Review Article

Metastatic basal cell carcinoma: a review of six cases

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Abstract: Basal cell carcinomas (BCCs) are locally invasive skin neoplasms of cells in the epidermal basal layer. BCC metastasis remains a rare phenomenon, although such an event is associated with high morbidity and mortality. It has been suggested that certain features may be used to predict metastatic spread, including histological subtype, size, and perineural or lymphovascular invasion. We reviewed cases of metastatic BCC seen at Royal North Shore Hospital over a 16 year period. Pathology reports and specimens of both the primaries and metastatic lesions were obtained, and reviewed by an independent pathologist for second opinion on histopathology and confirmation of metastatic BCC. Six cases were found and reviewed (age 60±12, 17% F). Three of the six cases involved primaries located in the head and neck. The most common primary histological subtypes were morpheaform & infiltrative. This was accompanied by perineural and/or lymphovascular invasion in two cases. Three of the cases demonstrated large primaries of greater than 50 mm in diameter. One was found to have squamous differentiation in both the primaries and metastases. The most common site of metastases was the lungs, occurring in three of the cases, whilst other metastatic locations included bone and lymph nodes. We propose that primary BCCs with suspicious clinical/histopathological features be monitored closely, especially those from the head and neck region. We also propose further consideration of immunohistochemical markers as potential metastatic predictors.

Keywords: Carcinoma; basal cell; neoplasm metastasis; biomarkers

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Introduction

Basal cell carcinomas (BCCs) are locally invasive skin neoplasms of cells in the epidermal basal layer, representing 70% of all skin cancers in Australia, with a 30% lifetime risk of development (1). Whilst BCC metastasis has a documented incidence of only 0.0028% to 0.5% (2,3), there is significant morbidity and mortality associated with such an event. The most likely locations of metastasis are to the lungs, bone and lymph nodes, via both lymphatic and hematogenous spread (2,4). The majority of metastasizing BCCs originate in the head and neck, with evidence that over 65% of BCCs arise from the face alone (5).

Although metastatic BCCs are a rare occurrence, there has been evidence to suggest that there are certain features that may be used to predict metastatic spread. These include histological subtype, size, and perineural or lymphovascular invasion. Here, we aim to analyse features of primary and metastatic BCCs, and identify possible predictors of spread in the primary lesions.

Methods

We reviewed six cases of metastatic BCC, which were seen in our institution (Royal North Shore Hospital, Sydney, Australia) between the years 2000 and 2016. The pathology reports of the original tumours were obtained and, where possible, the pathological slides from the primary tumour were reviewed. The pathological slides of all metastases were also independently reviewed by a

second subspecialist surgical pathologist and, if required, additional immunohistochemistry (p53, SMA, BCL2, Ki67) was performed to confirm the diagnosis of metastatic BCC. The patients' histories, including age, gender and relevant comorbidities, especially immunosuppressive risk factors (history of cancer, poorly controlled diabetes and immunosuppressive medications) were also reviewed, as was the time between identification of primary BCC and detection of metastasis.

Cases

Case 1

A 66-year-old female first noticed a BCC to the left side of the nose in 1990. This was managed with cryotherapy at the time. A biopsy taken one year later showed ongoing disease, but she delayed further treatment due to social reasons and was then lost to follow up. In 2007, she presented with a very large, deeply infiltrative rodent ulcer of the left half of the face, obliterating the anterior eye, medial and lateral canthus, supraorbital skin, nasolabial fold and entire medial aspect of the nose. This lesion was found to virtually obliterate the globe, tracking inferiorly through the posterior nasal structures and maxilla to the hard palate. Histological examination revealed an infiltrative BCC with focal areas of necrosis, focal squamous differentiation, and perineural involvement. This was managed with surgical excision and radiotherapy to the nose and face. Three years later, a PET scan & MRI demonstrated two nodules in the lower lobe of the right lung. Core biopsy confirmed metastatic BCC with similar morphology to that seen in the primary. This was managed with pulmonary radiotherapy and targeted therapy, utilizing a novel hedgehog pathway inhibitor, to which a partial response was obtained.

Case 2

A 68-year-old male with a history of multiple solar elastoses initially presented with an invasive BCC of the back, of nodular/morpheaform subtype, infiltrating into the lower third of the reticular dermis. It demonstrated small nests of epithelial cells within focally sclerotic stroma. There was no angiolymphatic or perineural invasion identified. This was removed by surgical excision. Two years later, a CT lumbar spine revealed ill-defined, mixed lytic and sclerotic densities in the posterior aspect of the right ilium, first sacral segment and bilateral sacral ala. A core biopsy confirmed metastatic BCC demonstrating similar morphology to that seen in the primary tumour. Oval to spindle shaped nuclei were found with some palisading around nests & acinar spaces within nests. It showed a partial response to radiotherapy and targeted therapy with a hedgehog pathway inhibitor.

Case 3

A 79-year-old male presented with a lesion of the right forehead, exhibiting an irregular area of nodular thickening in the centre. Histological analysis revealed it to be a morphoeic BCC, with infiltration through the dermis and into the subcutis. There was no lymphovascular invasion or perineural spread. Over the following decade, he returned with multiple localized BCCs, including an infiltrative BCC of the right parotid region, a nodular & infiltrative BCC of the left back and an infiltrative BCC of the right cheek. Subsequent to this, he re-presented with a suspicious node in the right submandibular region. A core biopsy confirmed BCC with morphology similar to that seen previously, but none associated in soft tissue. Although it was difficult to classify and immunohistochemistry for BerEP4 and BCL2 was ambiguous, on review it was thought more likely to represent metastatic BCC than a new primary cutaneous BCC.

Case 4

A 56-year-old man presented with an ulcerated lesion of the right ear. Histology demonstrated a nodular BCC that infiltrated into the margin of the meatus, not involving cartilage. However, the excision margins appeared incomplete, and a revision was performed later that year. The re-excised lesion demonstrated similar pathology, but appeared incompletely excised once again. The patient was unfortunately lost to follow-up, until 3 years later when he returned with a recurrence of the BCC. He was assessed and scheduled for temporal bone resection, but did not follow-up as he was not keen on surgery. Eight years later, the patient presented with a large fungating mass of the right ear. MRI showed marked involvement of the right ear and petrous temporal bone, including the mastoid and zygoma. The patient underwent right ear and temporal bone excision and petrous apicectomy, this time with clear margins. Histological analysis showed an extensive BCC with ulceration, of morpheaform & infiltrative morphology. It was 30 mm deep, extending to involve the deep fascia, cartilage and parotid. It had widespread necrosis, and

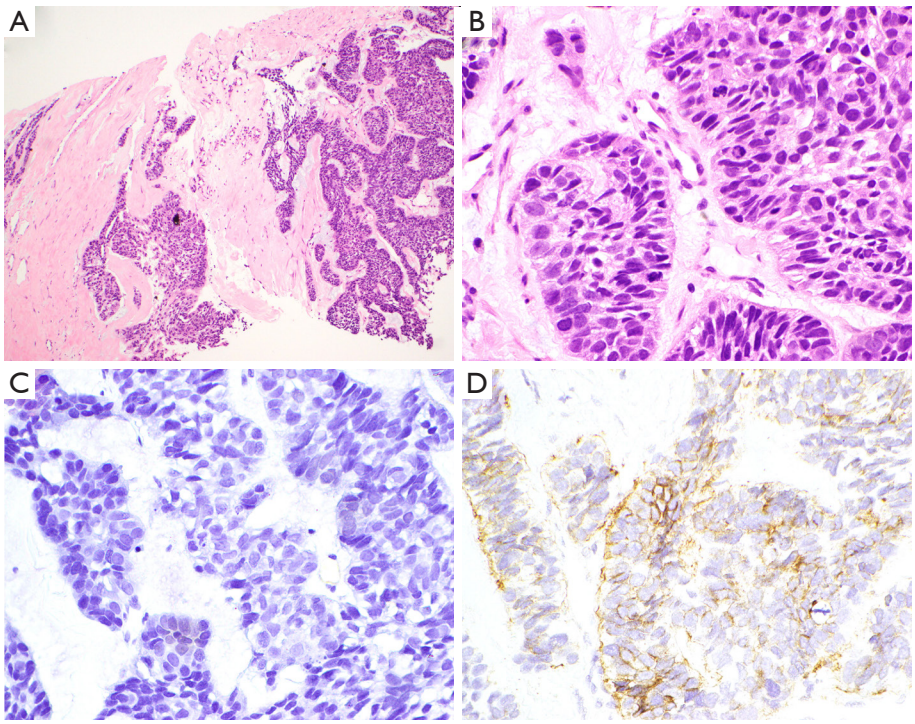

Figure 1 Photomicrographs of the core biopsy of the lung metastasis from patient 5. Both the morphology and immunohistochemical profile are very typical for basal cell carcinoma and are identical to the primary tumour. (A,B) Haematoxylin and eosin demonstrating typical basaloid morphology with a peripheral nuclear palisade; (C) immunohistochemistry for EMA is negative; (D) immunohistochemistry for BerEP4 is positive. Original magnifications: A, 100× (H&E); B, 600× (H&E); C, 600× (EMA); D, 600× (BerEP4).

demonstrated perineural invasion of the facial nerve, but no blood vessel invasion. There was no squamous dysplasia. A PET scan at the time had demonstrated not only the large FDG-avid lesion of the right ear and temporal bone, but also increased uptake at multiple spinal levels and the 8th right rib. Core biopsy of the bone confirmed metastatic BCC with extensive necrosis. The patient underwent radiotherapy to the parotid and base of skull & neck following surgical excision, with palliative radiotherapy to the spine.

Case 5

A 52-year-old male flight attendant presented for review with a lesion to the left anterior chest wall with a centrally ulcerated nodule. Initially, this was thought to be a tropical ulcer secondary to an insect bite sustained on a visit to India one month prior. However, it exhibited rapid growth with purulent ooze. This was found to be an infiltrating BCC invading into the subcutis. There was no perineural or lymphovascular invasion seen. Two years later, he was found to have multiple pulmonary nodules, confirmed on PET scan. Core biopsy demonstrated metastatic BCC with similar morphology to that seen in the primary tumour. Photomicrographs of the lung biopsy are shown in *Figure 1*. The patient was subsequently lost to follow-up.

Case 6

A 42-year-old male presented with a BCC of the left axilla with some minor metatypical (squamoid) differentiation. This was managed by excision of the axillary lesion and lymph node clearance (0/19 nodes involved). In the subsequent years, he developed further BCCs that were managed surgically, including a multifocal superficial BCC of the right outer canthus, an upper back invasive papulonodular BCC and a recurrence of the original axillary BCC. Although his clinical course was uncomplicated, he re-presented eight years later with multiple lung nodules and a parasternal mass on CT chest. Biopsies of these masses confirmed metastatic BCC with similar morphology to the upper back cutaneous lesion. Further management

Table 1 A summary of the clinical and histopathological features of each case

Case	Age	Site of primary	Histological subtype of primary	Suspected duration of lesion (years)	Site of metastasis	Presence of squamous differentiation in metastasis	Perineural and/or lymphovascular invasion in primary	Size of primary (length × width × depth, mm)	Number of excisions required	Recurrence
1	66	Face	Infiltrative, with squamous differentiation	17	Lung	Present	Perineural	55×40×40	1	0
2	68	Back	Nodular/ morpheaform	2	Sacrum & ilium	Absent	Absent	20×15×2.1	1	0
3	79	Forehead	Morphoeic BCC	7	Submandibular	Absent	Absent	10×11×7.5	1	0
4	56	Ear	Morpheaform & infiltrative	11	Spine & ribs	Absent	Perineural	45×35×30	3	2
5	52	Chest wall	Infiltrating	2	Lung	Absent	Absent	85×40×13	1	0
6	42	Back	Papulonodular	8	Lung	Present	Absent	Unavailable	1	0

BCC, basal cell carcinoma.

was suspended, as the patient was lost to follow-up.

A comparison of the clinical and histological features of the cases is presented in *Table 1*.

Discussion

Although BCC represents the most common cutaneous malignancy, metastatic BCC remains a rare phenomenon. It has been postulated that certain clinical or histopathological features of BCCs may serve as indicators for the propensity to metastasize. Traditionally, BCCs have been divided into two categories: indolent and aggressive; the indolent variants comprising nodular and superficial BCCs, and the aggressive ones comprising morpheaform, infiltrating and micronodular subtypes (6). The most common clinical variant of BCCs is the nodular BCC, with histopathology characterised by discrete nests of basaloid cells in the dermis, with peritumoral retraction from a stroma that exhibits myxoid change, and peripheral palisading of cells. Single cell necrosis, plump fibroblasts and a high mitotic rate are uncommon (6,7). In contrast, the more aggressive morpheaform variant consists of thick columns of basaloid cells that extend into a densely collagenous stroma containing plump fibroblasts. There is more individual cell necrosis and mitotic activity, and a higher propensity for invasion into the reticular dermis (7). With increasing aggressiveness, as seen in the infiltrative subtype, there is marked stromal fibrosis with dense collagen bundles, and abundant proplastic fibroblasts. These more aggressive subtypes present an increased risk of invasion into adjacent skin layers, as well as perineural invasion. Despite this traditional classification, up to one third may exhibit an admixture of variants.

The most common primary histological subtypes in the six cases reviewed were morpheaform & infiltrative, with mixed histology frequently present. Evidently, aggressive histological subtypes were predominant in the BCC primaries. This was accompanied by perineural and/or lymphovascular invasion in two of the cases. This lends support to the traditional thinking that BCCs of the more aggressive subtypes are more likely to metastasize (4), and possibly also those with perineural spread and blood vessel invasion (2,4,8).

It has also been suggested that larger BCCs, and BCCs of a higher TNM stage (> T2) are also more likely to metastasize (5). A review of 238 cases by Snow *et al.* suggested that tumours larger than 30 mm in diameter had a 2% incidence of metastasis, compared to the overall

rate of <1% for morpheaform BCCs. Furthermore, the data demonstrated that 80% of metastatic BCCs arose from tumours larger than 50 mm in diameter. Our cases reviewed here showed metastatic BCCs arising from large lesions (greater than approximately 50 mm in diameter) in 3 of the cases (with unavailable records in one case); the largest lesion being 85 mm × 40 mm. The other 2 cases demonstrated smaller primaries from around 15–25 mm in diameter. Of interest was that the size of the lesion did not necessarily predict recurrence at the same site, with the majority being cleared by a single excision with or without adjuvant radiotherapy.

A certain type of BCC exhibits a combination of both BCC and SCC features – known as basosquamous carcinoma or metatypical BCC. It is histologically characterized by infiltrating jagged strands of tumour cells, with relatively uniform nuclei and peripheral palisading (although this is not always seen) (8,9). Within these nests, some cells exhibit a loss of basaloid differentiation and a progression to squamous differentiation, characterized by a more eosinophilic cytoplasm and keratinization. Basosquamous carcinomas exhibit more atypical mitoses, cell pleomorphism and nuclear hyperchromatism (8), and are clinically more locally invasive. The question of what pathological features should define a basosquamous carcinoma, and whether basosquamous carcinomas truly are a variant of BCCs, or whether they should be classified as a separate lesion with different behaviour has been a topic of controversy in the past (10,11). It has been presumed that BCCs with elements of squamous differentiation are more likely to metastasize, but some studies have observed that there is often very little squamous differentiation in the histology of any of the primaries (2), suggesting that metastatic potential may not be solely predicted by squamous differentiation. Of our six cases reviewed, one was found to have squamous differentiation in both the primaries and metastases. One other case was noted to have an axillary BCC primary with squamous differentiation, but was the unlikely primary lesion giving rise to a lung metastasis, as the morphology of the lung lesion more resembled that of a prior papulonodular BCC primary of the back. Several studies have examined the behaviour of basosquamous carcinomas, and found them to be more aggressive with a higher rate of recurrence when compared with BCCs lacking metatypical features (10,12-14). As such, although the majority of metastatic BCCs do not appear to arise from basosquamous types, the diagnosis of a BCC with squamous differentiation on original biopsy carries both prognostic and management implications. Complete surgical excision with negative margins, with consideration of radiotherapy if this cannot be achieved, and ongoing follow-up for recurrence are essential to the management strategy of basosquamous carcinomas. Although there has been no consensus on the appropriate excision margins for basosquamous carcinomas, one study suggested a 3–5 mm margin for head and neck lesions, and 5–10 mm margins at other areas (although a 10% rate of recurrence was still found with these margins) (12).

Other clinical features which have been thought to be risk factors for metastases include: male gender (with a male:female ratio of 2:1) (2), and location in the head and neck region (2). Previous authors have suggested that the frequency of metastasis from the head and neck region may be associated with the thin skin of the scalp and high concentration of large-calibre vessels (15). Five out of the six cases reviewed involved male patients, and three of the six involved BCCs originating from head and neck primaries, including the face, forehead and ear (although our institution as a tertiary head and neck referral centre may have been a source of bias). Of particular interest was the propensity for metastasis to the lungs, a well-documented phenomenon of metastatic BCCs which drastically reduces survival in comparison to metastases limited to lymph nodes (16-19). It was also noted that local relapse was observed in only one of the cases that received treatment.

There have been several immunohistochemical markers which have been identified as possible indicators of BCC metastatic potential. Of these, the tumour suppressor p53 has arguably been the most widely researched given the evidence that chronic sun exposure is an important risk factor to p53 mutation and carcinogenesis (20). Other markers that have been examined include D2–40 (a monoclonal antibody classic to fibrous histiocytomas), Ki-67 (a marker of cell proliferation) (21,22), the anti-apoptotic gene Bcl-2 (18,23,24), and smooth muscle actin (SMA).

Most studies regarding p53 in BCCs have found a significant upregulation of p53 in aggressive variants, compared with non-aggressive (25-28). However, whether this correlates to increased metastatic potential is not clear (18). Further studies have examined the role of Ki-67 with equivocal results: whilst studies concur on the role of Ki-67 in proliferative activity, the correlation between aggressive histological subtypes and Ki-67 expression is less clear (22,29). Furthermore, there is no defined association between Ki-67 and tumour size, which has been shown to be a predictor of metastatic potential (5,22). Although

the majority of BCCs are positive for Bcl-2, there is no clear link between Bcl-2 and tumour aggressiveness or potential for invasion (18,23,24,28). Perhaps the newest immunohistochemical marker with greatest potential to predict metastasis is alpha-SMA: typically used as a marker of myofibroblasts, and in the detection of pancreatic cancer. A number of studies have found that aggressive BCCs tend to express alpha SMA in the stroma, whilst non-aggressive BCCs express it in tumour cells themselves (30-32).

At the time of writing it appears that the primary role of immunohistochemistry is to confirm the diagnosis of BCC, particularly in the setting of metastasis, and exclude other more aggressive lesions in the differential diagnosis, including melanoma and Merkel cell carcinoma; and there are no validated markers which predict an increased risk of metastasis.

Conclusions

Our review of six cases of metastatic BCCs confirms that metastasis appears most likely in large BCCs, BCCs with vascular space invasion or perineural spread and tumours with some metatypical squamoid differentiation. This has implications for treatment and prognosis, requiring careful caution at first presentation and diligent excision to ensure negative margins. In support of previous data, the primaries of metastatic BCCs preferentially arise from the head and neck region, which should further promote careful surveillance from initial presentation. Whilst males tend to predominate, this may just reflect the higher incidence of primary BCCs in males.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ajo.2018.09.05). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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