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Basal cell carcinoma: multimodal treatment and the role of neoadjuvant vismodegib

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ABSTRACT

Basal cell carcinoma (BCC) is the most common skin cancer. It generally has an indolent course with low rates of metastasis and mortality. However, BCC is locally invasive and can cause significant morbidity due to destructive local spread. We report our experience with a patient who was referred to our skin cancer unit due to a previously neglected lesion on the parietal region of the scalp, which had developed for 7 years. The patient was prescribed vismodegib on the basis that surgery could cause excessive functional and aesthetic damage. The patient had an objective partial response after 20 months of treatment. He was then submitted to radical skin excision, leaving a large defect that was reconstructed using a free latissimus dorsi muscle flap. The patient recovered well, and at the 1-year follow-up there were no signs of local recurrence. Our case demonstrates the value of vismodegib treatment prior to surgery in a locally advanced, high-risk scalp BCC and highlights the importance of an individualized and specialized approach with these patients, within a multidisciplinary team.

Keywords
Carcinoma, Basal Cell; Interdisciplinary Research; Neoadjuvant Therapy; Reconstructive Surgical Procedures

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cutaneous malignancy.[1] It generally has an indolent course with low rates of metastasis and mortality. However, BCC is locally invasive and can cause significant morbidity due to destructive local spread. A broad range of therapeutic modalities is available for the treatment of BCC.[2] The recent progress of more effective topical and non-surgical therapies has increased the treatment options for many lesions, although surgery and radiotherapy appear to be the most effective treatments, with surgery showing the lowest failure rates.[3] For the majority of BCCs, simple excision is enough to achieve the cure. However, a small proportion of these tumors—whether by anatomical location, size, and number of lesions or patient comorbidities—are not amenable to surgery. In recent years, inhibitors targeting the hedgehog (HH) pathway have shown great promise in this complex subset of patients.

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Mutations in HH pathway genes frequently occur primarily in BCC genes, encoding patched homolog 1 (PTCH1), and smoothened homolog (SMO),[4] and have been shown to play a role in the pathogenesis of sporadic BCC.[5] PTCH mutations were found in 67% of the sporadic BCCs tumors.[6] Due to the role of HH signaling in the pathogenesis of BCC, the HH signaling pathway has been the genetic basis for the development of BCC targeted therapies. The first HH-pathway inhibitor approved for patients with locally advanced, metastatic BCC, or who are not candidates for surgery or radiotherapy, was vismodegib.

Vismodegib is a small-molecule compound that selectively inhibits SMO. The initial phase 1 trial with vismodegib showed that from 33 patients with locally advanced or metastatic tumors, 18 had a response; in the remaining 15 patients, 11 had stable disease for up to 10.8 months and 4 had progressive disease.[7] The phase II trial ERIVANCE study[8] confirmed the efficacy and safety of vismodegib in the management of advanced BCC and resulted in its approval in 2012. Its 12-month study update[9] shows that the objective response rate increased from 30.3% to 33.3% in patients with metastatic disease, and from 42.9% to 47.6% in patients with the locally advanced form.

Vismodegib was also evaluated as a neoadjuvant followed by surgery for high-risk BCC. Overall, vismodegib reduced the surgical defect area by 27% from baseline and only one patient experienced recurrence.[10] After a longer follow-up period of approximately 22 months, no further recurrences were seen.[11] This strategy has been reported a few times in other studies.[12-17] At this time, there are no randomized trial data to support the use of vismodegib as a neoadjuvant strategy, but data are increasing. Several clinical trials are ongoing to study the effect of vismodegib in this setting.[18-21] Recently, the first results of a multicenter, non-comparative, open-label, phase 2 trial (VISMONEO study) evaluating the benefit of vismodegib as neoadjuvant treatment of BCC were released.[22] This study includes patients with BCC of the face, inoperable or operable with functional or major aesthetic sequelae risk.[23] Forty-four patients had a procedure after vismodegib treatment. Of these 44 responders, 27 had a complete response proved by biopsy.[23]

Herein, we report the case of locally advanced BCC of the scalp and discuss the importance of multidisciplinary management, including neoadjuvant systemic treatment with vismodegib, surgery, and a reconstruction method.

CASE REPORT

A 61-year-old man with a medical history of type 2 diabetes mellitus, ischemic heart disease, and smoking (30 pack-years), and no history of previous skin cancer, radiotherapy, or immunosuppressive treatment, was referred to our skin cancer unit due to a previously neglected lesion on the parietal region of the scalp, which had developed over the last 7 years. An incisional biopsy confirmed BCC. He presented good performance status (Eastern Cooperative Oncology Group [ECOG] score 0) and, on physical examination, the patient presented an extensive lesion, measuring 26 × 23cm, involving most of the left scalp and invading the left auditory canal. The lesion was ulcerated, exudative, and with spontaneous bleeding (Figure 1). No clinically detected regional lymph nodes and no bone affection was seen on computed tomography scan. After the initial evaluation, the tumor board decided that there was no indication for radiotherapy and that surgery could cause excessive functional and aesthetic damage, so systemic treatment was proposed.

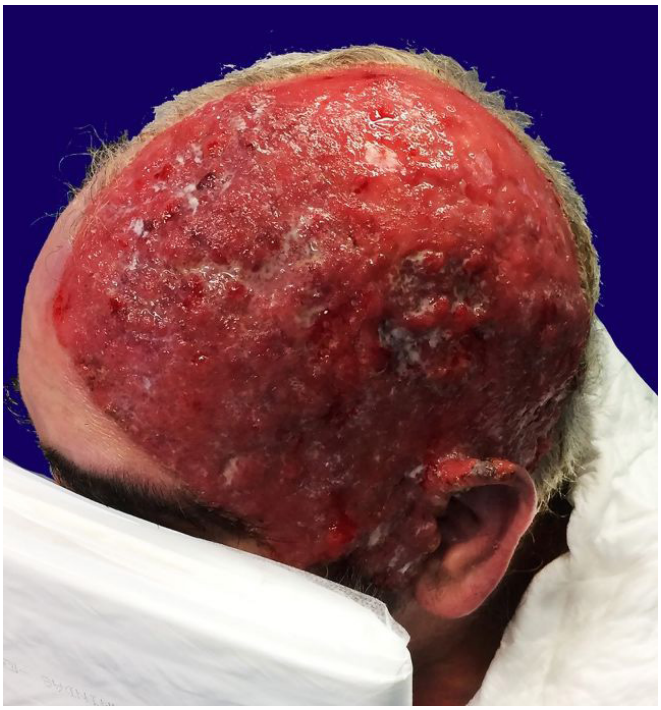

Figure 1. The preoperative view of the giant (26 × 29 cm) basal cell carcinoma on the left side of the scalp.

He was started on vismodegib 150 mg daily, 2 months after the initial evaluation. During treatment, the patient experienced different adverse events, such as alopecia grade 2, dysgeusia grade 2, and muscular spasms grade 1. The patient had an objective partial response (35% reduction of tumor area) after 20 months of treatment (Figures 2A and 2B).

Upon such a response, the tumor board once again discussed this patient's case. The decision was made to propose surgery to him, given his overall good health state, his response to vismodegib, and his preference.

He underwent a radical skin excision in depth to the bony calvaria. The resection included the left auricle and left a large defect (20 × 20 cm) (Figures 3A and 3B). The reconstruction was performed using a free latissimus dorsi muscle flap with thoracodorsal vessels anastomosed to the left facial artery and vein (Figures 3C and 3D).

The patient recovered well, and 3 weeks later a second surgery was performed to cover the muscle with a split-thickness skin graft harvested from the posterior aspect of his right thigh. The patient was discharged after 10 days. At the 2-month follow-up, the patient revealed a completely healed free flap, and the residual scars of the recipient site were acceptable (Figure 4).

The histological evaluation report revealed a BCC with extensive areas of hyaline fibrosis (post-therapeutic) and foci of epidermoid differentiation. It invaded adipose tissue and auricular cartilage. Perineural invasion was observed, and the surgical margins were free. Three lymph nodes were identified, without metastases (Figure 5). Since then, the patient has had regular visits to our department with no relapse 1 year after surgery (Figures 6A and 6B).

DISCUSSION

This case illustrates some of the challenges in treating locally advanced BCC. Generally, the patient's neglect is seen as the main reason for the extensive tumor growth, as was the case with this patient who had a disease duration of approximately 7 years. The surgical resection of BCC is the treatment of choice, but limitations exist for these advanced tumors, mostly in locations that pose a challenge for the surgeon to completely remove the tumor and—at the same time—preserve a satisfactory cosmetic appearance, with minimal impact on the patient's

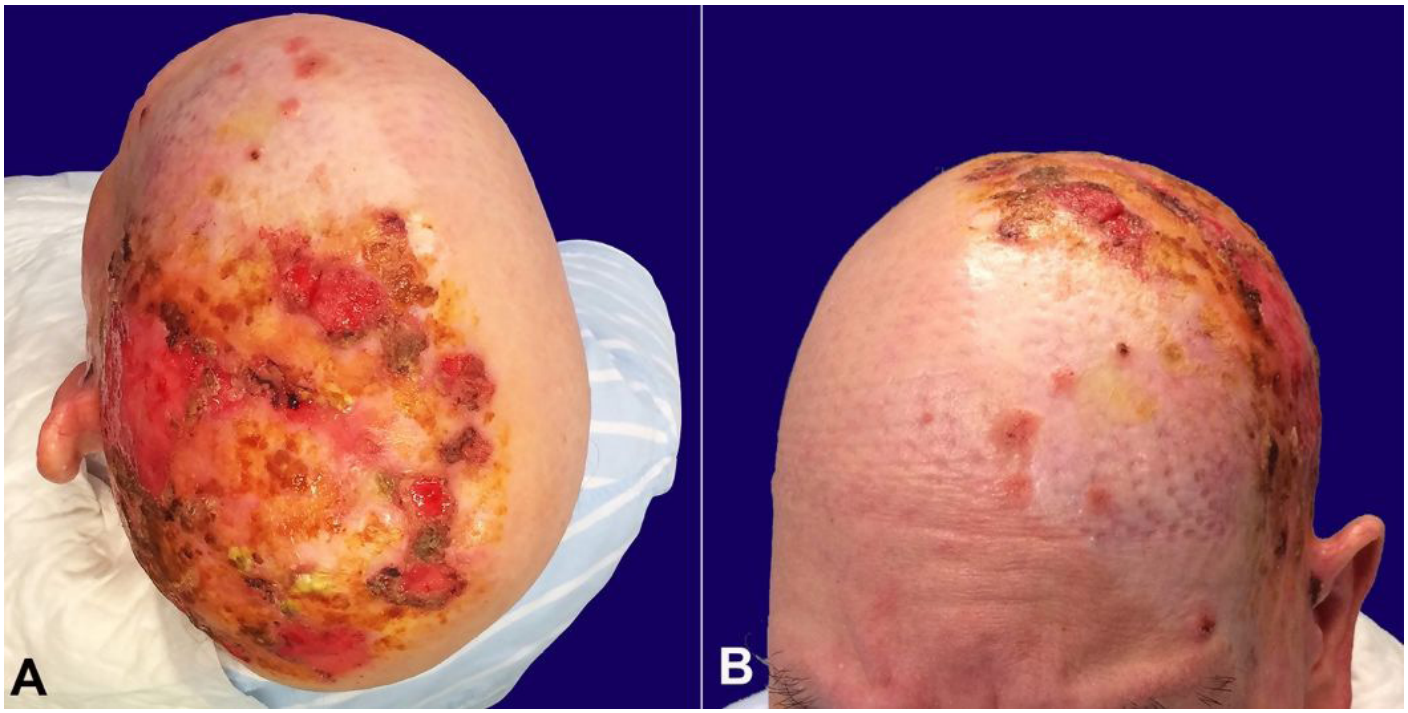

Figure 2. A and **B –** The patient's locally advanced scalp BCC regressed under treatment with neoadjuvant vismodegib but demonstrated multiples areas of drug resistance (after 20 months of treatment).

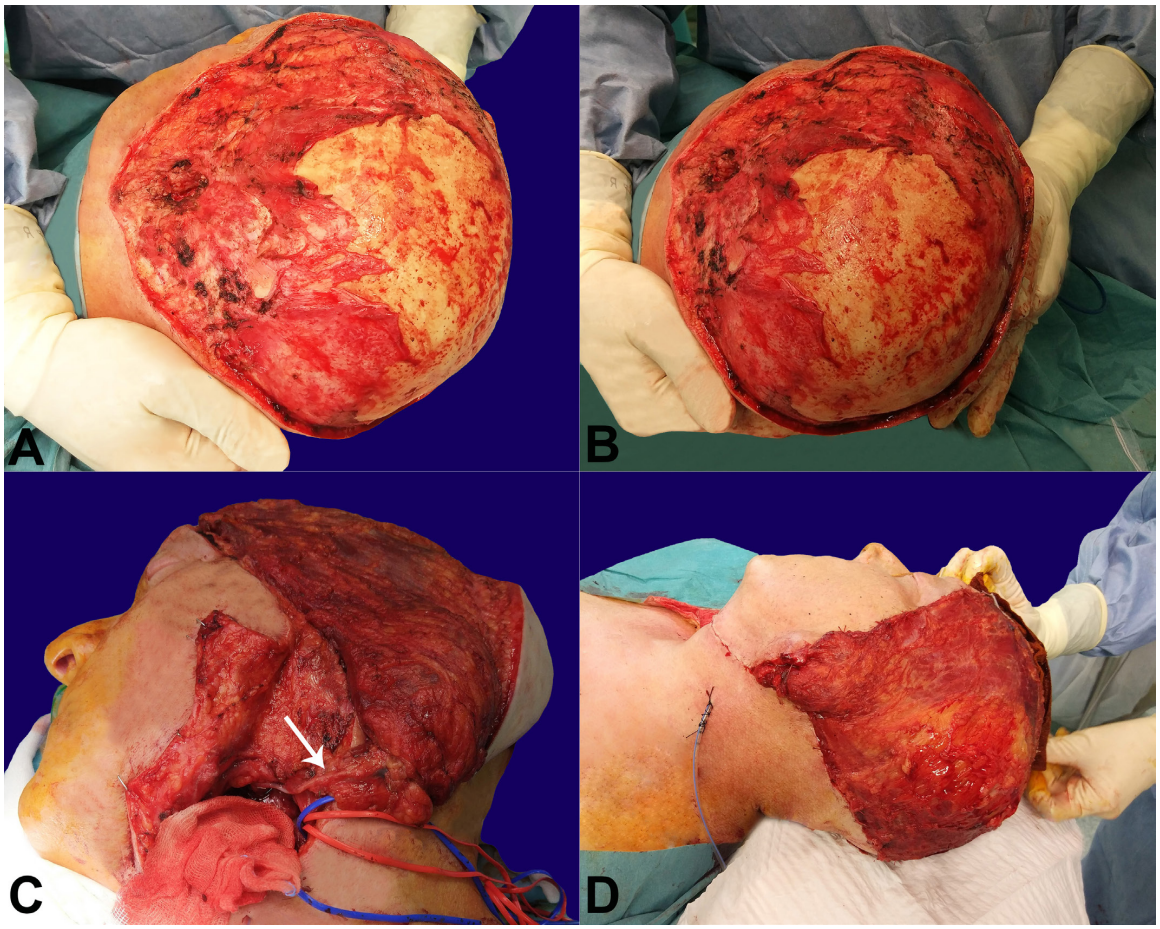

Figure 3. A and **B –** Surgical defect (20 × 20 cm) after radical skin excision in depth to the bony calvaria and hemostasis. **C –** A free latissimus dorsi muscle flap was harvested and the thoracodorsal vessels (arrow) were anastomosed to the left facial artery and vein; the tunnel for the vascular pedicle had to be large enough to prevent any compression. **D –** Flap inset without tension. The edge of the scalp defect was elevated through the subgaleal plane and the muscle edge was sutured to the galea to improve the flap–scalp junction contour.

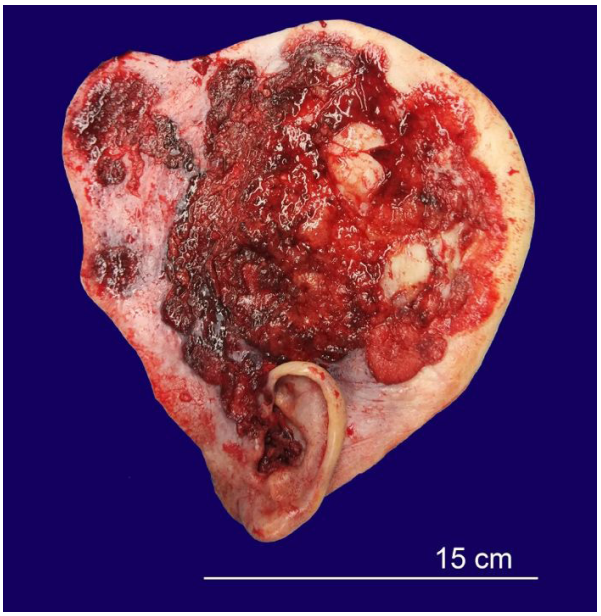

Figure 4. Surgical specimen with residual BCC and resistant areas. Almost all the specimen was occupied by a hemorrhagic neoplasm, partly flat and partly protruding, with 20 × 19.5 cm, which involved the auditory canal.

quality of life. In this case, vismodegib was used to control a very large lesion, and afterward, due to the good response, surgery was feasible. Vismodegib assumed a neoadjuvant role, potentially leading to a less morbid procedure.

The inconvenience associated with vismodegib treatment relies upon the side effects, which tend to incapacitate patients, leading to the high discontinuation rates. In the STEVIE trial, 36% of patients treated with vismodegib discontinued the treatment because of the adverse events, and 22% were recorded as having serious adverse events.[24] Our patient presented adverse events such as alopecia, dysgeusia, and muscular spasms, which occur when the patient has been taking the drug from 12 months or more, according to the known side effects of vismodegib therapy.[24] However, none of adverse events was incapacitating and, except for alopecia, they all disappeared with treatment suspension.

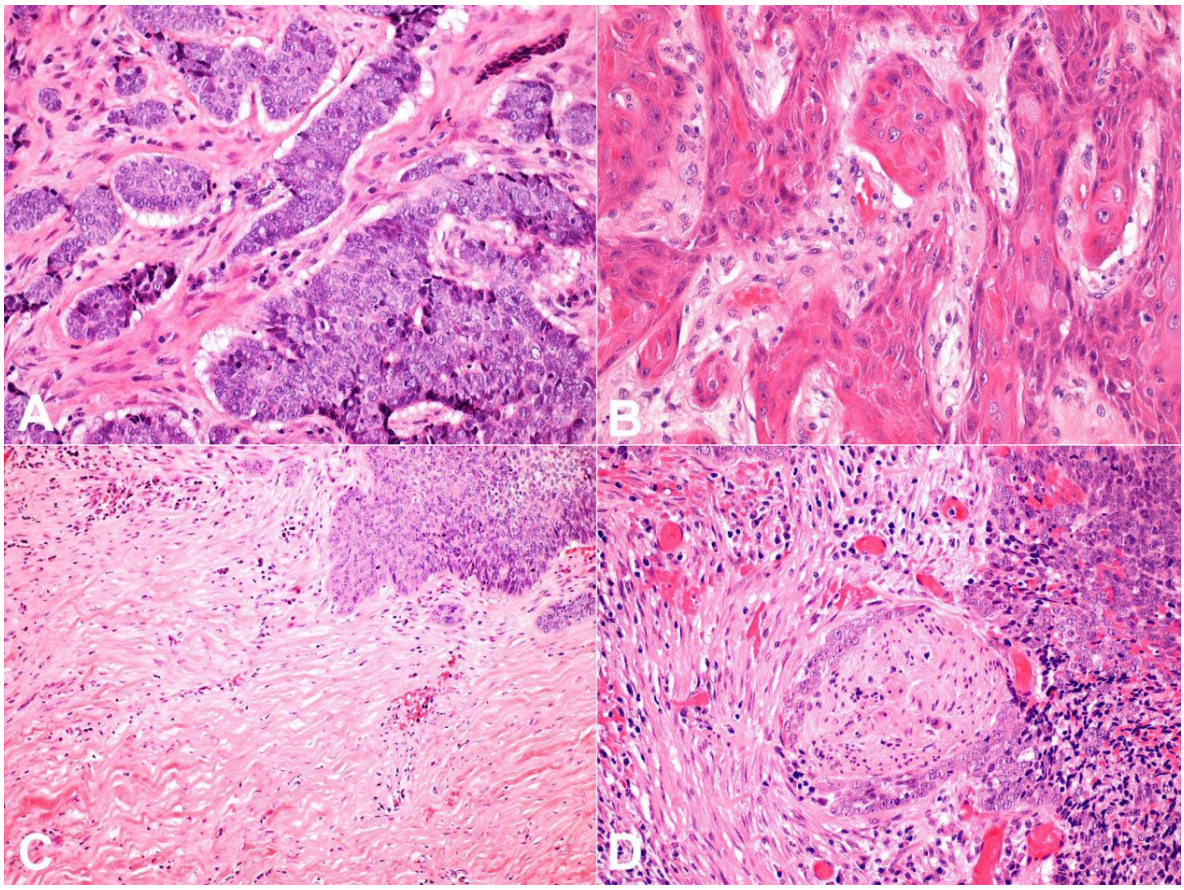

Figure 5. A - Photomicrographs of the tumor showing the basal cell carcinoma (200X). **B –** Posttreatment squamous cell carcinoma differentiation, a common finding after treatment with vismodegib (200X). **C –** Sclerotic collagenous stroma (100X). **D –** Perineural invasion (100X).

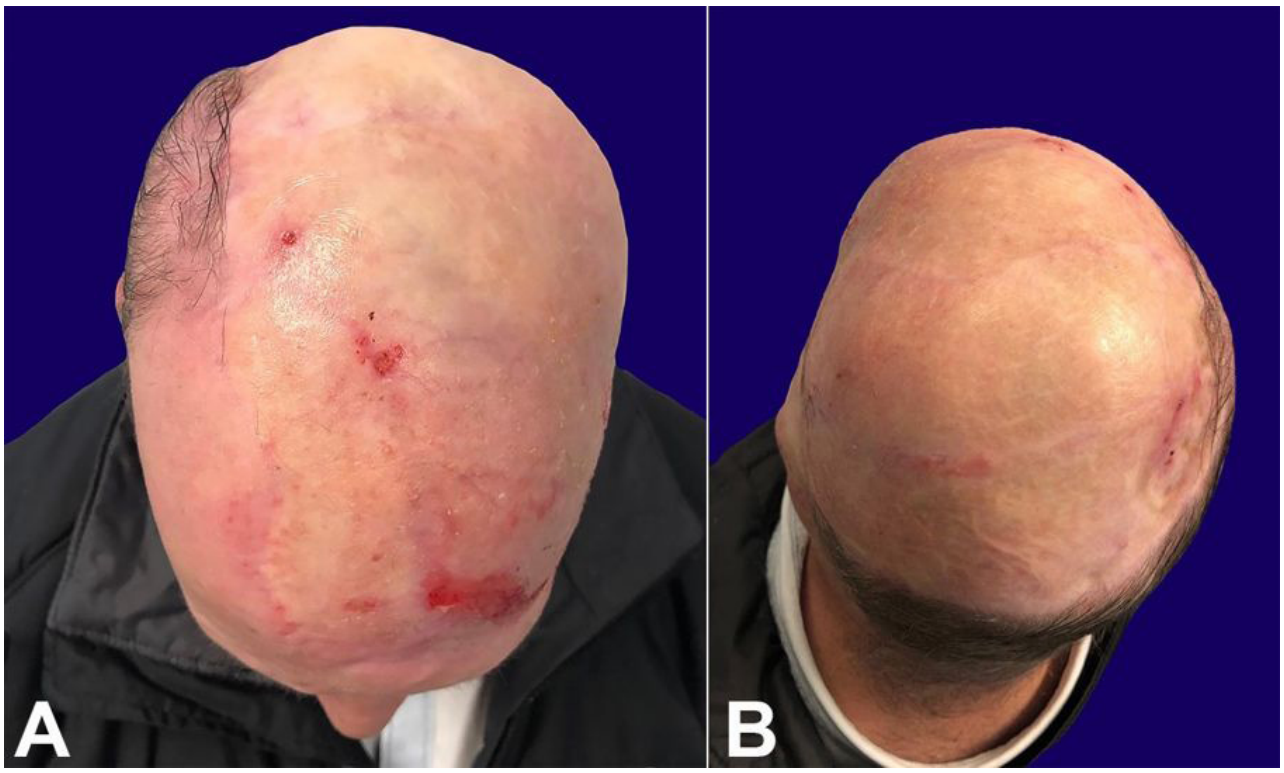

Figure 6. Postoperative gross view (**A** and **B**). The patient received full-thickness skin grafts to cover the right scalp and the external auditory canal, shown here at 10 months (**A** and **B**) after surgery. Note the marked atrophy of the muscle, closely resembling the natural thickness of the native scalp.

This patient has some negative factors predisposing him to tumor recurrence: (i) the length of time to diagnosis; (ii) the large size of the tumor; (iii) involvement of preauricular and postauricular sulci; (iv) an infiltrative growth pattern; (v) perineural involvement; and (vi) poorly defined borders after vismodegib treatment. However, we achieved tumor-free surgical margins, which are paramount for disease control, and still had an acceptable aesthetic outcome.

Another important issue in the treatment of locally advanced BCC tumors, is the choice of the appropriate method of reconstruction. Reconstructive options are determined by the extent of the defect, focusing the primary wound healing with aesthetic and functional outcomes. Microsurgical reconstruction offers the advantage of a single-stage closure of large defects with well-vascularized tissue, particularly in this case of scarred tissue. The latissimus dorsi muscle is one of the most used free flaps because of its safety and relative ease of acquisition. The large size of the latissimus dorsi muscle allows for a broad coverage providing proper contours on a large scalp defect and often leaving an acceptable cosmetic result.[25-28] This patient had some risk factors for microsurgical reconstruction (type 2 diabetes mellitus, ischemic heart disease, and smoking), which were taken into consideration regarding the choice of the flap. The good caliber of the vascular pedicles, the excellent trophic quality, and the reliability of the flap were critical in the final decision. In this patient, it was not possible to perform an anastomosis with superficial temporal vessels due to tumor involvement, so anastomosis was made to the facial vessels.

This case has demonstrated the potential benefit of the utilization of vismodegib in combination with surgery to treat advanced BCC. Additionally, it is important to underscore that the management of these complex patients is challenging. It requires an individualized and highly specialized approach and demands close collaboration between the surgical and oncological team in order to determine appropriate treatment options.

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The authors retain an informed consent and the manuscript is in accordance with the procedures and regulations of the Institutional Research Ethics Committee.

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