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# A large unilateral basal cell carcinoma treated with Hedgehog inhibitor sonidegib: a case report

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**Abstract**

Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer. BCCs are categorized into “easy-to-treat” and “difficult-to-treat” groups, with the latter including all BCCs that are challenging to manage due to technical, patient-related, or tumor-related factors, such as locally advanced BCCs. In this report, we describe an 84-year-old patient with an extensive, unilateral BCC. Following a decision by the multidisciplinary skin cancer board, the patient was successfully treated with a daily dose of 200 mg of sonidegib, an inhibitor of the Hedgehog pathway, for eight months, acquiring complete clinical and histopathological remission. No significant side effects were reported. The follow-up period of 24 months has shown no negative results.

## Introduction

Basal cell carcinomas (BCCs) constitute the most prevalent type of cancer in the white population, representing approximately 75% of all keratinocyte cancers.[1] This high incidence underscores the significance of understanding and effectively managing BCCs.

BCCs can arise in various clinical forms, ranging from small, localized lesions to more extensive, invasive tumors that may be challenging to treat. According to recent European consensus guidelines, BCCs are categorized into “easy-to-treat” and “difficult-to-treat” groups, with the latter including all BCCs that are challenging to manage due to technical, patient-related, or tumor-related factors, such as locally advanced BCCs.[1] The pathogenesis of BCCs is intricately linked to Sonic Hedgehog signaling, a critical regulator of cell growth and differentiation during embryonic development, which is usually inactive in adult tissues. Both sporadic BCCs and basal cell nevus syndrome (BCNS) are known to arise from dysfunction in the Sonic Hedgehog pathway.[2] In the majority of cases, mutations in the PTCH1 gene, a key component of the Hedgehog pathway, lead to constitutive activation of the pathway, resulting in uncontrolled cellular proliferation and tumorigenesis. This dysregulation not only drives the hyperproliferation of keratinocytes but also modulates the tumor microenvironment, including suppression of immune responses that might otherwise target tumor cells.[3] In recent years, the advent of targeted therapies, specifically Hedgehog pathway inhibitors (HHi), has revolutionized the management of locally advanced and metastatic BCCs. Vismodegib and sonidegib are currently the primary HHis approved for clinical use, offering an effective treatment option for patients who are not candidates for surgery or radiation therapy.[4] The management of advanced BCCs necessitates a

multidisciplinary approach, often involving dermatologists, oncologists, and surgeons, among other specialists.[1] Treatment decisions should be tailored to the individual patient, considering the tumor's characteristics, patient comorbidities, and preferences. The utilization of HHis in this context represents a significant advancement, providing an option for those patients who are ineligible for conventional therapies. Basal cell nevus syndrome (BCNS) is a genetically inherited condition characterized by mutations in genes that encode key components of the Sonic Hedgehog signaling pathway. Somatic mutations in these same genes have also been identified in sporadic BCCs.[5]

**Case Report**

We hereby present the case of an 84-year-old patient who accessed our outpatient service due to a history of extensive, ulcerated lesions in a unilateral distribution involving a large part of his right hemithorax (Figure 1 a,b).

He reported that the lesions had developed in less than one year. His medical history included the excision of a BCC on his back, and he denied any previous clinical diagnosis of herpes zoster. He denied the application of any topical treatment. The patient was not immunosuppressed, with a medical history negative for conditions or treatment that would impair immune function. During a dermoscopic examination, the lesions exhibited multiple blue-gray globules, spoke-wheel areas, focal ulceration, linear arborizing telangiectasia, and an absence of a pigment network. A punch biopsy confirmed the clinical suspicion of pigmented basal cell carcinoma. Our case revealed no identifiable mutations in the Hedgehog pathway genes (PTCH1, PTCH2, or SUFU) known to be associated with BCNS in the affected areas. The staging of the neoplasm was completed by performing a total body CT scan with and without contrast, which did not reveal any masses or alterations suggestive of deep tissue invasion or metastasis. Given the large size and unilateral localization, following a decision by the multidisciplinary skin cancer board formed by dermatologists, oncologists, pathologists, and general surgeons, the patient was started on sonidegib at the dose of 200 mg daily, achieving clinical and histopathological remission, confirmed by the analysis of multiple punch biopsy specimens, by the eighth month of treatment and maintaining it to this date, 24 months after treatment withdrawal. The patient experienced no significant side effects from taking sonidegib. The clinical photos (Figures 1 a, Figure 2) provide visual

documentation of the lesion and treatment progression. Radiotherapy was considered but deemed unnecessary given the effectiveness of sonidegib in this case.

## Discussion

In the existing scientific literature, reports of BCCs with such an extension and unilateral distribution are notably scarce. A few reports describe BCCs with distinct distribution patterns and mutations in the Hedgehog signaling pathway that were absent on non-lesional skin, thereby classifying these cases as type 1 mosaicism, attributable to a postzygotic mutation.[6,7]

One significant case was detailed by Kahmaysi *et al.*, who documented a rare presentation of a segmental basal cell nevus syndrome in a 12-year-old boy. This case was distinguished by multiple BCCs located predominantly on the upper part of the patient's body, demonstrating a unilateral distribution pattern. Crucially, genetic analysis revealed a mutation in the Hedgehog signaling pathway, specifically in the smoothened receptor, confined to the affected skin areas. This mutation was absent in the patient's blood and unaffected skin.[6] Similarly, Saedian *et al.* reported a distinct case of a BCC exhibiting a blaschkoid distribution pattern. This case was notable for a heterozygous mutation within the Hedgehog pathway, specifically in the Patched 1 gene (PTCH1), found exclusively in the lesional skin. The absence of this mutation in non-lesional skin confirmed the diagnosis of segmental mosaicism.[7] We were unable to detect a known mutation in the Hedgehog pathway in the lesional skin. Moreover, the advanced age of the patient did not suggest mosaicism.

In the context of our specific case, the patient presented with a BCC covering a substantial body surface area and was not a candidate for surgery or radiotherapy. As a result, we have employed Hedgehog inhibitors, such as sonidegib, as an alternative treatment strategy for managing locally advanced BCCs in our experience.[8] Notably, despite the patient's advanced age, sonidegib was well-tolerated with no significant adverse effects, aligning with real-world clinical observations.[9] As highlighted by Dasgeb B. *et al.* in 2022, following the whole-exome sequencing of DNA from a series of biological specimens, including samples of some exceptionally large BCCs in patients with multiple and recurrent tumors, specific mutations in PTCH1 and TP53 may account not only for the recurrent nature of the lesions but also for their considerable size.[10] Although we were unable to detect a known mutation, the patient's rapid and significant response to sonidegib strongly suggests the presence of an underlying Hedgehog pathway dysfunction that remains unidentified. According to a recent review, somatic mutations in the PTCH1 gene have been observed at a remarkably high frequency,

reaching up to 75%. This highlights the gene's significant role in the pathogenesis of the disease.[11] Additionally, the considerable size and the unique distribution pattern exhibited by the lesions in this case, provide valuable clinical insights, highlighting the complex landscape of this malignancy and the need for further investigation into its molecular underpinnings. With the significant progress made in recent years, new therapeutic strategies are being developed that focus on the precise molecular pathways underlying basal cell carcinoma. These advances have opened the door to more targeted and effective treatment options.

**Conclusions**

Our findings highlight the need for a better understanding of the clinic heterogeneity and management of these cases, advocating for personalized treatment and underlying the efficacy and tolerability of the Hedgehog inhibitors.

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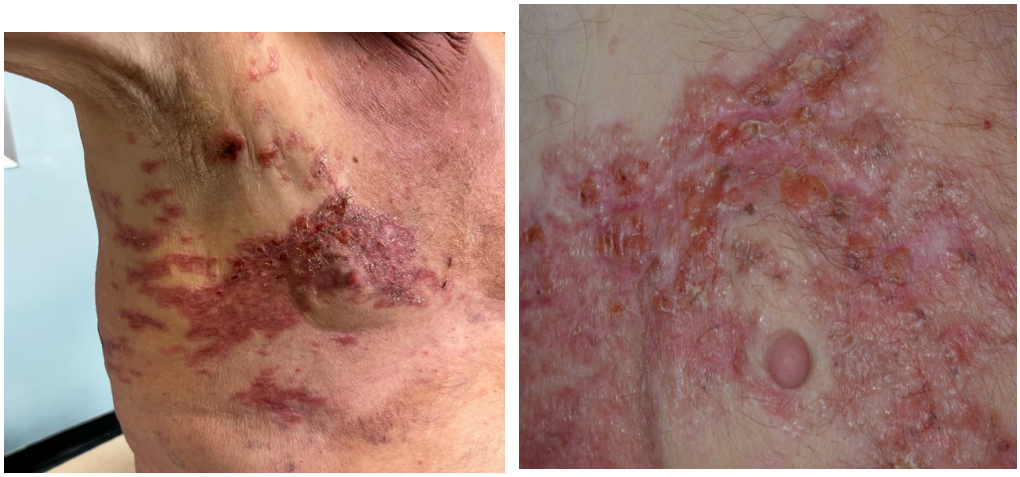

**(a)** **(b)**

**Figure 1.** (**a**) Image captures prior to commencing treatment with sonidegib 200 mg daily; (**b**) a close-up view of the lesions in a more detailed photo.

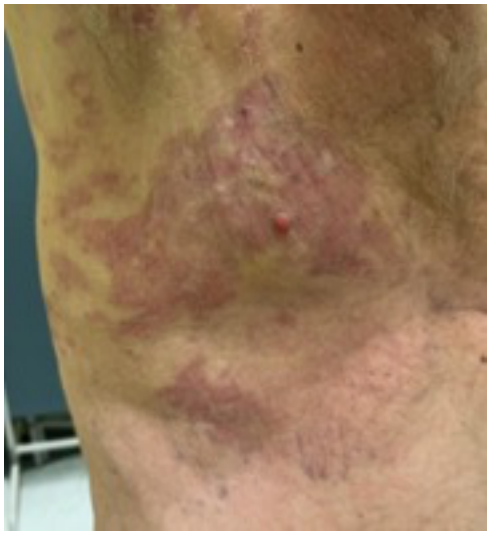

**Figure 2.** The lesions after the completion of treatment with sonidegib. Clinically, primarily residual effects are observed. The lesions appear flattened and faded.