CASE REPORT

Metastatic basal cell carcinoma: a frequent disease with rare clinical evolution

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SUMMARY

Basal cell carcinoma (BCC) is the most common malignancy worldwide. BCC has a benign evaluation, despite the high rate of local recurrence. Conversely, metastatic BCC (mBCC) is extremely rare. In this article, we present a case of an 86-year-old woman with a history of forearm mBCC, excised in 2009. In 2011, she experienced a left axilla enlargement and the evaluation revealed metastasis of mBCC. The patient began chemotherapy but had regional progression. After she had undergone radiotherapy, initiation of a clinical phase II trial was proposed, which she refused. The patient died in March 2013, 17 months after metastases diagnosis. mBCC poses a significant management challenge and current treatment options are limited. The gold standard treatment is surgical excision. Given the rarity of metastatic spread of cancer and the limited effectiveness of cytostatic agents, it has been a challenge to treat these types of patients.

BACKGROUND

Basal cell carcinoma (BCC) is the most common malignancy in Caucasians,^{1–5} with over two million estimated cases diagnosed in the USA each year.⁴ It is believed that BCC originates from the basal layer of the epidermis, the interfollicular epidermis and the hair follicle.⁶ Approximately 95% of individuals are diagnosed with BCC between the age of 40 and 79 years. The incidence is approximately 30% higher in men than in women. Risk factors include fair skin pigmentation, radiation (ultraviolet and/or ionising), exposure to arsenic or polycyclic aromatic hydrocarbons, immunosuppression, scars and certain genetic syndromes, such as nevoid BCC syndrome.⁶ BCC frequently has a benign evaluation, despite a high rate of local recurrence. About 80% of BCCs are located in the head or neck. Several lines of evidence suggest that the worldwide incidence of BCCs is increasing.⁷ Conversely, metastatic BCC (mBCC) is extremely rare, with incidence rates of 0.003–0.5%. mBCC is defined as a primary cutaneous BCC that spreads to distant sites as histologically similar metastatic deposits of BCC.⁸ Risk factors for mBCC include aggressive histological types (infiltrating, morpheaform), perineural invasion, tumour persistence for several years, tumours resistant to prior therapy, radiation exposure and large primary tumours (>2 cm). Similar to primary BCC, the main genetic aberration in mBCC is most commonly the result of mutations or loss of heterozygosity of the tumour suppressor PTCH1.⁶ mBCC spreads by lymphatic and haematogenous routes.⁹ The most frequent

Figure 1 Basosquamous (metatypical) carcinoma (H&E, original magnification×40).

sites of metastasis are lymph nodes (64.6%), lung (33.9%) and, more rarely, bone and skin (1.5%). The prognosis for mBCC is poor, with an average survival of 8–10 months following diagnosis.¹⁰

CASE PRESENTATION

An 86-year-old woman presented with a history of ulcerated lesion on the left forearm, which was excised in June 2009. The histological diagnosis was mBCC (figure 1), with 15 mm longest axis, invading the hypodermis and the deep surgical margin less than 1 mm. The patient was hypertensive, diagnosed at 50 years of age and treated with ACE inhibitor, she had no history of other cancers or other diseases. There was no family history of cancer. In October 2011, she experienced a painless enlargement of the left axilla (LA). A physical

Figure 2 Painless nodes in the left axilla.

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Figure 3 Axillary nodes disclosed by chest CT scan (arrow).

examination revealed two painless nodes in the LA, one in the anterior region, hard, with 5 cm in the greatest diameter and another in the median region, stony, with 4 cm in the greatest diameter (figure 2).

INVESTIGATIONS

There was no evidence of local recurrence in the BCC excision scar. Chest–abdominal–pelvic CT (figure 3) for staging revealed two suspicious lesions: LA nodes of 2×2.2 and 4.5×5.5 cm, and multiple mediastinal adenopathies (the largest being 2×1.7 cm).

DIFFERENTIAL DIAGNOSIS

The biopsy of lymphadenopathy is extremely important because it determines the diagnosis and may change the therapy. In this case, the most probable diagnoses would be lymphoma and metastatic carcinoma of the breast or lung. If a patient has a history of neoplasia, the indolent course of the disease, metastases of basaloma should not be placed in the first diagnostic hypothesis.

The biopsy of the axilla node showed cylinders fully constituted by well-defined neoplastic lobules of squamous aspect with clear-cut basal, high mitotic index and focal necrosis in a desmoplastic stroma, immunohistochemical profile: positive EMA, P63 and BerEp4, and negative TTF1, CK7 and CK 20, compatible with metastasis of mBCC (figures 4 and 5), subsequently referenced to medical oncology.

Figure 4 Metastasis with morphological characteristics identical to the primary tumour: basosquamous (metatypical) carcinoma with basal cell and also atypical squamous cells (arrow). Express BCL2, cytokeratin methyl methanesulfonate (MMF) (H&E, original magnification ×100, Bcl2 and MMF116×100).

Figure 5 Metastasis of basosquamous (metatypical) carcinoma. Express BerEp4, p63, epithelial membrane antigen and high proliferative index with high Ki67 (H&E, original magnification×400, BerEp4×400, p63×400 e ki67×100).

TREATMENT

The planned procedure was carefully discussed in a multidisciplinary team. The patient began chemotherapy with cisplatin 50 mg/m² (D1) and capecitabine 500 mg/m² (two times per day) for 14 days in 21/21 days. She completed four cycles but had LA locoregional progression (figure 6). She then took radiotherapy treatment for locoregional control. She was to begin a clinical phase II trial with vismodegib, however, she refused it.

OUTCOME AND FOLLOW-UP

Despite the treatment received, the disease continued to grow locally with oedema and ulceration of the left arm and left thoracic region. The patient died in March 2013, about 17 months after the diagnosis of metastasis.

DISCUSSION

BCC has a high incidence and the behaviour is mostly benign. Complex cases of mBCC pose a significant management challenge and current treatment options are limited.² Determining features of high risk of recurrence are fundamental for establishing therapeutic strategy. The gold standard treatment is surgical excision with histological control of excision margins.⁵

Figure 6 Locoregional progression with oedema in the left arm.

Initial surgical treatment with safety margins is the best treatment. Advanced BCCs are often difficult to treat and life-threatening.⁷ Given the rarity of metastatic spread of cancer and the limited effectiveness of cytostatic agents, the adopted systemic treatment was based on the combinations used for metastatic squamous cell. The oral agent vismodegib has recently been approved. Phase I/II clinical trials revealed that vismodegib was associated with objective response rates of 30–55% and tumour control rates of 80–90%, but these non-randomised trials were conducted without a control arm.^{3 11}

Learning points

- ▶ Basal cell carcinoma (BCC) is the most common cancer in individuals with a fair skin type.
- ▶ Surgical excision with histological control of excision margins is the gold standard treatment because the tumour grows slowly and only rarely metastasises.
- ▶ As mBCC is rare, some clinicians might be unaware that BCC can metastasise and might not recognise or correctly diagnose the disease.
- ▶ Potentially metastasising BCCs cannot be certainly identified; thus early intervention with adequate treatment of all BCCs is advised.
- ▶ It is extremely important to refer these patients to clinical trials.

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