Title: Metastatic basal cell carcinomas in Gorlin syndrome – a case series and literature review

Abstract

Metastatic basal cell carcinomas (mBCCs) are exceedingly rare, with an estimated variable prevalence rate between 0.003-0.55% among all basal cell carcinomas. Although there are hundreds of reported cases of mBCCs, a dearth of evidence exists of mBCCs in patients with Gorlin syndrome – an autosomal dominant genetic disorder. The purpose of this article is to present the first and largest case series of mBCC in Gorlin patients. A literature review (LR) compares our data with the existing evidence base to underscore the importance of early surveillance, diagnosis and surgical intervention of suspicious lesions as distant metastases significantly reduce survival rates.

Introduction

Basal cell carcinomas (BCCs) are the most commonly occurring skin cancer in the world, comprising approximately 80% of all nonmelanoma skin tumours with a mortality rate <1% .[1] Metastatic basal cell carcinomas (mBCCs) are exceedingly rare, occurring at an estimated variable rate of between 0.003% (28 mBCCs per one million BCCs) - 0.55% (one mBCCs per 182 BCCs) of histologically analysed cases.[2] Gorlin syndrome, also known as basal cell nevus syndrome, is a rare autosomal dominant disorder with a birth incidence of ~1 in 15,000 and prevalence of ~1 in 31,000[3] characterised by multiple BCCs, maxillary keratocysts and other malformations. [4]

Approximately 300 cases of mBCCs are reported in the literature; however, mBCCs associated with Gorlin syndrome are rarely observed. The purpose of this article is to present the single largest retrospective case series of Gorlin syndrome-related mBCCs. Data was collated from a United Kingdom Regional Genetics Centre – that has cared for 260 individuals with Gorlin syndrome. A literature review (LR) has also been conducted to evaluate the current evidence base.

Case 1

A male born in 1965 was diagnosed with mBCC in 2013, aged 47 years old. He had a background of a *de novo* heterozygous *PTCH1* germline, likely pathogenic missense variant type Gorlin syndrome diagnosed in his 20s with multiple BCCs scattered around the eye, lip, nose, cheek and back that had developed progressively. He underwent 24 resections of the right cheek BCC between 1985-2013, followed by photodynamic therapy (PDT). Histology of BCCs varied from nodular and infiltrative BCC of the right ala with a depth of 3.3mm; morphoeic BCC of the right upper lip with a depth of 3.5mm; infiltrative and focally nodular pattern of the R cheek with a depth of 10mm; an infiltrative BCC of lower eyelid; superficial multifocal type BCC from excision of lower back identified in 2011. In 2012, a small swelling on the ramus over the mandible, identified as suspicious of metastasis on MRI, was confirmed on CT to be a lytic erosion of the maxillary sinus. Fine needle aspiration (FNA) of a submandibular node confirmed metastatic spread. In 2013, A PET scan discovered further metastasis to the submandibular gland and lung with a CT-guided biopsy confirming the lung mass to be compatible with metastatic basosquamous carcinoma (BSC) – with eyelid BCC as likely primary. Palliative vismodegib 9 cycles were started in 2015 but stopped the following year as the disease

progressed. The patient underwent a right lower lobectomy for pulmonary metastasis and further excisions of submandibular and zygomatic masses; however, a CT scan in 2016 showed further pulmonary and bone metastases (10/11th rib). Unfortunately, the patient died in 2018, aged 53 years old.

Case 2

A female born in 1974 was diagnosed with mBCC in 2017, aged 43 years old. She had a background of a paternally inherited pathogenic splice donor variant in *PTCH1* Gorlin syndrome, first presented in 1995 with a BCC of her right upper lip that was treated with cryotherapy. In 1999, four BCCs of the face (left cheek and nose) were treated with cryotherapy and surgery. Between 2002-2014 multiple BCCs of the face (nose, both cheeks and upper lip) were treated with cryotherapy and PDT. The patient started vismodegib; however, this was discontinued as the disease progressed. A submandibular lymph node biopsy and MRI head in 2017 confirmed metastasis to the neck nodes and left submandibular gland, respectively, without any evidence of bony destruction. Excision of the lump in her jawline found an infiltrative BCC, 20.5mm thick, invading deep into the submandibular gland. In 2019, nose and lower jaw lesions increased in size, with a CT scan showing multiple soft tissue masses within the left side of the face adjacent to the mandible and nose, extending into orbit and left maxilla. The patient underwent extensive maxillofacial surgery for local disease (invasive tumour of left maxilla, orbit and extensive orocutaenous fistula). In 2023, a PET-positive lesion was found behind ribs and transverse process with core biopsies suggestive of mBCC. Unfortunately, the patient died in October 2023 at age 47 years old.

Case 3

A male born in 1957 was diagnosed with mBCC in 2012, aged 55 years old. He had a background of Gorlin syndrome with a frameshift pathogenic *PTCH1* variant inherited from his father, presented initially in 1992 with multiple BCCs of the right ear, right outer canthus, right upper lip, left cheek and right nostril. The BCCs underwent a series of excisions over the next eight years, with new BCCs of the temple, scalp, and forehead excised. Between 2000-2011, the patient underwent multiple PDT sessions and excisions of BCCs located in the head, neck, arm and trunk. In 2006, nodular BCCs were excised from multiple BCCs on the scalp. Nodular-type BCCs were also found on the right temple and left forehead, with infiltrative identified histologically from the left arm. The patient was seen in 2010 with further excisions of the left side of the forehead with an MRI in August, identifying multifocal disease with plaque-like extension of disease extending to the periosteum of the skull.

The lesions from his left and right mastoids and the right temple had been reported as incompletely excised BCCs. As per the multidisciplinary team meeting, those from the upper lip and left side of the nose had been completely excised, with further surgery not advised, as clear margins would not be achieved. However, a pedunculated back lesion was excised: nodular BCC with 4.5mm thickness. In 2012, he had a very large deep ulcer affecting the left temporal bone, including the mastoid, and progressed to the parietal scalp. He also had a large deep ulcer in the right preauricular region involving the parotid and most of his lower ear. Furthermore, metastatic disease was identified in

the femur (and spine) after a pathological hip fracture. The patient unfortunately died in early 2013 at the age of 55 years old. This was prior to vismodegib being available in the UK.

Discussion

We have presented three cases of mBCC in patients with Gorlin syndrome. MBCC is defined as primary BCCs disseminating to non-contiguous sites coupled with histological similarity. Gorlin syndrome has a prevalence of 1 in 30,827 people according to a population study in the Northwest of England[3], with Rahbari et al.[5] finding that 2% of patients <45 years old with BCCs have Gorlin syndrome. BCCs in Gorlin syndrome arise most commonly between puberty and 35 years of age[6] secondary to mutations in the *PTCH1* gene (or less commonly *SUFU*), and are transmitted in an autosomal dominant fashion with high penetrance and variable expressivity.[7] Lattes and Kessler[8] outlined the criteria to diagnose mBCCs: (i) both primary lesion or metastatic lesion cannot predominantly comprise squamous cells; (ii) primary lesion cannot originate from salivary glands or mucous membranes and (iii) metastatic lesions must distinct from the primary lesion.

A LR of English language journals with extractable data via PubMed, MEDLINE, Embase and Scopus was conducted, identifying only 11 cases of mBCC in Gorlin syndrome between 1975 and 2016 *(Table 1).* All studies were individual case reports, rendering our study the first and, therefore, the largest case series of mBCC in Gorlin syndrome. The age range of the study was 49-56 years old compared to 46-66 years old in the LR. The median age of diagnosis of mBCC was 47 years in our case series compared with 52 years in the LR. Moreover, our case series found bone to be the most common site of metastasis (all three cases) compared with regional lymph nodes in the LR.

Histologically, BCCs can be categorised as indolent (nodular and superficial) or aggressive (morpheaform, infiltrating, and micronodular).[9] The most common histological subtype in our three cases was nodular and infiltrative. Our cases demonstrate frequently mixed histology compared to a largely unknown histological type in data extracted from the LR.

Author (s)	Year	Age	Sex	Location of primary	Histology of primary	Location of metastasis
Murphy et al	1975	46	M	Head	Basosquamous	Sacrum
Winkler et al.	1987	48	M	Head	Unknown	Heart, pleura and diaphragm
Bilir et al	2014	66	M	Head	Unknown	Ethmoid sinus and lung
Lamon et al	2010	54	M	Head and neck	Unknown	Vertebrae, chest wall, parietal bone, maxilla
Ramon-Faba et al.	1997	47	M	Head and neck	Unknown	Lung (suspicion as patient refused examination)
Zhu et al.	2014	'In his 50s'	M	Cervical lymph nodes	Unknown	Lung

Goldberg et al.	1977	58	F	Cervical lymph nodes	Unknown	Jugulodigastric lymph node
Moser et al	2011	64	F	Cervical lymph nodes	Adenoid	Regional lymph nodes
Keriya et al	2004	63	F	Trunk	Basosquamous	Sacrum, hips, proximal femurs, iliac bones
Stewart et al	2016	51	M	Trunk	Unknown	Axillar lymph node and vertebra
Tawfik et al.	1999	48	M	Left lower extremity, left inguinal skin	Unknown	Iliac and para-aortic lymph nodes, T4 vertebrae

Table 1 – Literature review of reported cases of mBCC in patients with Gorlin syndrome

As evidenced in our case series, management of mBCC in Gorlin syndrome can be very challenging, with surgical excision remaining the gold standard and palliative radiotherapy, for bone metastases, considered in advanced cases. Prognosis depends on whether metastases are regional or distant, as clinical course and outcome vary. Our case series demonstrates that the length of survival was shorter when patients developed distant metastases to the bone, for example, compared to regional metastases, e.g., lymph nodes. A study of 100 patients with mBCC, without Gorlin syndrome, found median survival post mBCC diagnosis to be 54 months, with shorter survival of 24 months in distant metastases compared to 87 months in regional metastases.[10] Concerning lifetime risk, we have shown that 3/260 (1.15%) Gorlin syndrome patients have developed mBCC. However, based on three cases, it is not possible to assess lifetime risk accurately because many patients are still below the ages expected for mBCC development; however, an estimate of lifetime risk would be >2%. Given the number of BCCs developed by Gorlin patients, it is likely that the risk of transformation of BCCs in Gorlin syndrome is not higher than in the general population. It is worth noting that one of our cases and two cases from the LR found primary lesions of BSC type. BSCs have a metastatic potential closer to that of squamous cell carcinomas (SCCs). Limited data suggests that vismodegib may exacerbate SCC progression however more robust studies conclude no evidence of increased risk.[11] Although hedgehog inhibitors such as vismodegib and sonidegib have been proven effective in treating Gorlin patients, there is limited high-quality data with heterogeneous trials rendering comparison challenging.

Notably, a retrospective study by Murgia et al.[12] reported that sonidegib exhibited superior efficacy and safety compared to vismodegib in Gorlin patients with BCCs. Head-to-head studies comparing both oral and topical HHIs are required to strengthen the evidence base.[13]

Conclusion

Our case series expands the limited evidence base on the clinical course and outcomes for patients with mBCC in Gorlin syndrome, underscoring the importance of surveillance, early diagnosis and careful excision to ensure negative margins. Further research is required to better prognosticate mBCC in Gorlin patients along with more effective and better-tolerated therapies.

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