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Metastatic and locally aggressive BCC: Current treatment options

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Abstract
The treatment of locally advanced and metastatic BCC presents a significant clinical challenge. Treatment options have evolved recently to include the use of hedgehog inhibitors Vismodigib and Sonidigib and immunotherapy with Cemiplimab.

KEYWORDS
basal cell carcinoma, locally aggressive BCC, metastatic BCC

1 | INTRODUCTION

Basal cell carcinoma (BCC) accounts for 80% of nonmelanoma skin cancers. Metastasis is extremely rare, with prognosis remaining poor. Here, two cases of metastatic BCC are outlined, with lymphatic spread to neck nodes and hematogenous spread to the lung. Current treatment options for metastatic and locally aggressive BCC are discussed. Basal cell carcinoma (BCC) accounts for 80% of nonmelanoma skin cancers. Classically, these skin lesions develop on sun-exposed areas of skin, with the head and neck most frequently affected. Metastasis is extremely rare, ranging between 0.0028 and 0.55 of BCC cases, with prognosis remaining poor.[1] Here, two cases of metastatic BCC (mBCC) are outlined; one with lymphatic spread and one with hematogenous spread. This paper will discuss the presentation of these cases and the multidisciplinary team (MDT) approach to management, followed by a discussion of current treatment options for this challenging condition.

2 | CASE 1

A 70-year-old male patient was referred by his general practitioner with a biopsy-proven BCC on his right central cheek (Figure 1). The lesion had been notably increasing in size in the weeks preceding the biopsy. He was reviewed in clinic within 2 months of referral, where a 2.6 cm ulcerated lesion was seen. Histology from his biopsy identified nodular BCC that was invading the dermis. Past medical history was significant for smoking, appendectomy, insulin-dependent diabetes, diabetic nephropathy, obesity, hypertension, and atrial fibrillation. While waiting for surgery, he developed a level II neck lump. Fine-needle aspiration cytology was arranged, which confirmed malignant basaloid carcinoma. Staging investigations were performed with computed tomography of brain, neck, abdomen, and pelvis. This was negative for distant metastasis. Following MDT discussion, wide local excision of the lesion with superficial parotidectomy and selective neck

FIGURE 1 Case 1: BCC right cheek with right neck lymphadenopathy

FIGURE 2 Case 2: Right temporoparietal erosive BCC

FIGURE 3 MRI image showing intracranial extension of the tumor

dissection of levels I-III was performed, with cervicofacial flap reconstruction. His postoperative recovery was complicated by the development of type-4 renal tubular acidosis, which required an intensive care unit stay for dialysis, and pneumothorax from suspected barotrauma, which required chest drain insertion. Despite this, he recovered well and was discharged well on postoperative day eight.

Final histology confirmed mixed nodular and infiltrative BCC subtypes, 34 mm in diameter and 13 mm in depth, without perineural or lymphovascular invasion. Three of 25 lymph nodes were positive for metastatic BCC with extranodal extension identified in all three. Following postoperative MDT discussion, the patient was referred for radiation therapy.

3 | CASE 2

A 69-year-old male farmer presented with a 12-year history of a right temporoparietal skin lesion. Punch biopsies from the lesion revealed infiltrative BCC. Past medical history was significant for heavy smoking, left-sided blindness, and uncontrolled hypertension. Upon examination, a large erosive lesion was seen that had completely eroded the right pinna and right lateral skull with exposed middle cranial fossa dura and external auditory canal (Figure 2). He also displayed a right-sided grade 6 House-Brackmann facial palsy and a palpable right level II neck node. Upon staging, a 2.7 cm FDG-avid right middle lobe lesion was discovered in the lung. Radiologically guided biopsy was performed which queried a squamous carcinoma. He subsequently had a right upper and middle lobectomy. Histology from the resection confirmed a completely excised metastatic basal cell carcinoma without nodal disease.

At the MDT meeting, surgical resection of the primary lesion was deemed inoperable, as MRI evaluation identified intracranial extension into dura and brain (Figure 3). Downstaging of the disease with systemic treatment was decided upon so that future surgical intervention might be possible. He rapidly developed multiple subcutaneous deposits over his face and abdomen. Biopsy of an abdominal
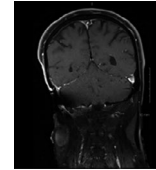
lesion confirmed metastatic BCC, without any basosquamous differentiation. Repeat CT identified multiple lung and liver metastasis. The patient died of multiorgan failure within a number of weeks.

4 | DISCUSSION

Lattes and Kessler[2], in 1951, proposed specific criteria to accurately define the presence of true mBCC; the primary tumor must be BCC, located on the skin, not a mucus membrane, and with direct tumor extension ruled out. Two cases of true mBCC are outlined in this report, one with regional, lymphatic spread and one with hematogenous, distant spread. Histology in both cases was of infiltrative BCC with confirmed metastatic BCC in lymph nodes and lungs, respectively.

As BCCs are most common in the head and neck region, it is understandable that the majority of mBCC cases have been associated with primaries in this region.[3,4] Further risk factors associated with metastasis of BCC have been identified, including tumor size, male gender, long period of evolution, recurrent BCCs, history of radiation therapy, and immunosuppression.[5-8] Perineural invasion is an important consideration, as its presence is associated with a higher risk of recurrence.[9] Histological subtype is also associated with recurrence risk, particularly the morpheaform, sclerosing, infiltrating, micronodular, and metatypical subtypes.[10,11] It is recognized, however, that more than 30% of BCCs have a mixed histological subtype.[11] Interestingly, vascular invasion does not seem to have any impact on prognosis.[9]

Regarding size, the larger the primary tumor, the more likely it will metastasize. Lesions of 5 cm have been

associated with a 25% incidence of metastasis, while tumors >10 cm in diameter have a metastatic incidence of 50%.[6,12] The most common site of metastasis identified is lymph node, followed by lung and bone.[13]

Improved survival has consistently been identified in cases of lymphatic compared with hematogenous spread.[14] In a survival analysis of all published metastatic BCC cases from 1981–2011, McCusker, Basset-Seguin[14] identified median survival times of 24 months for the cases of distant metastasis and 87 months for the cases of regional metastasis. Furthermore, the presence of bone metastasis conferred shorter survival times than cases without bone metastasis, while lung metastasis was associated with significantly longer survival times than cases of non-lung metastasis. This may suggest that survival could be associated with site of metastasis rather than disease burden.[14]

The prognosis for locally advanced, recurrent, and mBCC remains poor, with limited treatment options.[15] These cases should be discussed MDT meetings so that all potential management options are considered and the most appropriate treatment plan pursued. Surgery is the primary therapeutic option, but can also be used as a palliative option, or following a neoadjuvant approach to reduce tumor burden.[16] Radiotherapy can be employed as a primary treatment in patients who are inoperable or as an adjunctive therapy with surgery.[17] It is important to note that rates of local disease control with radiotherapy alone decrease with increasing tumor size and depth of invasion to 80%–85%. In cases of cartilage or bone invasion, local control rates drop as low as 50%–75%.[18]

Two systemic therapies have documented efficacy in locally advanced and mBCC: *vismodegib* and *sonidegib*.[19,20] It is recognized that the Hedgehog signaling (HHS) pathway is aberrantly upregulated in up to 90% of BCCs.[21] The Hedgehog inhibitors *vismodegib* and *sonidegib* block the HHS pathway by binding to the smoothened receptor (SMO; Figure 4). Both drugs are approved by the FDA and EMA for the treatment of patients with locally aggressive BCC or inoperable BCC, while *vismodegib* is approved for metastatic BCC.[22] Adverse events associated with Hedgehog inhibitors are believed to be mechanism-related and include muscle spasms, dysgeusia, weight loss, alopecia, and fatigue.[20] In the Erivance phase-2 clinical trial, *vismodegib* showed a 30% response rate in patients with metastatic BCC and a 43% response rate in patients with locally aggressive BCC.[20] Serious adverse advents were noted in 25% of participants with seven deaths due to adverse events. In the BOLT phase-2 clinical trial, *Sonidegib* showed an acceptable safety profile and 36% response rate with 200 mg daily dosing.[19]

In February of this year, the FDA approved the first immunotherapy to treat patients with advanced BCC, *cemiplimab*. This drug is a monoclonal antibody targeting the PD-1 (Programmed cell death-1) receptor on T and B cells. Treatment has been approved for use in locally aggressive BCC that has not responded to Hedgehog inhibitors or in patients with metastatic BCC in whom Hedgehog inhibitors are not appropriate. A phase-2 clinical trial identified significant antitumor activity by *cemiplimab*, with an objective response to treatment identified in 32% of patients and a duration of treatment response exceeding 1 year, with an acceptable safety profile.[23] There is one further phase-2 clinical trial of immunotherapy for advanced BCC ongoing, investigating the use of *nivolumab* alone or in combination with *ipilimumab* for the treatment of locally aggressive or metastatic BCC (https://clinicaltrials.gov).

Chemotherapy has a limited role in mBCC.[15] While reports of partial and complete response to chemotherapy have been published, there has never been a prospective randomized trial demonstrating therapeutic benefit.[24,25] It is advised to consider chemotherapy as second or third-line treatment in patients who have not responded to, or progressed with, Hedgehog inhibitors.[16]
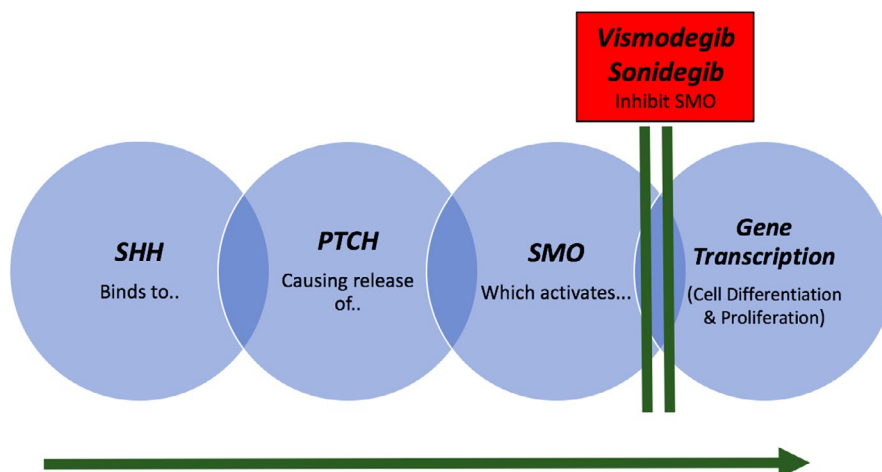

FIGURE 4 *Vismodegib* and *sonidegib* act to inhibit SMO to prevent unregulated cell differentiation and proliferation. SHH, sonic hedgehog ligand; PTCH, patched a transmembrane receptor; SMO, smoothened transmembrane protein

5 | CONCLUSION

Two cases of mBCC are presented here, demonstrating lymphatic and hematogenous spread to the lymph nodes and lungs, respectively. There have been recent advances in the systemic treatment of mBCC such as the use of *vismodigib* and *sonidigib*, with *cemiplimab* recently approved for patients with locally advance or metastatic BCC after Hedgehog inhibitor treatment. Although rare, it is important to recognize the mBCC patient cohort, given the significantly increased morbidity and mortality associated with this disease.

AUTHOR CONTRIBUTIONS
Máire-Caitlín Casey wrote the paper and collected the data. Roisín Pollock and Rachel H Enright collected the data. James Paul O'Neill, Neville Shine, and Paul Sullivan reviewed the manuscript. Fiachra T Martin and Barry O'Sullivan supervised and reviewed the manuscript.

CONSENT
Informed consent was obtained from all individual participants included in this study.

DATA AVAILABILITY STATEMENT
Data available on request from the authors.

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