Metastatic Basal Cell Carcinoma: Case Report and Review of the Literature

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Abstract
Basal cell carcinoma (BCC) is the most commonly occurring carcinoma among humans. However, despite their overall frequency, cases of BCC featuring metastases are extremely rare. We present the case of a 57-year-old male patient with BCC located in the chest, measuring 10 cm in diameter, located at the center of the chest [Figure 1a], with an evolution of 15 years. After several years, an axillary recurrence developed as a tumor mass affecting the lymph nodes. After 14 months, a further lymph node recurrence was observed and resected. Six months later, a pulmonary nodule was detected, which was resected with tumor-free margins. Histopathological report revealed infiltration by BCC. After 13 years of follow-up (after the removal of the primary tumor), the patient remained alive and received close clinicoradiological monitoring. Taking advantage of this opportunity, we also provide a brief review of the corresponding literature.

Key Words: Metastatic, basal cell carcinoma, oncology

Introduction
The appearance of metastasis in the course of basal cell carcinoma (BCC) is exceptional, with incidence rates of <0.55% (0.0028%–0.55%). Its diagnostic criteria were first defined in the 1950s by Lattes and Kessler and include the following: (1) the primary tumor is located in the skin, not in the mucous membranes; (2) the metastasis does not occur by direct extension and is located in a distant region (such as lymph nodes, bone, or internal organs); (3) the primary and distant tumors are histologically similar; and (4) there is no component of squamous cell carcinoma. Metastatic BCC (mBCC) is highly infrequent. This article presents a new case of mBCC, together with a review of the literature in this respect, to improve the characterization of this type of tumor.

Case Report
A 57-year-old male with a history of hypertension, ischemic heart disease, and cerebrovascular accident consulted in 2005 for a BCC measuring 10 cm in diameter, located at the center of the chest [Figure 1a], with an evolution of 15 years. Conventional tumor excision was performed with a 1-cm margin and closure of the defect by means of a double advancement flap. The histological study revealed infiltrative BCC with no vascular or perineural involvement [Figure 1c-e], and with surgical margins free of neoplasia.

After initial loss to follow-up, the patient returned 8 years later due to a subcutaneous, apparently retractor, lesion in the left armpit [Figure 1b], with no palpable locoregional adenopathies. Ultrasound examination of the ganglionic chains revealed no suspicious adenopathies. Imaging tests (ultrasound and magnetic resonance) indicated the presence of a tumor in contact with the pectoralis major muscle. Staged micrographic surgery was then performed, with two interventions and the removal of part of the pectoralis major muscle in order to obtain tumor-free margins. Ten palpable lymphadenopathies detected during this procedure were also extracted. The anatomicopathological study revealed infiltrative BCC in the extracted mass and a focus of basaloid cells without extracapsular involvement in one of the adenopathies (Bcl-2 and cytokeratin positive) [Figure 2a and b]. In view of these findings, the oncology committee decided to closely monitor the patient’s evolution.

Fourteen months later, another subcutaneous left axillary tumor was detected. Puncture aspiration revealed the presence of BCC cells. The extension study performed by computed tomography revealed no involvement.

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elsewhere. Therefore, a surgical resection of the tumor mass was performed, together with scheduled axillary lymphadenectomy. The histological study revealed a lymph node that had been completely replaced by BCC metastasis with periganglionar extension and infiltration of the adjacent striated muscle. Analysis of the remaining four excised lymph nodes revealed no tumoral presence. The treatment was complemented with adjuvant radiotherapy (ten 5 Gy sessions, twice weekly).

Follow-up was continued without incidents of note until 6 months later, when a small nonspecific subcentimetric nodule appeared in the lower lobe of the right lung. Given the difficulty of determining its nature by puncture, radiological follow-up was carried out, which after 6 months showed the nodule to have grown slightly [Figure 2c]. The case was discussed in the local oncologic committee and the type of surgery that should be performed as the only treatment according to the common guidelines (surgery is preferable to chemotherapy if metastases are resectable) was decided. The patient was then referred to thoracic surgery, where a wedge-shaped resection was performed of the right lower lobe, together with lymph node mapping (of segments 7-9). The histological study of the pulmonary specimen revealed basaloid cells infiltrating the lung parenchyma [Figure 2d], but the study of the excised lymph nodes came out to be negative. At 13 years after the eradication of the primary BCC, the patient remained disease free and was periodically followed up till reporting.

Discussion and Review of Literature

BCC is the most commonly occurring malignant tumor, but metastatic BCC (mBCC) is very exceptional. In fact, since its initial description in 1894,[3] only some 300 cases have been published. The incidence of mBCC has been calculated (Denmark)[4] as 0.0001% and among patients with previous BCC as 0.0016%–0.0083%.

mBCC is observed more frequently in males and in the Caucasian race.[5-8] The age at diagnosis of the primary tumor varies from 14 to 88 years, but most cases have appeared in young adults.[7,8] The mean age was higher in patients with regional metastases than in those with distant metastases.[5] The time between the diagnosis of the primary tumor and that of metastasis is variable, but the last two major reviews placed it at around 9 years.[7,8]

The most frequent location of the primary BCC is the head or neck, followed by the trunk and much less commonly, the genital area.[7,9,10] mBCC occurs more frequently in large tumors. Some studies have reported the average size of the primary tumor to be 7 cm, and that these tumors tend to be both larger (T2 or T3) and deeper (T4) than that in non-mBCC.[9] The most common histological subtypes in primary tumors are, in this order of frequency, infiltrative, metatypical, and morpheaform.[5] However, there is little homogeneity in the published histological data, and so firm conclusions in this respect cannot be drawn regarding whether the histological subtype really impacts the ability to metastasize.[5] In the case we present, several of the

Figure 1: (a) Clinical image showing an ulcerated plaque 10 cm in diameter in the presternal zone, which corresponds to the primary basal cell carcinoma. (b) Preinterventional scar and mass in the left armpit of retractile aspect with central depressed area. (c and d) Histological images (H and E, ×40 and H and E, ×100, respectively) showing a basal cell carcinoma with a superficial and infiltrative component. (e) Immunohistochemistry of the primary tumor (immunohistochemistry for Bcl-2, ×40) with intense positivity of the neoplastic cells

Figure 2: (a) Histological image of the lymph node with foci of metastases of basal cell carcinoma (H and E, ×40). (b) Immunohistochemistry of the same anterior lesion with intense positivity of the basocellular carcinoma cells (immunohistochemistry Bcl-2, ×40). (c) Pulmonary computed tomography scan showing a hyperintense nodule in the right lower lobe. (d) Histological image of the lung lesion (H and E, ×40) showing basal cell carcinoma cells infiltrating the lung parenchyma (H and E, ×40)
above criteria were met, such as male sex, large tumor size, period of evolution, and location (the second most frequently affected).

With regard to pathogenic hypotheses, it was initially believed that the aggressiveness of mBCC arose from the characteristics of the tumor itself. Currently, it is believed that the stroma plays an important role in the production of metastases. In fact, the expression of transcription factors that stimulate the epithelial–mesenchymal transition, such as the Twist1 factor,[11,12] and the alpha-smooth muscle actin in the stroma have been described as possible markers of mBCC.[12]

The most common route of dissemination is via the lymph nodes (regional lymph node metastases), followed by hematogenous extension. In these cases, by order of frequency, lung, bone, skin, and soft-tissue metastases are most commonly found, although metastasis has also been observed in the salivary glands, liver, meninges, mediastinum, kidneys, and pleura.[5] Cases of multiple metastases have also been reported (affecting up to 36% of patients), in which lymphatic and hematogenous metastases coexist.

With regard to treatment, there are no guidelines or consensus as to the approach that is most appropriate. However, surgery is the treatment of choice when the tumors are resectable. Classically, chemotherapy (especially when based on cisplatin) or radiotherapy has been considered the second line of therapy.[13] Nevertheless, response rates are uneven and significant toxicity is provoked. Moreover, according to a recent review by Wysong et al.[8] their use does not significantly increase survival. Fortunately, the incorporation of new anti-epidermal growth factor receptor drugs and inhibitors of the hedgehog pathway, such as vismodegib, together with new ones still under study,[14-16] constitutes more promising alternative for patients with mBCC. Furthermore, in carcinomas that are resistant to smoothened inhibitors,[17] a reduction in the function of the hedgehog pathway has recently been reported in patients treated with arsenic trioxide and itraconazole who had previously received vismodegib; however, the clinical results are unclear and more studies and long-term follow-up are necessary for appropriate clinical evaluation.

In general, the prognosis of mBCC is poor, and large-scale reviews have estimated an average survival of only 8–10 months.[7,8] However, these low values may be accounted for, at least in part, by the fact that the studies in question included basosquamous carcinomas (considered by the National Comprehensive Cancer Network[2] to be a variant of squamous cell carcinoma) and that they did not include patients treated with new target drugs. Thus, Danial et al.[18] in a recent study of ten patients with mBCC (six of whom had received treatment with inhibitors of the Hedgehog pathway) reported much higher overall survival figures, with a mean value of 7.3 years. The metastatic pathway is another factor that determines survival. Thus, greater survival has been observed if the metastases are regional (average survival: 7 years and 3 months) rather than hematogenous (survival: 2 years). In our case, the patient was treated surgically for pulmonary metastases and is currently free of progression. However, given the low survival rate described in other cases, close monitoring, including imaging testing, is essential.

In summary, although mBCC presents a very low incidence, it has well-defined epidemiological characteristics, which allow us to identify high-risk patients and provide close, long-term follow-up, thus facilitating the earliest possible management. Together with early diagnosis, new target therapies for BCC are especially important to improve survival rates.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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