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Case report

An unusual case of basal cell carcinoma of the vulva with lung metastases

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ABSTRACT

Basal cell carcinoma (BCC) is the most common non-melanomatous skin cancer, typically arising in sun-exposed areas such as the head and neck. Defective signaling through the Hedgehog (HH) signaling pathway forms the molecular basis for BCC. Surgery remains the mainstay of treatment. Basal cell carcinoma of the genital tract is rare as is metastatic BCC. We report a case of metastatic BCC in a young woman with previously resected vulval BCC presenting six years later with inguinal nodal recurrence and multiple lung metastases.

1. Introduction

Basal cell carcinomas (BCC) are the most common cutaneous neoplasms, representing 80% of all non-melanoma skin cancers worldwide [1]. The first clinical description of BCC was provided by the Irish surgeon Arthur Jacob, who described findings of extensive rodent ulcers on the faces of three patients [2].

Basal cell carcinoma of the genitalia is a rare entity, and has been described only in isolated case reports. The vulva, as a primary site for BCC, has been observed in <1% of all BCCs and represents <5% of all vulval cancers [3]. Metastatic spread from this site is exceedingly rare. Prognosis in patients with metastatic spread is generally poor, with systemic chemotherapy failing to significantly impact high morbidity and mortality rates.

However advances in the understanding of the molecular pathogenesis of this cancer type has resulted in the development of novel targeted therapies, such as smoothened (SMO) inhibitors (Hedgehog inhibitors), which have had dramatic effects on progression free survival [4,5]. Vismodegib is a SMO antagonist, and was recently approved for the treatment of advanced BCC. Vismodegib acts by selectively inhibiting the Hedgehog (HH) signaling pathway, mutations in which lead to aberrant activation, ultimately resulting in the growth and development of these malignancies.

We present a case of recurrent BCC of the vulva with lung metastases. To our knowledge there has been only one similar case reported in the literature [6].

2. Case report

A 51 year old female was diagnosed with BCC of the vulva in 2010 after presenting with an exophytic, papillomatous, erythematous lesion on the left side of her vulva that had been present for several years. A CT abdomen pelvis at that time showed an asymmetric soft tissue mass in the left vulval region. The lesion was excised and pathology was consistent with a basal cell carcinoma, nodular subtype, with areas of squamoid differentiation. Margins were focally positive but further resection was technically not possible due to the location and the patient's wishes.

She remained on surveillance with 6 monthly visits for gynaecological assessments however in later years was not compliant with follow up visits. In year six post resection she presented with lymphedema, cellulitis of her right thigh and palpable left inguinal lymph nodes.

A chest X-ray showed multiple bilateral pulmonary nodules. A CT thorax, abdomen and pelvis (TAP) was performed and was remarkable for a right inguinal node measuring 25 mm and multiple pulmonary nodules measuring up to 14 mm (Fig. 1). An ultrasound guided biopsy of the right inguinal node showed BCC consistent with original pathology (Fig. 2). The tumour cells stained positive for BerEP4 and CK5/6 expression was patchy and weak, with stronger expression in areas of squamoid differentiation. The tumour was negative for p16,

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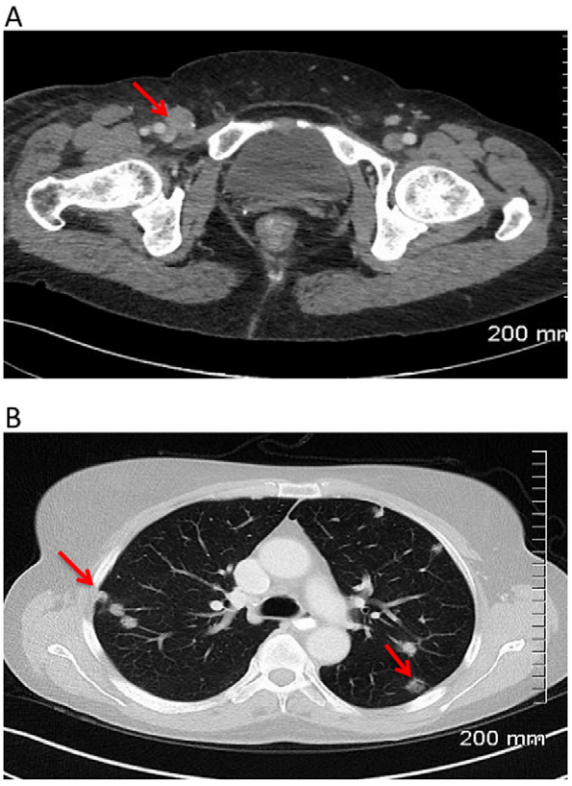

Fig. 1. (A) Axial contrast enhanced CT through the lower pelvis demonstrates a 2.5 cm distal right external iliac lymph node. (B) Axial CT image through the mid thorax on lung windows demonstrates multiple rounded nodules, imaging features consistent with pulmonary metastases.

chromogranin, synaptophysin, and TTF-1. Proliferation index as assessed by MIB1 expression was ~40%. A wedge resection of a lung lesion was also consistent with BCC with squamoid differentiation. Tumour cells showed patchy expression of BerEP4, with strong positive staining for p63, CK5/6 and p16.

The patient initiated treatment with vismodegib at a dose of 150 mg daily. She was seen at two weekly intervals for assessment. She reported muscle cramps (grade 2 as per NCI CTCAE v4), alopecia (grade 2) dysgeusia (grade 2), anorexia (grade 2). A restaging scan after three months showed a decrease in the size of her inguinal adenopathy as well as a decrease in the size and number of pulmonary nodules (Fig. 3). Treatment was continued for a further two months however it was then discontinued due to toxicity (loss of taste and alopecia). A restaging scan at 6 months shows stable disease and the patient remains asymptomatic.

3. Discussion

Basal cell carcinoma is the most common skin malignancy accounting for about 80% of all non-melanoma skin cancers. It originates from the basal layer of the epidermis [1]. Australia has the highest rate of BCC worldwide, with certain regions reporting an incidence of 2% per year [1]. Recent data from the National Cancer Registry of Ireland reports over 6300 cases of invasive skin cancer diagnosed per year, with 68% (4284 cases) representing BCC and 30% (1890 cases) representing squamous cell carcinomas (SCC) [7].

Basal cell carcinoma is most frequently observed in fair skinned individuals and 90% tend to arise in sun-exposed areas such as the head and neck region [1]. Additional risk factors include radiation and certain genetic syndromes such as Xeroderma pigmentosum, Rombo Syndrome and Nevoid BCC syndrome (NBCCS) [1].

Clinical presentation may vary, however three main types appear to predominate. The first type is a nodulo-ulcerative lesion, which may manifest as a deep ulcer with raised margins. This represents the classical form of BCC [1]. The second type is described as a more superficial, flat lesion with a waxy surface that is macular and slightly erythematous. A third type may appear as a polypoid tumour with an intact surface.

Although rare, BCCs may arise from unusual sites such as axilla, perianal region and genitalia [1,3]. The genitalia in particular as a primary site of BCC is very rare, accounting for <1% of cases [8,9]. To our knowledge there are approximately 250 cases reported in scientific literature [3,8,9].

The most common presenting symptoms include vulvar pain or swelling, ulceration, bleeding, pain and pruritus [3]. Treatment for BCC is surgical excision which is well established as the gold standard in local management. Prognosis is excellent with 5 year cure rates of over 99% for primary tumours not involving the head [10].

While BCC is typically a slow-growing, locally invasive tumour, there is the potential for distant spread. Metastasis is a rare phenomenon however with rates ranging from 0.0028% (28 cases per 1,000,000 BCC diagnoses) to 0.5% [11]. The median interval between appearance of the primary tumour and metastasis is 9 years [12]. Prognosis for metastatic BCC is poor, with an average survival time of 8 months, although this extends to 3.5 years in those patients with lymph node only disease [13].

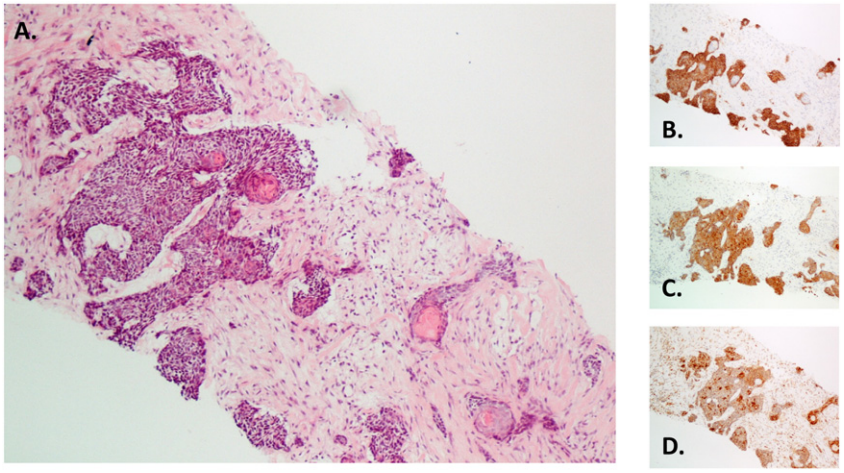

Fig. 2. Right-sided groin lymph node core biopsy. Figure shows hematoxylin and eosin stain of tumour at 200× (A) and immunohistochemistry for BerEP4 (B) CK5/6 (C) and p16 (D).

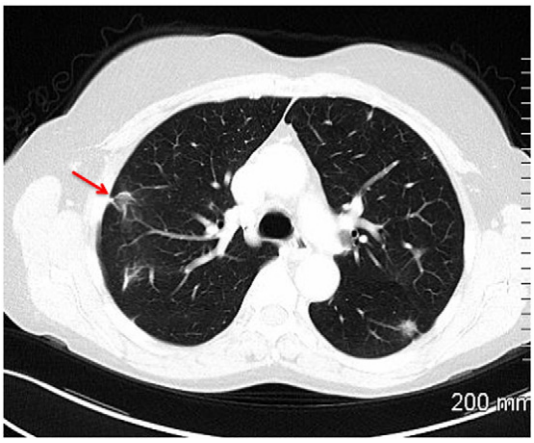

Fig. 3. Axial CT image through the mid thorax acquired five months later demonstrates a good response to treatment. Many lesions have disappeared while others have decreased in size.

The first case of metastatic BCC was reported by Beadles in 1894, describing a 46-year-old male presenting with an extensive rodent ulcer on his face that metastasized to a sub-maxillary lymph node [14]. Since then there have been almost 300 reported cases in the literature [3,8,9].

In 1951, diagnostic criteria for mBCC were proposed by Lattes and Kessler, who stated that three criteria must be met in order to be considered metastatic BCC [15]. These criteria are:

- Primary tumour originating in the epidermis
- Tumour spread to a distant site, not local extension
- Both primary and metastatic tumours have the histological appearance of BCC but not solely squamous cell histology

There have been extensive efforts to determine the clinical risk factors for metastasis however they have not been fully elucidated. Male gender, tumour size >2 cm, location on the head and neck, previous radiation therapy, fair skin, incomplete surgical resection, and increased depth of tumour with infiltrative histology have all been proposed as risk factors for recurrence and metastasis [1].

The lung as a site of metastasis is rare, however almost 50 such cases have been described in the literature to date [8,12]. In the present case, metastasis to the lung was observed as a rare site of recurrence six years after an initial diagnosis of vulvar BCC. To our knowledge only one previous case of vulvar BCC with lung metastasis has been described [6].

There are currently no established guidelines for the management of metastatic BCC [13]. Several chemotherapeutic agents including 5-FU, cisplatin, vincristine, etoposide, bleomycin, cyclophosphamide, methotrexate, and doxorubicin have been studied however the response rates have been poor.

Recently increased understanding of these tumours at a molecular level has resulted in the development of targeted treatments and has stimulated research into BCC. Basal cell carcinogenesis is largely due to inappropriate activation of the Hedgehog (HH) signaling pathway, and has been shown to be associated with both sporadic and familial cases of BCC.

Targeting the HH signaling pathway in cancer therapeutics is an active field in drug development. Vismodegib is an oral, selective inhibitor of the HH signaling pathway, and acts as a SMO antagonist. It was approved by the US Food and Drug Administration for treating BCC recurring after surgery or presenting as locally advanced or metastatic. The approval of vismodegib was based on the results of a phase I study showing durable responses [5]. More recently results from a phase II single-arm multicentre trial of vismodegib in mBCC showed a 33.3% response rate and a median progression-free survival of 9.5 months [4]. However almost half of these patients discontinued the drug due to side effects. Grade 3 or 4 adverse events included muscle cramps (4%), decreased appetite (3%) and fatigue (4%). Any grade dysguesia and alopecia were recorded in 51 and 63% of patient respectively. Managing these side effects or developing similar agents with better toxicity profiles so patients can remain on treatment will be a challenge for the future.

Determining whether to continue on treatment until progression or interrupt it when best response is achieved is an area of active research. Recently Sonidegib, another oral, selective smoothened (SMO) inhibitor, has been approved by the FDA [16]. Combination treatments may be required to overcome resistance.

4. Conclusion

Localised BCC is a common cutaneous malignancy with a favourable prognosis. Identifying and excising these lesions at an early stage is fundamental and can only be achieved through patient and physician education.

Metastatic BCC is a rare entity with high morbidity and mortality. Physicians should be aware of the potential for distant spread, and consider it as a possibility in particular in patients presenting with locally advanced disease.

Vismodegib, an oral agent targeting SMO essential for the regulation of the Hedgehog signaling pathway, is the first agent to receive FDA approval for the treatment with locally advanced/metastatic melanoma. This offers the first important treatment option for these patients. Future research will focus on identifying the mechanisms of resistance to the drug, the optimal sequencing and scheduling of the drug, understanding the biological causes of the unusual toxicities experienced by patients taking this medication and the development of newer agents with better toxicity profiles.

Conflict of interest

The authors declare that there is no conflict of interests.

Informed consent

Informed consent was obtained prior to article submission.

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