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CASE REPORT

Refractory Morpheaform Basal Cell Carcinoma Successfully Treated with Oral Sonidegib

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Abstract: Morpheaform basal cell carcinoma (BCC) is a high-risk histologic subtype accounting for approximately 5–10% of all basal cell carcinoma cases. We report a case of facial morpheaform BCC successfully treated with oral sonidegib in a patient for whom surgery was contraindicated because of severe thrombocytopenia. A 68-year-old woman presented with an indurated sclerotic plaque with papules and crusts on the left cheek. Histopathological examination confirmed the diagnosis of morpheaform BCC. Because of the high bleeding risk associated with thrombocytopenia, surgical treatment was not considered feasible. The patient was treated with oral sonidegib at a dose of 200 mg daily, resulting in progressive regression of the lesion. After approximately two years of therapy, near-complete clinical remission was achieved, and follow-up histopathological examination with five-point sampling showed no residual tumor. This case highlights the potential role of Hedgehog pathway inhibition as an effective tissue-sparing therapeutic option for patients with difficult-to-treat morpheaform BCC.

Keywords: basal cell carcinoma, morpheaform basal cell carcinoma, histopathology, Hedgehog pathway, sonidegib

Introduction

Basal cell carcinoma (BCC) is the most common cutaneous malignancy worldwide and is typically managed with surgical excision.[1] Among its histological variants, morpheaform basal cell carcinoma represents approximately 5–10% of all BCC cases and is considered a high-risk subtype because of its infiltrative growth pattern and poorly defined clinical margins.[2] Clinically, morpheaform BCC often appears as a firm, scar-like plaque resulting from strands of tumor cells embedded within dense fibrotic stroma, which can obscure tumor boundaries and increase the risk of incomplete excision and recurrence. Surgical excision, including Mohs micrographic surgery for high-risk lesions, remains the standard treatment for most BCCs. However, alternative treatment approaches such as radiotherapy or systemic targeted therapy may be considered when surgery is contraindicated due to comorbidities, tumor extent, or potential functional or cosmetic impairment.[1]

Aberrant activation of the Hedgehog (Hh) signaling pathway plays a central role in BCC tumorigenesis.[3] In the canonical pathway, binding of Hedgehog ligands to the Patched (PTCH) receptor relieves inhibition of the Smoothened (SMO) receptor, resulting in activation of downstream GLI transcription factors and tumor growth. Additionally, Hedgehog signaling has also been shown to influence the tumor immune microenvironment, including modulation of cytokine expression and immune cell infiltration. Hedgehog pathway inhibitors such as vismodegib and sonidegib therefore exert both direct antitumor effects and potential immunomodulatory activity.[3] Targeted inhibition of SMO

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has therefore become an important therapeutic strategy for advanced or inoperable BCC. Sonidegib is an oral SMO inhibitor that blocks Hedgehog signaling and has demonstrated durable efficacy in patients with locally advanced BCC.[4]

Here, we report a case of extensive facial morpheaform BCC in a patient with severe thrombocytopenia in whom surgery was contraindicated. The patient achieved near-complete clinical remission after treatment with oral sonidegib, highlighting the potential role of Hedgehog pathway inhibition as a tissue-sparing therapeutic option in difficult-to-treat BCC.

Case Presentation

A previously healthy 68-year-old woman presented with erythema, crusting, and scaling on the left cheek. The lesion began as red papules that gradually enlarged with crust and scale formation. She denied systemic symptoms such as fever, cough, or weight loss.

Laboratory evaluation revealed severe thrombocytopenia with a platelet count of 28×10^9/L (reference range $125–350 \times 10^9$/L). Other investigations, including renal function and other biochemical parameters were within normal limits. Screening for HIV and syphilis was negative. Chest computed tomography showed no evidence of pulmonary involvement. Hematologic evaluation did not identify a clear secondary cause for thrombocytopenia.

Physical examination revealed an indurated sclerotic plaque measuring approximately 4.5×3.0 cm on the left cheek with papules and crusts and a clinically apparent peripheral rim (Figure 1a). No lymphadenopathy was observed.

Histopathological examination of a lesional biopsy specimen demonstrated infiltrative nests and thin cords of basaloid cells within the dermis accompanied by stromal sclerosis (Figure 2). Tumor cells showed pleomorphism and a high nuclear-to-cytoplasmic ratio. These findings were consistent with morpheaform basal cell carcinoma.

Given the patient's severe thrombocytopenia and the associated bleeding risk, surgical intervention was considered unsafe. Radiotherapy was discussed as an alternative treatment option; however, systemic therapy was preferred because of the lesion's size and infiltrative characteristics.

Treatment with oral sonidegib (200 mg once daily) was initiated. Progressive clinical improvement was observed during therapy, with noticeable reduction of the lesion after approximately six months of treatment. After two years of continuous therapy, the lesion had almost completely resolved (Figure 1b). During treatment, the patient reported no

Figure 1 (**a**) Indurated sclerotic plaque with papules and crusts on the left cheek/face, with a peripheral rim. (**b**) Lesions almost completely cleared after 2 years of oral sonidegib.

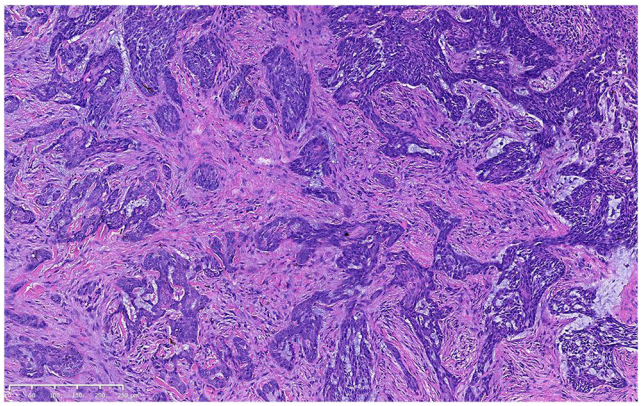

Figure 2 Histopathology showing infiltrative nests and cords of basaloid cells within the dermis accompanied by stromal sclerosis/desmoplasia (Hematoxylin and Eosin staining, Scale bar = 50 μm).

severe adverse events such as alopecia or significant weight loss. At the two-year follow-up, repeat histopathological evaluation using five-point sampling showed no residual tumor tissue. The patient continues to undergo regular clinical follow-up.

Discussion

Morpheaform basal cell carcinoma is a high-risk histologic subtype characterized by an infiltrative growth pattern with prominent stromal sclerosis. Clinically, lesions often present as indurated, scar-like plaques with ill-defined borders, and the true tumor extent may be underestimated because of subclinical spread. These features contribute to local tissue destruction, delayed diagnosis, and an increased risk of recurrence compared with low-risk BCC variants, particularly when lesions occur on cosmetically and functionally sensitive facial sites. Morpheaform BCC accounts for approximately 5–10% of all basal cell carcinoma cases and is considered one of the more aggressive histologic subtypes.[2]

Surgery remains the standard of care for most BCCs; however, treatment selection must integrate tumor-related risk factors and patient-specific constraints. The 2023 European consensus-based interdisciplinary guideline proposes a pragmatic classification that includes "easy-to-treat" and "difficult-to-treat" BCC, emphasizing multidisciplinary decision-making when conventional local therapies are not feasible. In our patient, the combination of a high-risk morpheaform subtype and severe thrombocytopenia (a major bleeding risk and practical contraindication to surgery) aligned with a "difficult-to-treat" scenario, making systemic targeted therapy an appropriate primary strategy.[1] Alternative treatment options such as radiotherapy may also be considered in selected patients when surgical excision is not feasible; however, systemic therapy was preferred in this case given the infiltrative nature and facial location of the tumor.

Aberrant Hedgehog pathway activation is central to BCC tumorigenesis, and Smoothened (SMO) inhibition represents a mechanism-based treatment for advanced or inoperable disease. In the canonical Hedgehog signaling pathway, binding of Hedgehog ligands to the Patched (PTCH) receptor releases inhibition of the Smoothened receptor, resulting in activation of downstream GLI transcription factors that promote tumor growth.[3] Sonidegib, an oral SMO inhibitor, has demonstrated durable efficacy in the pivotal Phase II BOLT trial. In the 42-month analysis, sonidegib 200 mg once daily achieved an objective response rate of approximately 56% (central review) in locally advanced BCC, with a median duration of response of about 26 months.[4] Accumulating evidence from clinical trials and real-world studies also supports the efficacy of Hedgehog pathway inhibitors in patients with locally advanced or inoperable BCC.[5,6] Another SMO inhibitor, vismodegib, has also demonstrated efficacy in advanced BCC, although differences in pharmacokinetic properties and clinical tolerability may influence treatment selection in individual patients.[7] In our clinical setting, vismodegib was not available in mainland China at the time of treatment; therefore, sonidegib was chosen as the systemic therapy.

Against this evidence base, our case is notable for near-complete clinical clearance after 2 years of continuous sonidegib therapy, accompanied by repeat histopathological assessment using five-point sampling that revealed no residual tumor. While histologic confirmation strengthens the inference of deep response, sampling error cannot be entirely excluded in morpheaform tumors with potentially discontinuous infiltration; therefore, prolonged surveillance remains warranted.

Follow-up is essential because BCC patients remain at risk for local recurrence, metachronous BCCs, and other keratinocyte malignancies. The European consensus guideline recommends tailoring follow-up intervals to recurrence risk, with more rigorous long-term follow-up for higher-risk populations, and multidisciplinary team–directed surveillance for difficult-to-treat or metastatic disease.[1] In our case, continued structured surveillance is particularly justified given the morpheaform subtype and the need to monitor both late recurrence and potential long-term treatment-related toxicity.

This report is limited by its single-patient design and the absence of standardized imaging-based response assessments. Nevertheless, the sustained clinical response over 2 years, together with repeat histopathology showing no detectable tumor on five-point sampling, provides supportive evidence that sonidegib may achieve profound disease control in selected inoperable morpheaform BCC cases. Larger studies are needed to define optimal treatment duration, discontinuation strategies, and combinational or sequential approaches to maximize durable remission while minimizing toxicity.

Conclusion

Oral sonidegib achieved near-complete clinical clearance of extensive facial morpheaform BCC in a patient with severe thrombocytopenia that precluded surgery, with five-point follow-up biopsies showing no residual tumor at 2 years. This case supports considering hedgehog pathway inhibition as a tissue-sparing primary option for "difficult-to-treat" facial BCC when surgical intervention is not feasible.

Data Sharing Statement

Data sharing does not apply to this article.

Ethical Approval

According to the policy of the Hospital for Skin Diseases, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, formal institutional review board approval was not required for the publication of a single anonymized case report. Written informed consent for publication and accompanying images was obtained from the patient.

Consent to Publish

Consent was obtained from the participant for publication in this report and any accompanying images.

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Disclosure

The authors report no conflicts of interest in this work.

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