

Multiple non-syndromic basal cell carcinoma with the chest as primary site and lung metastases: A rare case

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Abstract

Basal cell carcinoma (BCC) is the most commonly diagnosed cancer in humans, usually affecting elderly Caucasian men and skin regions mostly exposed to the sun, that rarely metastasizes. We report an unusual and aggressive case of multiple, non-syndromic metastatic BCC with an uncommon primary site in the chest and pulmonary metastases, treated successfully with surgery and vismodegib. A 51-year-old woman presented with a large pigmentary lesion of the chest, close to the sternum. She had the lesion for > 25 years and lately noticed multiple facial lesions. The diagnosis of multiple BCC was suspected and a punch biopsy of the primary lesion was performed. Diagnosis was confirmed by immunohistochemistry (BerEp4+, EMA- phenotype). After excision, staging with a thorax computed tomography scan revealed metastatic micro-nodules in the left lung, confirmed histologically after video-assisted thoracic surgical biopsy. Adjuvant chemotherapy with vismodegib was proposed and administered. At 30 days follow-up, thorax computed tomography scan was unaltered and her facial lesions showed significant regression. Although

prognosis remains poor, early diagnosis and prompt management complemented by novel biological agents, like vismodegib, targeting disease pathogenesis, seems to bring promising results.

Introduction

BCC represents 80% of all non-melanotic skin malignancies. It usually affects elderly Caucasian men and skin regions mostly exposed to the sun.^{1,2} About two-three million people/year get affected globally, 730-1000/100.000 in the United States, 1000-2000/100.000 in Australia and 132/100.000 in Europe.^{1,3} BCC is a slowly growing, usually not metastatic due to its strong stromal dependence,⁴ but invasive cancer. Its size varies greatly, with giant BCCs of maximum diameter > 5 cm representing 1% of all lesions, while multiple lesions are often associated with hereditary disease like in Gorlin, Rombo or Bazex syndromes.⁵

Metastatic BCC (mBCC) incidence ranges between 0.003% and 0.55%,^{1,2,6} with a men/women ratio between 2:1 and 3:1,⁷ and head, neck and face regions get predominantly affected.^{1,2} It spreads primarily to the lymph nodes, followed by the lungs, bones and other organs.^{1,2,6} Only ~ 400 cases have been reported since 1894.^{2,7,8} Therefore, the present case, a multiple, non-syndromic mBCC of the chest, treated successfully with surgery and vismodegib (GDC-0449, Erivedge®/Roche Registration Ltd, Germany) at a tertiary Greek hospital, is rather rare and worth mentioning.

Case Report

A 51-year-old female with a history of depression, presented with a large pigmentary lesion close to the sternum (Figure 1a), 6×3 centimeters in dimension, with dermoscopic features of large converging blue-black ovoid nests, central ulceration and peripheral regression (Figure 1b). She had the lesion for more than 25 years, while multiple facial plaques and papules (Figure 1c), also pigmentary, with blue-gray and blue-black ovoid nests and ulcerations, as seen dermoscopically, and many with a distinct pearl-like edge, appeared during the last three years. No lymphadenopathy was present. Multiple BCC was suspected and a punch biopsy was performed. Pathology results showed a neoplasm with morphological characteristics of either a skin adnexal

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tumor or a BCC. More specifically, it was characterized as a basaloid epithelial tumor of the epidermis with peripheral palisades, with mitotic crowded centrally located nuclei, presence of various pale cells and few infiltrating strands of atypical epithelium. Histochemistry and immunohistochemistry uncovered a BerEp4+, EMA- phenotype (Figure 2), in favor of BCC, and surgical excision of the lesion was recommended. Final pathology validated BCC diagnosis, revealing a tumor with microscopic characteristics of BCC,

with various sites of focal ulceration, partial infiltration of the subcutaneous nerves and vessels, and minor focal metaplasia to metatypical basal cell carcinoma, with negative excision margins. A thorax computer-assisted tomography scan (CT) for staging revealed a 7-mm nodule (Figure 3a) and several “ground glass”-like micronodules in the left lung, representing possible distant metastases. A video-assisted thoracic surgical (VATS) biopsy of the 7-mm nodule was performed followed by histological examination of the specimen, revealing nests of basaloid epithelial cells with peripheral palisading, thus confirming its metastatic nature. Due to disease extent, adjuvant treatment with vismodegib was initiated at 150mg/day and she was discharged. An unaltered CT-thorax (Figure 3b) and regression of her facial lesions were observed at 30-days follow-up.

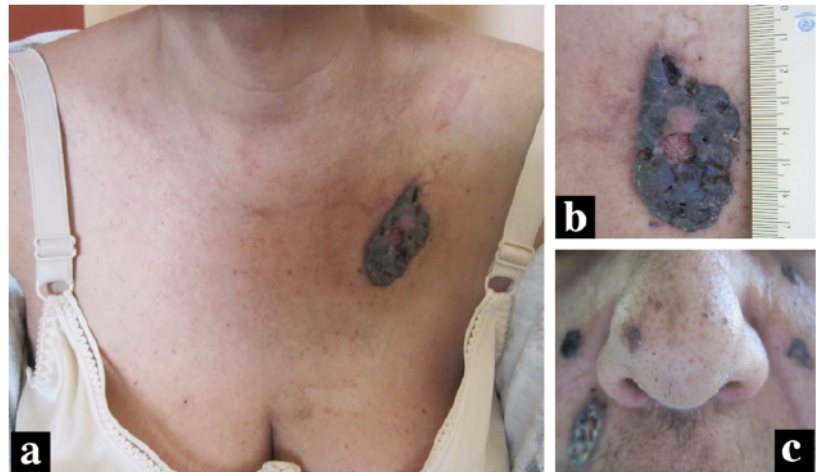


Figure 1. a) Unusual location of the primary lesion in the chest, close to the sternum, b) close view (5×) of the primary lesion, sized 6×3 cm with central ulceration and peripheral regression, c) multiple facial pearl-like edged lesions with partial ulceration.

Discussion

The usual BCC case is a male, middle-aged patient, with a singular small (<5 cm) non-metastatic lesion located in the head or neck. Here, we present a multiple mBCC in a female patient, with a giant (6×3 cm) primary lesion located in the chest and left lung metastases, in other words, an unusual and aggressive form of this common disease.

Known risk factors, namely light skin color (Fitzpatrick skin types I and II), smoking history and occasional exposure to ultraviolet-A light (UVA), were present, while exposure to arsenic, ionizing radiation or dry ice, immunosuppression, albinism, keratoacanthoma or xeroderma pigmentosum were absent. Hereditary multiple BCC was excluded in our case due to negative family history of genodermatoses.^{1,3,5}

Although the fourth, fifth and sixth decades are considered the mean or median age of presentation of the primary lesion,^{2,7} our patient developed her first BCC at age 26. Nevertheless, it was left untreated for 25 years and not only it metastasized, but she also developed multiple primary lesions, as expected by described high 1-year and 5-year cumulative risks to develop secondary lesions.^{5,6,9}

Metastatic BCC occurs two times more often in males than females with the most common site of metastases being lymph nodes, followed by the lungs. Presentation age, the site and size of primary lesion, perineural and perivascular spread, duration and recurrence of disease, incomplete resection or positive margins, multiple

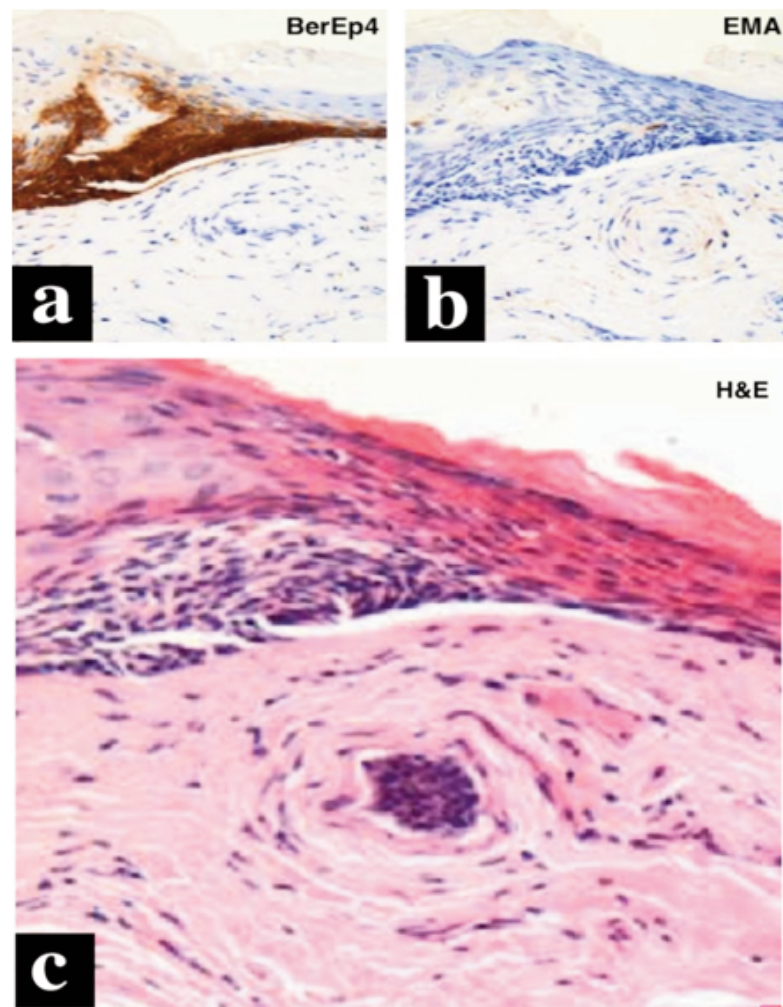


Figure 2. Comparison BerEp4 (+) immunohistochemistry stain (200×) (a) with EMA(-) (200×) (b) and H&E (400×) (c) stains of the primary tumor punch biopsy.

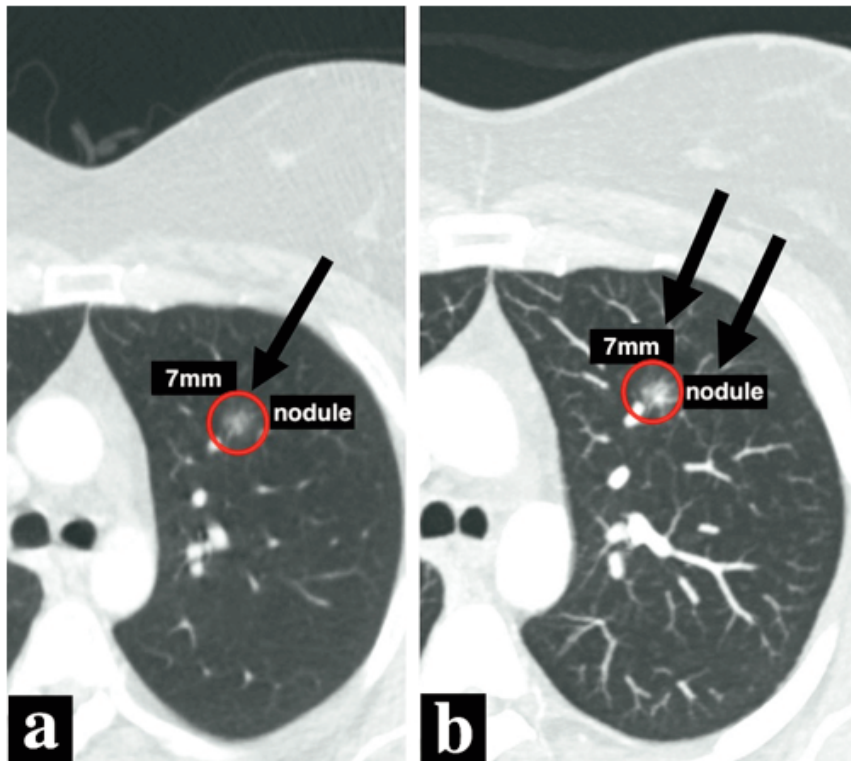


Figure 3. CT-thorax scan images of the metastatic 7 mm left lung nodule: (a) single arrow - at presentation, (b) double arrow - at 30-days follow-up.

tumors and aggressive histological types may predict metastasis.¹⁻³ Tumors greater than 3 cm in diameter have a 2% incidence of metastasis and/or death.^{2,6} Prognosis is poor,^{1,2,6,7} with a longer average survival of three-and-a-half to seven years, when lymphatic spread is involved,² in contrast with an average of eight months to two years that accompanies hematogenous metastases.^{1,2,4,7}

Surgery and radiotherapy combined or not with targeted therapy are the most common therapeutic options used.^{2,5} Aberrant activation of the Hh pathway has been associated with pathogenesis of sporadic, non-syndromic BCCs as well as in hereditary syndromes with multiple BCCs.^{1,5} Small molecule antagonists of the Hedgehog pathway, like vismodegib and sonidegib, can both be used as adjuvant targeted therapy in locally advanced disease, however, only vismodegib is

indicated for metastatic disease.¹⁰ Although nausea/loss of appetite and vomiting, diarrhea or constipation, weight and hair loss, muscle spasms and joint pain have been described among others as common side-effects, response rates can reach 37%, thus proving their therapeutic potential against mBCC.² Our patient received this novel therapy and showed positive primary results.

Conclusions

In conclusion, the earlier the identification of this potentially curable form of cancer, the better the therapeutic results and the least the morbidity complications.

Comprehensive sensitization of the population and awareness raising by all relevant physicians, as well as fostering a healthy

doctor-patient relationship regarding communication of knowledge on the primary BCC disease and its metastatic potential, can indeed play a crucial role in increasing favorable outcomes. Precise excision of the primary tumor and adjuvant targeted therapy with Hedgehog inhibitors, can bring promising results in aggressive cases of mBCC and must be encouraged.

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