SHORT COMMUNICATION

Clinical Clearance Following Improvement of Histologic Subtype of Basal Cell Carcinoma with Sonidegib

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Basal cell carcinoma (BCC) is the most common malignancy worldwide (1, 2). The histology of BCC is classified as either aggressive or non-aggressive (1, 3). Complex BCC tumours, such as metastatic and locally advanced BCC, are associated with substantial tissue invasion and morbidity (1, 3). Sonidegib, a hedgehog pathway inhibitor, is used in the treatment of complex BCC unsuitable for curative surgery or radiotherapy. Previous studies have demonstrated the efficacy of sonidegib in treating complex BCC and controlling tumour progression (4–7). We report here a novel case of complete clinical clearance of BCC with sonidegib, following improvement of its histologic subtype from aggressive to non-aggressive BCC.

CASE REPORT

A 68-year-old man presented with an ulcerated BCC of the right nasal ala measuring 20×12 mm (**Fig. 1**a). A biopsy of the tumour (Fig. 1b) reported BCC with a nodular (non-aggressive) and infiltrative (aggressive) growth pattern ramifying throughout the papillary and reticular dermis, with a thickness of approximately 2 mm at the base of the erosion and no perineural invasion. Mohs surgery/standard excision with flap or graft reconstruction was discussed, and ultimately rejected by the patient due to operative/postoperative downtime and financial costs. Similarly, due to the patient's occupation as a farmer and his remote geographical location, radiotherapy was also declined on the basis of an unfavourable tumour site and extensive and frequent travel to treatment centres. Sonidegib, an oral hedgehog pathway inhibitor (HHI) approved in Australia to treat adults with metastatic disease or locally advanced BCC (laBCC) unsuitable for curative surgery or radiotherapy (8), was chosen as the preferred option considering its practical oral administration.

Three months after commencement of oral sonidegib 200 mg daily, a significant reduction in tumour size was observed in the right nasal ala BCC to 2×1 mm (Fig. 1c). Meanwhile, a new lesion of the left ear appeared, consistent with squamous cell carcinoma (SCC). The patient reported no adverse event (AE) with sonidegib at that time, while haematology and clinical chemistry results were unremarkable. Both tumours were excised 2 weeks later, and erythromycin 400 mg twice daily was prescribed prophylactically. Histology of excised tissue from the nose (Fig. 1d) encompassing sun-damaged skin down to superficial subcutis and skeletal muscle confirmed BCC with superficial and nodular (non-aggressive) growth patterns and no perineural involvement. However, residual BCC was noted on one lateral surgical margin. The left ear specimen confirmed well-differentiated SCC without lymphovascular or perineural involvement. The patient then continued treatment with sonidegib. One month later, there was no clinical evidence of residual left ear SCC, while on the nose, dermoscopy of the surgical site revealed residual BCC at the midpoint of the main suture line. Two months later, monthly clinical chemistry reported elevated creatine phosphokinase (CK) of 484 U/l (with a normal reference point of <294 U/l). As a result, sonidegib was ceased pending more repeat testing. CK normalised to 248 U/l 2 weeks later, and

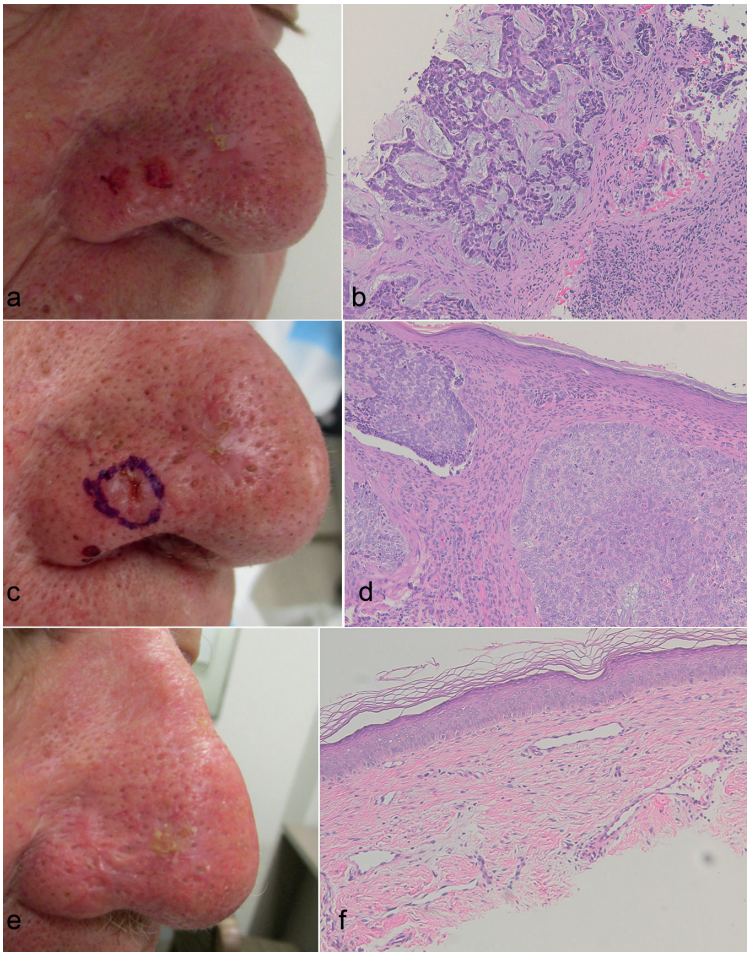

Fig. 1. (a) Clinical appearance of basal cell carcinoma (BCC) of the right nasal ala at initial presentation. (b) Biopsy showing nodular (non-aggressive) and infiltrative (aggressive) growth patterns ramifying throughout the papillary and reticular dermis. (c) Tumour shrinkage following 3 months of treatment with sonidegib prior to excisional surgery. (d) Histology of excision tissue from the nose encompassing sun-damaged skin down to superficial subcutis and skeletal muscle confirmed BCC with superficial and nodular (non-aggressive) growth patterns and no perineural involvement. (e) arborising telangiectasia was observed on the right nasal ala following 9 months of treatment with sonidegib. (f) Histology demonstrating only fibrous scar incorporating telangiectatic blood vessels, with no evidence of malignancy (b, d, f: ×200, H&E).

sonidegib was recommenced with alternate day dosing, which was well-tolerated. One month later, as arborising telangiectasia was observed on the right nasal ala (Fig. 1e); shave biopsy was performed to ascertain possible causes, such as scarring, heliosis, or residual BCC. Histology revealed a fibrous scar incorporating telangiectatic blood vessels, with no evidence of malignancy (Fig. 1f). Sonidegib treatment was then ceased with this confirmation of complete clearance.

DISCUSSION

Clinical subtypes of advanced BCC include nodular, superficial, morphoeaform, infiltrative, micronodular, and basosquamous, with the latter four subtypes tending to demonstrate aggressive behaviour with a high recurrence rate and extensive local tissue destruction compared with non-aggressive nodular or superficial subtypes (1). This clinical classification mirrors the WHO's histologic classification, which categorises BCC as either "higher risk" (basosquamous, sclerosing/morphoeic, infiltrating, BCC with sarcomatoid differentiation, and/or micronodular) or "lower risk" (nodular, superficial, pigmented, infundibulocystic, and/or fibroepithelial) (9).

To our knowledge, this is the first reported case of a patient with BCC who experienced histologic improvement of tumour subtype from infiltrative (aggressive) to superficial and nodular (non-aggressive), as well as complete clinical clearance, following sonidegib treatment. Another possible mechanism is that the infiltrative component was more sensitive to HHI than the non-aggressive subtypes. However, there is no definitive way to determine this histologically, and previous studies have demonstrated a consistent response to sonidegib across aggressive and non-aggressive subtypes (10). Tumour site and size, the degree of invasion, as well as skin quality and laxity contribute to the complexity in management (3, 11). Treatment options for complex BCC may be limited, as surgical removal can cause considerable morbidity, loss of function, and/or disfigurement when the tumour is located at challenging anatomical sites, such as the face; while radiotherapy may be contraindicated by tumour site, tissue characteristics, patient factors (such as age, mobility, and geographical location), and the high risk of causing additional BCCs (3, 11). Since aberrant hedgehog signalling plays a critical role in the pathogenesis of BCC, targeted inhibition of this pathway is a promising treatment option for patients with advanced BCC (11). In the pivotal phase 2 BOLT trial (Basal Cell Carcinoma Outcomes with LDE225 [sonidegib] Treatment; NCT01327053), sonidegib 200 mg daily demonstrated durable efficacy and control of tumour progression in patients with laBCC (4–7). In a pre-planned sensitivity analysis of the BOLT trial at 42 months, 21.2% and 28.8% of patients achieved complete response to treatment per central and investigator review, respectively (12). Conversely, in a recent case series of patients with laBCC, treatment with sonidegib 200 mg daily alone achieved tumour clearance in 80% of patients studied, and in the remaining patients, sufficient tumour reduction was achieved following treatment, allowing straightforward surgical removal of any residual BCC (13). In an analysis of the efficacy of sonidegib according to various histologic subtypes of BCC, no significant difference in tumour response was observed (10).

Notably, CK elevation is a commonly reported AE in clinical trials for sonidegib and is believed to be an HHI class effect. However, dose reductions and interruptions have shown to be successful in managing many patients' AEs, improving treatment tolerability, and enabling required treatment durations (14). In relation to muscle spasms, one of the most commonly reported AEs with HHIs, a case series of patients with laBCC demonstrated that this AE was in fact uncommon when treating non-aggressive vs aggressive tumour subtypes (15).

To our knowledge, there is currently no other published record of histologic subtype improvement to less aggressive forms, or of relative differences in sensitivity to HHI treatment between BCC subtypes, which highlights the unprecedented findings of this case report. Moreover, the results from this case emphasise the importance of regular haematology and clinical chemistry testing during HHI treatment to manage potential AEs associated with sonidegib therapy. Clinicians treating complex BCC with sonidegib should be aware of potential histologic subtype improvement when monitoring patients' responses to treatment.

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