Metastatic basal cell carcinoma to the bone: A case of bone metastasis in uncommon sites

Olga Nigro,[1] Claudio Chini,[1] Ilaria Gioia Angiola Marcon,[1] Annamaria De Giorgi,[1] Linda Bascialla,[1] Elisa Gallerani,[1] Alice Giaquinto,[1] Diego De Palma,[2] Maurizio Lombardo[3]

[1]Medical Oncology, [2]Nuclear Medicine, [3]Dermatology Department, ASST-Settelaghi, Ospedale di Circolo Fondazione Macchi, Varese, Italy

Abstract

Basal cell carcinoma (BCC) is the most common malignant tumor of the skin. Despite the indolent nature, metastatic BCC can occur, albeit rarely. Metastasis to the bone is very rare. From its approval, mBCC patients are treated with vismodegib, a selective hedgehog pathway inhibitor. Unfortunately, in recent period, it was demonstrated an emergence of drug resistance, due to Smoothened (SMO) mutation. To date, several groups are studying the effectiveness of immunotherapy in BCC. Clinical trials with Immune Checkpoint Inhibitors are ongoing. We report the rare case of a man with multiple bony metastasis, with a resistance to vismodegib, and we evaluated all manuscripts in literature reporting bone metastasis. Moreover, we review all the manuscripts in literature reporting bone metastasis, and we summarize the main therapeutic strategies, and the further perspectives.

Case Report

About eleven years ago, a 73-year-old Caucasian man performed a surgical removal of a dorsal skin lesion, histologically compatible with basal-cell carcinoma. Since then, patient started a clinical/radiological follow-up at the Dermatology Department of our Hospital. Ten years later he presented local recurrence of the disease. Histological examination showed diffuse basal-cell carcinoma with dermal infiltration, and a dorsal MRI described multiple dorsal skin nodules with extensive infiltration of subcutaneous tissues and dorsal fascia (Figure 1).

In addition, these lesions adhered to D9-D10 vertebral spinous and to the insertion of the muscular structure. Due to the complexity of the clinical case, it was discussed with Surgeons, Radiologists, Radiotherapists, Oncologists, and Dermatologists. Radiotherapeutic treatment was excluded, because of the extention of the disease. Therefore, he was referred to our Medical Oncology Department and started a treatment with an oral molecule, Vismodegib (150 mg die). Before starting, a FDG PET/CT scan confirmed cutaneous and subcutaneous dorsal disease, including the dorsal fascia and extended to bones (left humerus, right shoulder blade, D4, D5, D11, S1, left femur), to the mediastinal lymph nodes, and bilaterally to the lungs (Figure 2a).

Two months later, a thorax and abdomen CT scan confirmed bone disease and showed multiple pulmonary nodules with characteristics of primitiveness, and a number and size increase of the intra-thoracic lymph nodes. Patient underwent a biopsy of the largest pulmonary lesion. It was compatible with sarcoidosis. ACE's (Angiotensin Converting Enzyme) dosage was 66 mcg/L (normal values: 6-12 mcg/L). Thus, he started pneumological follow-up, without interrupting treatment with Vismodegib. A FDG PET/CT scan (Figure 2b) performed four months later showed almost complete pulmonary response, cutaneous and subcutaneous partial response, bone stability disease and mediastinal lymph nodal progression disease. Collaterally, it was reported a left kidney lesion, undergone to surgical removal. It was a G2 type 1 renal papillary Carcinoma, pT1a. Given the lymph nodal progression of the disease, the patient was admitted to the Thoracic Surgery Department, and underwent VATS (Video Assisted Thoracoscopic Surgery) and lymph node biopsy. The histology was compatible with granulomatous pleurisy. Thus, he started renal cancer follow-up, and carried on sarcoidosis follow-up. In the meantime, the patient continued the treatment with Vismodegib. Three months after the previous radiological examination, he performed a FDG PET/CT scan: further metabolic cutaneous and subcutaneous response disease (Figure 3) and bone progression disease (D3-D8 with spinal cord involvement), with a new left femoral condyle lesion, that was biopsied: metastases from basal cell carcinoma (Figure 2c). He performed a radiotherapeutic treatment on the column and left femoral condyle and started an anti-resorptive treatment with Denosumab 120 mg every month. He continued the treatment with Vismodegib 150 mg die. After twenty months of treatment with Vismodegib, a new FDG PET/CT scan showed a diffuse progression of the disease. In particular, it appeared a local cutaneous recurrence (Figure 2d). It was biopsied and confirmed the basal cell origin (Figure 4).

Thus, he continued the treatment with Vismodegib. After 5 months, we treated a bone recurrence with RT 20 Gy on left shoulder and sacrum. The last FDG PET/CT scan revealed a diffuse progression

Correspondence: Maurizio Lombardo, Dermatology Department, ASST-Settelaghi, Ospedale di Circolo Fondazione Macchi, Varese, Viale Borri 57 Varese, 21100, Italy.
Tel.: +39-393437
E-mail: maurizio.lombardo@asst-settelaghi.it

Key words: Metastatic basal cell carcinoma; Vismodegib; SMO; Immunotherapy.

Contributions: All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. NO, LO devised the work. NO, CC, LM analysed the data. NO, CC, MIGA, DGA, BL, GE, DPD revised the literature. MIGA, DGA, BL, GE, DPD, LM revised the paper

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Ethical approval and consent to participate: Written informed consent was obtained from the patient.

Availability of data and material: Data and materials are available by the authors.

Please cite this article as: Nigro O, Chini C, Marcon IGA, et al. Metastatic basal cell carcinoma to the bone: a case of bone metastasis in uncommon sites. Dermatol Rep 2022;14: 9267.

Received for publication: 15 May 2021.
Accepted for publication: 21 May 2021.

Dermatology Reports 2022; 14:9267
doi:10.4081/dr.2022.9267

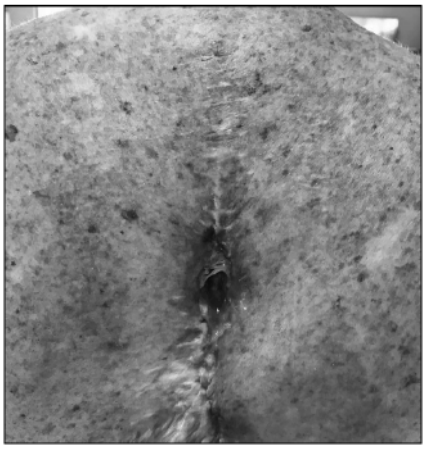

Figure 1. Time 0. Skin nodules with extensive infiltration of subcutaneous tissues and dorsal fascia.

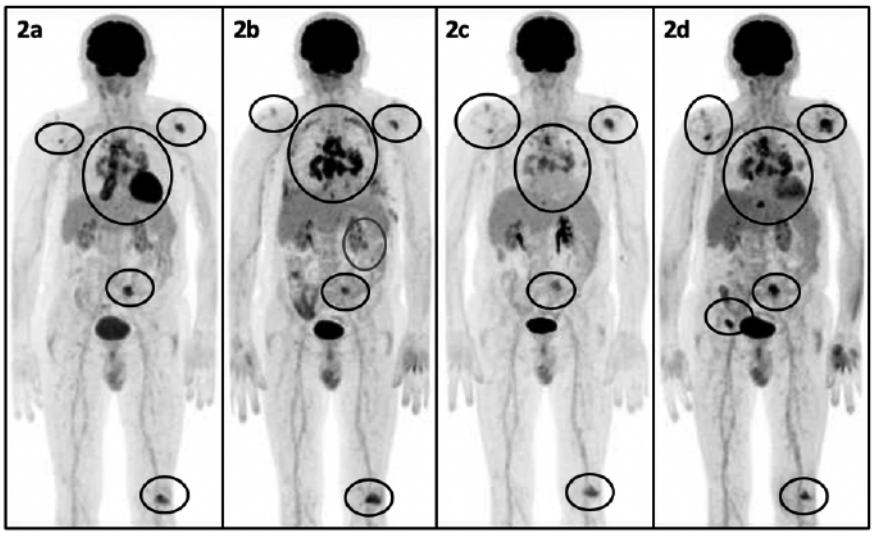

Figure 2. PET images before starting and during Vismodegib. a) Time 0. b) +9 months. c) +12 months. d) +33 months.

of the disease (bone, lymph nodes, subcutaneous); in particular, it showed a bone marrow infiltration at D5. Thus, patient stopped VISMODEGIB after 2.10 years of treatment and underwent laminectomy and posterior dorsal arthrodesis. Histological examination: diffuse BCC infiltration. Open question: could immunotherapy be the winning strategy?

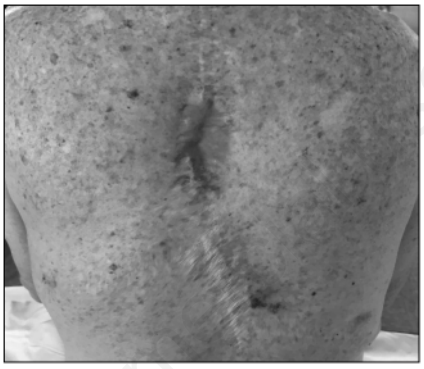

Figure 3. Cutaneous and subcutaneous disease after 8 months of treatment.

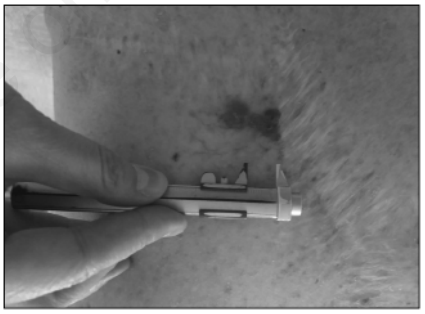

Figure 4. Dorsal skin recurrence after 15 months of treatment.

Discussion

Basal cell carcinoma (BCC) is the most common malignant tumor of the skin and is also the most common human malignancy. The underlying cause of BCC is unknown, but ultraviolet light exposure and genetic predisposition seem to be the most significant etiological factors.[1] Mutations in *PTCH1* or *p53* represent the most frequent genetic alterations.[2] Most BCCs arise from sun-exposed areas and 80% develop in the head and neck.

Early treatments (excision, radiotherapy, topical imiquimod, photodynamic therapy) are curative in most cases.[3] The likelihood of recurrence following treatment is used to categorize lesions as low or high risk. Surgery and radiotherapy are the treatment of choice for most patients with high-risk lesions.[4] Despite that advanced disease is rare, BCC can progress to a point unsuitable for local therapy and prognosis for these patients is quite poor.

Metastatic BCC accounts for 0.0028-0.55% of all BCCs.[5] The median age of patients with a primary lesion is around 45 years and metastatic disease appears a median of 9 years after initial diagnosis.[6] Male gender, primary lesions in the head and neck, large or locally invasive lesions, and recurrence after surgery or radiation have been predictive of metastatic spread. Tumors greater than 3 cm in diameter have a 2% incidence of metastatic spread and/or death. The incidence of metastatic spread and/or death is estimated to be 25% for tumors with a diameter of 5 cm and 50% for tumors with a diameter of 10 cm or greater.[7] Metastasis generally portends a poor prognosis, with survival rarely exceeding 1.5 years.

BCC metastasizes most frequently to the lymph nodes, but also through the hematogenous route to the viscera and bone.[8] Patients usually exhibit multiple concurrent organs of spread at the time of diagnosis.[9] In literature we found just 58 case reports, for a total of 69 patients with BCC metastatic to the bone; only 18 developed bone marrow metastasis over bone metastasis (Supplementary Table 1). The most frequent site of bone metastasis was the column. Our patient developed metastasis into the column with bone marrow involvement, but also in unfrequent sites: left femur, left omerus, right scapula.

Until 2012, the most commonly therapy for the treatment of metastases from BCC was the radiotherapy ®T, followed by surgery of metastatic site. The minority of patients was subjected to chemotherapy treatments. Starting from 2013, the inhibitors of the Hedgehog signaling pathway, the first specific therapeutic modality, emerged as an option for patients not candidates for surgery or radiotherapy and most of the cases reported in the literature provided for the use of vismodegib.[10-13]

Despite the encouraging results from the studies on Vismodegib, our patient showed a progression of disease with the emergence of new skin, lymph nodes, and aboce all, bone lesions and bone marrow infiltration. Thus, we supposed a mutation in Smoothened (SMO).

Mutation of SMO was tumorigenic and intrinsically resistant to SMO antagonists,

which was also called primary resistance that constituted approximately 10-20% of sporadic mutations in BCC.[14]

The recent breakthroughs in cancer immunology and immunotherapy have highlighted the necessity for a precise understanding of the immune-modulatory function of oncogenic signaling pathways and their actual role in tumor immunity. Recent studies demonstrated that mutational activation of HH/GLI signaling plays a causal role in the development and growth of BCC.[15] Given the immunosuppressive function of HH/GLI, HH antagonists may synergize with immune checkpoint blockers such as anti-PD-1 antibodies in fighting cancer.[16] Single case studies with BCC patients receiving anti-PD1 (anti-Programmed Cell Death 1) nivolumab or pembrolizumab have already yielded promising results, suggesting that the use of immune checkpoint inhibitors (ICIs) can provide a therapeutic benefit in HH/GLI-driven non-melanoma skin cancer.[17-20]

Clinical trials with ICIs, including cemiplimab, a fully human, anti-PD1, monoclonal antibody, and pembrolizumab, a humanized antibody targeting the PD-1 receptor, are ongoing (see https://www.clinicaltrials.gov/ trials identifiers: NCT03132636; NCT03521830): *NCT03132636* (phase 2 trial for metastatic Basal Cell Carcinoma (BCC) (group 1) and for unresectable locally advanced BCC (group 2) when treated with cemiplimab as a monotherapy), *NCT03521830* (phase 2 trial assessing the efficacy of nivolumab, alone or in combination with ipilimumab in treating patients with locally-advanced unresectable or metastatic basal cell carcinoma).

Conclusions

mBCC is a rare entity, even more rare is the metastatic BCC to the bone. Furthermore, we have little informations available. In recent years there has been a development in new drugs, in particular we studied HH signaling pathway inhibitors. With the elucidating of SMO protein, mechanisms of resistance were clearer and facilitating the design of novel SMO antagonists with anti-resistance profiles. Moreover, we need for a precise understanding of the immune-modulatory function of oncogenic signaling pathways and their actual role in tumor immunity. Several studies are ongoing to better know the role of ICIs in mBCC. Thus, we need future studies to better understand this cancer and its therapy.

References

1. Gailani MR, Leffell DJ, Ziegler A, et al. Relationship between sunlight exposure and a key genetic alteration in basal cell carcinoma. J Natl Cancer Inst 1996;8: 349–54.
2. Bonilla X, Parmentier L, King B et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. Nat Genet 2016;48:398-406.
3. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005; 353:2262–9.
4. Telfer NR, Colver GB, Morton CA. British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. Br J Dermatol 2008; 159:35–48.
5. McCuskerM, Basset-Seguin N, Dummer R et al. Metastatic basal cell carcinoma: prognosis dependent on anatomic site and spread of disease. Eur J Cancer 2014;50:774–83.
6. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. J Am Acad Dermatol 1984;10: 1043–60.
7. Snow SN, Sahl WJ, Lo J et al. Metastatic basal cell carcinoma: report of five cases. Cancer 1994;73:328-35.
8. Barksdale SK, O'Connor N, Barnhill R. Prognostic factors for cutaneous squamous cell and basal cell carcinoma. Determinants of risk of recurrence, metastasis, and development of subsequent skin cancers. Surg Oncol Clin N Am 1997;6:625–38.
9. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. J Am Acad Dermatol 1984;10: 1043–60.
10. Axelson M, Liu K, Jiang X et al. U.S. Food and Drug Administration approval: vismodegib for recurrent, locally advanced, or metastatic basal cell carcinoma. Clin Cancer Res 2013;19:2289-93.
11. Sofen H, Gross KG, Goldberg LH et al. A phase II, multicenter, open-label, 3-cohort trial evaluating the efficacy and safety of vismodegib in operable basal cell carcinoma. J Am Acad Dermatol 2015;73:99-105.
12. US Department of Veterans Affairs (VA) Pharmacy Benefits Management Services; Medical Advisory Panel; VIAN Pharmacist Executive. Vismodegib (Erivedge) National Drug Monograph. Washington, DC: US VA; 2013. Available from: www.pbm.va.gov/clinicalguidance/drugmonographs/vismodegib_drug_monograph.docx. Accessed March 22, 2016.
13. Erdem GU, Sendur MA, Ozdemir NY et al. A comprehensive review of the role of Hedgehog pathway and vismodegib in the management of basal cell carcinoma. Curr Med Res Opin 2015;31:743-56.
14. Sekulic A, Von Hoff D. Hedgehog pathway inhibition. Cell 2016;164:831.
15. Bonilla X, Parmentier L, King B, et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. Nat Genet 2016;48:398– 406.
16. Grund-Gröschke S, Stockmaier G, Aberger F. Hedgehog/GLI signaling in tumor immunity - new therapeutic opportunities and clinical implications. Cell Commun Signal 2019;17:172.
17. Lipson EJ, Lilo MT, Ogurtsova A, et al. Basal cell carcinoma: PD-L1/PD-1 checkpoint expression and tumor regression after PD-1 blockade. J Immunother Cancer 2016;21;5:23.
18. Fischer S, Ali OH, Jochum W, et al. Anti-PD-1 Therapy Leads to Near-Complete Remission in a Patient with Metastatic Basal Cell Carcinoma. Oncol Res Treat 2018;41:391–4.
19. Moreira A, Kirchberger MC, Toussaint F, et al. Effective anti-programmed death-1 therapy in a SUFU-mutated patient with Gorlin-Goltz syndrome. Br J Dermatol 2018;179:747–9.
20. Chang ALS, Tran DC, Cannon JGD, et al. Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study. J Am Acad Dermatol 2019;80:564–6.