas, exhibiting different clinical behavior, have a disparate etiology, and a distinct response to treatment (18). The latest edition of the World Health Organization (WHO) Classification of Skin Tumors recognizes the following 10 histological subtypes of BCC: nodular, superficial, micronodular, infiltrating, sclerosing/morphoeic, basosquamous, pigmented, fibroepithelial, BCC with sarcomatoid differentiation, and BCC with adnexal differentiation (1). Although the pathogenesis of basosquamous carcinoma (BSC) has historically been a subject of debate, as some authors considered it to be a subtype of BCC and others an independent tumor with a different evolution, WHO finally identifies it as a BCC variant (1). In any case, it is rather rare, and data concerning the precise percentage are also missing. It is estimated that BSC represents approximately 1.2 to 2.7% of all malignancies in the NMSC group (7,19-22).

Ultraviolet radiation (UVR) is known to be the prevalent risk factor for BCC, SCC, and therefore BSC (23) with a preferential localization on the sun-exposed areas, especially the head and neck region (3). Moreover, it appears that BSC occurs more frequently in men (3,24) in the six to eight decades of life (24) with a mean age at diagnosis of 72 ± 11.5 years (3).

It is difficult to make a diagnosis of BSC using only naked eye examination as it resembles other subtypes of BCC. It presents as a pink or flesh-colored plaque, papule, or nodule. Ulceration is usually present. The lesion can have a pearly or translucent feature with telangiectatic vessels being seen within it (3).

While clinical differentiation from other BCC variants is demanding, dermoscopy can provide some important hints allowing a more appropriate treatment planning. The dermoscopic evaluation of BSC detects features of both BCC and SCC such as unfocused arborizing vessels, blue-gray blotches, ulceration or blood crusts, white structures and white structureless areas. Identification of only one overlapping dermoscopic criterion both of BCC and SCC is an alarming clue for BSC (4,5).

The definitive diagnosis of BSC is made only by histopathological examination. The latest edition of the WHO Classification of Skin Tumors describes BSC as having features of both BCC and SCC such as islands of basaloid cells mixed with focal or scattered atypical squamous cells and transition zones containing cells with features intermediate between the two. The malignant cells are embedded in a cellular fibrotic stroma. The basaloid component expresses BerEP4 with a gradual loss of reactivity towards the squamous cell component. The squamous cells stain positively for EMA. There is also a high cyclin D1 expression as well as a low BCL2 expression (1).

Before treatment, assessment of recurrence risk is mandatory. According to the NCCN Clinical Practice Guidelines in Oncology concerning the risk of recurrence, there are two main categories of BCC: the low-risk group and the high-risk group (2). The following features are associated with lesions with a low risk of recurrence potential: immunocompetent patient, no history of radiation therapy at the site, not a

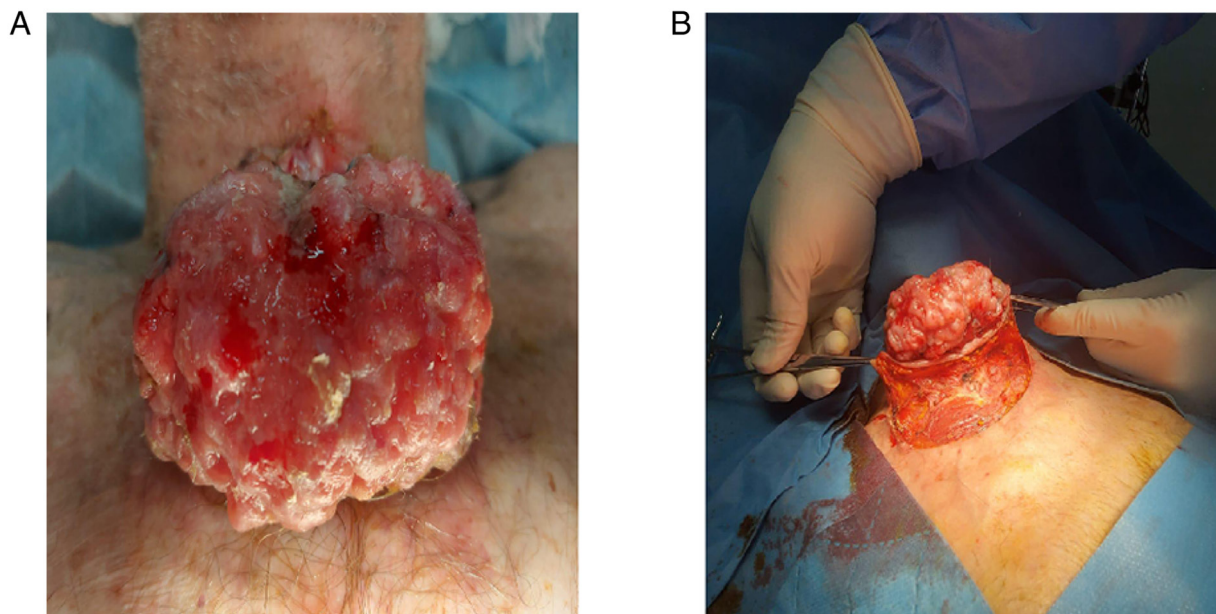


Figure 1. (A) Clinical presentation. (B) Intra-operative findings.

recurrent tumor (a primary tumor); well-defined clinical borders; <10 mm in diameter in tumors developed on the cheeks, forehead, scalp, neck, pretibial; <20 mm in diameter in tumors of the trunk and extremities, excluding pretibia, hands, feet, nail unit, and ankles; histological subtypes such as nodular or superficial; the absence of perineural invasion. On the other hand, lesions with an increased risk for tumor recurrence have the subsequent characteristics: immunocompromised patients, tumors located in sites of prior radiation therapy; recurrent tumors; tumors with ill-defined clinical borders; tumors of any size in high-risk areas of the face such as the central face, nose, lips, eyelids, eyebrows, periorbital skin, chin, mandible, ears, preauricular and postauricular areas, temples or of the hands and feet; tumors ≥ 10 mm in diameter in other areas of the head, neck, and pretibial; tumors ≥ 20 mm in diameter in all other areas like trunk and extremities, excluding hands and feet; aggressive pathologic variants such as morpheiform, sclerosing, mixed infiltrative, micronodular, basosquamous; the presence of perineural invasion (2).

BSC is considered an aggressive variant of BCC, therefore included in the high-risk group, because of the higher metastatic rate and local recurrence rate. BSC has a metastatic rate from 5 to 8.4% in comparison with more conventional subtypes of BCC which have a metastatic rate lower than 0.1% (5). Regional lymph nodes and lungs are the most frequent sites of metastases (6). Moreover, the recurrence rate is considered to be higher and estimated at 4.5% (7). Patients with metastatic disease have a median survival of 6.5 years and an overall 5-year survival rate of 54% (8).

As stated above, BCC treatment is highly influenced by the recurrence risk potential. First-line therapy for BCC at low risk of recurrence is standard surgical excision with margins of 4 to 5 mm (10,25). Alternative therapy in select cases with tissue conservation purposes, especially for lesions located on the face, is MMS (10,26). Second-line therapies for low-risk tumors are indicated mainly for superficial BCC in patients who cannot undergo surgery or prefer to avoid it.

This category includes topical therapies such as imiquimod 5% cream (27) or topical fluorouracil 5% cream or solution (28,29) and photodynamic therapy (PDT), the latter being available only in Europe at the moment (30). High-risk tumors, therefore also BSC, are treated primarily, if available, with MMS (2,10,11). When MMS cannot be performed because of lack of availability or in patients who cannot tolerate it, an alternative treatment could be standard surgical excision with postoperative margin assessment (2,10). Regarding the appropriate margin size, it is recommended to use margins wider than 4 to 5 mm, depending on the localization, although there are no data from randomized trials addressing the proper margin size for this category (2). Another option could be staged excision with circumferential margin assessment, although is not broadly available and can be less desirable for some patients (10,12). Finally, external beam RT administered in a fractionated schedule is an option for older patients with high-risk BCC who are not candidates for surgery (10,13). Topical treatments or PDT are not suitable for this category of patients (2,10).

We presented the case of an 81-year-old-male who was brought to the Emergency Department of the National Institute of Pneumology 'Marius Nasta' due to uncontrolled hemorrhage of a giant cutaneous tumor located in the suprasternal notch that was later diagnosed as BSC. The impressive size of this tumor could be explained by the aggressive histologic pattern, the high proliferative rate of the tumor, and neglect for a long period. The latter was probably the most important pathogenic factor, giving the fact that the patient had disregarded the tumor's enlargement for almost 12 years. Moreover, the COVID-19 pandemic increased the delay. The massive hemorrhage, on the other hand, was probably caused by the high neovascularization of this type of tumor and aggravated by the coagulation status of the patient.

In conclusion, cutaneous basosquamous carcinoma is a basal cell carcinoma subtype that has histopathological characteristics of both basal and squamous cell carcinoma. It is

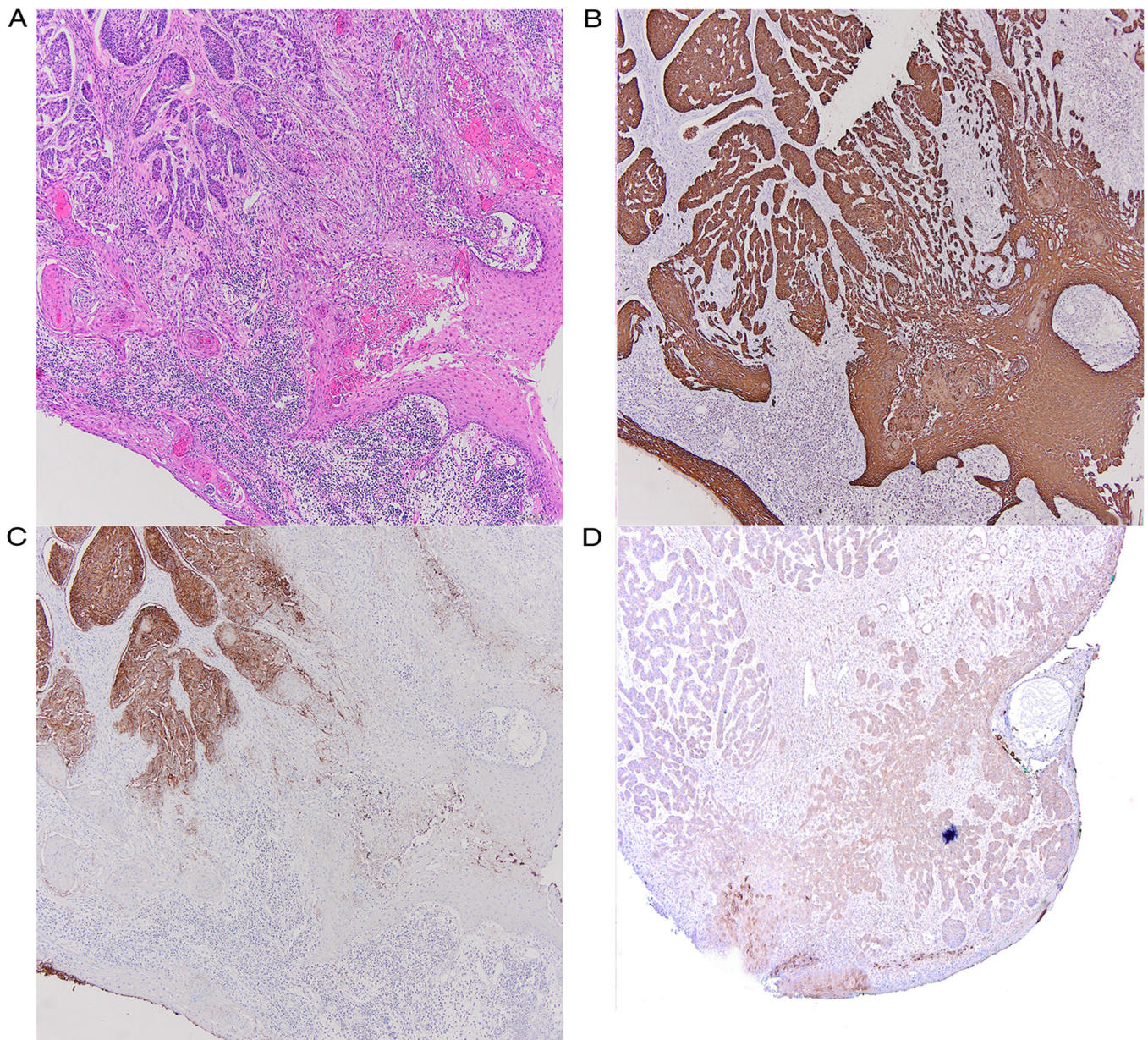


Figure 2. (A) Histopathological examination using hematoxylin and eosin staining at a magnification of x4. (B) 34 betaE2 immunostaining at a magnification of x4. (C) BerEP4 immunostaining at a magnification of x4. (D) EMA immunostaining at a magnification of x4.

considered one of the most aggressive subtypes because of the high-risk of local invasiveness, high frequency of recurrences, and metastases. The diagnosis is made almost exclusively by histopathological examination and the treatment is based mainly on surgery.

In this article, we presented the case of an 81-year-old-male with an uncontrolled hemorrhage deriving from a basosquamous carcinoma. As mentioned before, this entity has an aggressive behavior, presenting with ulceration and infiltration, but this is the first case report, at least to the best of our knowledge, that presented as a massive hemorrhage endangering the patient's life.

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Availability of data and materials

Any further information concerning the case report is available upon request of the corresponding author.

Authors' contributions

All authors had equally contributed to writing and editing the manuscript. TC contributed in all the stages of the article; he designed the article and revised the manuscript for important intellectual content. MMC, EDS and CAP contributed to the conception of the work, revision of the language and

contributed to drafting the final paper. CS, AVZ, SB and OCD revised the work critically in light of the literature data. The final manuscript for publication was approved by all authors.

Ethics approval and consent to participate

The patient provided informed written consent prior to inclusion in the present article. No ethics committee approval was necessary.

Patient consent for publication

The patient provided written informed consent for the publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests and they have no financial relationships to disclose.

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