Locally Advanced Basal Cell Carcinoma with Subtle Skin Findings

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Abstract

Osseous destruction of the cranium by basal cell carcinoma (BCC) is extremely rare. A case of a 73-year-old man with multiple recurrences of morpheaform BCC involving the right nasal ala is presented. Years after his last re-excision, he presented with a small erosion along the supra-alar crease. He additionally reported intermittent epistaxis and nasal congestion. He was subsequently found to have infiltration of the right orbital floor, hard palate, and anterior maxillary sinus by basal cell carcinoma. Due to the size and extent of infiltration of the tumor into the orbital floor and hard palate, the patient was considered a poor surgical candidate. He was placed on daily vismodegib, and follow-up CT scan demonstrated a partial tumor response.

Introduction

While basal cell carcinoma (BCC) is the most common malignancy found in humans, with more than 2 million cases diagnosed each year in the United States, the disease remains localized in the great majority of cases.1 Locally advanced and metastatic disease is quite rare, with an incidence ranging from 0.18% to 3%.2 Complications of local disease include local tissue destruction, functional impairment, and cosmetic disfigurement.3

There are many risk factors contributing to the development of recurrent, locally advanced, or metastatic basal cell carcinoma. Anatomical locations with higher risk of recurrence include the eyelid, periorcular region, nose, lip, temple, ear, hands, feet, and genitalia.1 Increased recurrence rates are further observed when poorly defined borders are present, in tumors larger than 2 cm in diameter, in tumors with aggressive histologic patterns (morpheaform, micronodular, metatypical, basosquamous), in tumors with perineural involvement, and in patients with prior history of recurrent BCC.1 Very few cases of osseous destruction of the cranium by advanced basal cell carcinoma have been reported. The incidence is estimated to be approximately 0.03%.4 The majority of reported cases involve longstanding lesions on the scalp or face. Presenting symptoms vary depending on the location and extent of infiltration. In one case, the patient presented with cerebrospinal fluid otorrhea, facial nerve palsy, and trigeminal nerve impairment secondary to destruction of the petrous bone by recurrent auricular BCC.3 The primary tumor had been excised three years prior, and there were no signs of recurrent disease on the skin surface at the time of presentation. Here we present an additional case of basal cell carcinoma with extensive bony infiltration but very subtle skin findings.

Case Report

A 73-year-old Caucasian male presented for evaluation of a 4 mm, non-healing erosion at the site of a prior excision. He had an extensive history of recurrent basal cell carcinoma involving the superior aspect of the right nasolabial fold. This was initially resected with frozen sections in 1998. The surgical defect was closed with an advancement flap. In July 2003, he presented with a large recurrence, which was resected. Two subsequent re-excisions (August 2003 and October 2003) were necessary due to positive margins and were again performed with frozen sections. His nose was then reconstructed with a paramedian forehead flap and right auricular cartilage graft.

In addition to the non-healing area involving the right supra-alar crease, the patient also admitted to intermittent bleeding from the right naris. He denied facial numbness, paresthesia, weakness, change in vision, or epiphora.

Physical exam demonstrated a well-healed forehead flap donor scar along the left paramedian forehead. Due to the extensive past excisions, most of the right nasal ala was gone. The right soft tissue triangle and most of the right nasal sidewall were replaced by a flap (Figure 1). A superficial, 3 mm x 4 mm erosion was noted in the supra-alar crease. There was no obvious recurrent cancer externally either on the nose or on the paranasal cheek. A 3 mm punch biopsy was performed. Pathology demonstrated morpheaform BCC extending to the margins.

The patient was evaluated by Otolaryngology for further delineation of the epistaxis. On anterior rhinoscopy, the right nasal cavity was significantly narrowed and obstructed by amorphous masses of yellowish, irregular granulation tissue. The patient was subsequently sent for a CT scan, which demonstrated an irregular, infiltrating, enhancing mass along the right side of the face, centered along the right nasal soft tissues and nasal ala. The mass extended from just below the frontal sinus, at the level of the upper orbits, and crossed the midline, involving the anterior olfactory recesses and the right nasolacrimal duct. Significant osseous destruction was identified, including the orbital floor, hard palate, and anterior maxillary sinus. The first four maxillary teeth were encompassed by soft tissue. Overall, the mass measured approximately 7 cm craniocaudally x 4.4 cm transversely x 3.8 cm anterior-posterior (Figures 2-4).

A multi-disciplinary conference was held, including specialists from dermatology, otolaryngology, oncology, pathology, radiology, and dentistry. Due to the size and infiltration of the tumor into the orbital floor and hard palate, the patient was considered a poor surgical candidate. After a discussion with the patient, he was placed on vismodegib 150 mg daily. His treatment course was complicated by non-compliance. Over the course of six months, he took 103 doses. He reported muscle spasms, a 30-pound weight loss, dysgeusia, fatigue, hair loss, and diarrhea. A repeat CT scan was performed and demonstrated a modest tumor response to treatment. This study showed that the tumor was approximately 6.2 cm craniocaudally x 2.5 cm transversely x 1.4 cm anterior-posterior (Figures 5, 6). For the time being, the patient is continuing vismodegib in hopes that the tumor will continue to shrink. In the future, surgery may become a treatment option.

Discussion

Treatment of locally advanced and metastatic basal cell carcinoma is managed on a case-by-case basis. Standard therapy does not exist due to the rarity of cases and the variations in presentation. Treatment

Figure 1. Overview of patient’s face showing extensive post-surgical changes.
is mostly individualized, depending on the patient’s co-morbidities, anatomical location of the lesion, extent of infiltration, previous treatment history, and patient preference. For advanced localized disease, surgical excision followed by radiation therapy is commonly performed if the lesion is amenable and there are no contraindications. A patient may not be a surgical candidate for a number of reasons including co-morbidities, inoperable disease, substantial anticipated disfigurement, or a low likelihood of surgical cure due to history of multiple recurrences. Inhibitors of the hedgehog signaling pathway, including vismodegib, offer an alternative treatment in metastatic or unresectable BCC.

In the majority of basal cell carcinomas, both sporadic and those arising in Gorlin’s syndrome, alterations in the hedgehog signaling pathway have been identified. Most commonly, a loss of function mutation in patched homologue 1 (PTCH1) leads to unopposed activity of smoothened homologue (SMO). Smoothened signal transduction leads to activation and nuclear translocation of GLI transcription factors and induction of genes involved in cell proliferation, survival, and differentiation. In approximately 10% of basal cell carcinomas, there is an activating mutation in SMO that results in constitutional activation.

Vismodegib is a small-molecule inhibitor of smoothened. In 2012, it was approved by the Food and Drug Administration (FDA) for the treatment of metastatic or locally advanced BCC. Phase 1 studies from 2009 showed an objective response to treatment in 18 out of 33 patients; two had a complete response, and 16 had a partial response. This study combined data from 15 patients with locally advanced disease and 18 patients with metastatic BCC. In the phase 2 study (ERIVANCE BCC), 27 of 63 patients with locally advanced disease responded to vismodegib, with 13 patients having a complete response. The Safety Events in Vismodegib (STEVIE) trial, a large, ongoing, multicenter, open-label study, is monitoring the safety and efficacy of 150 mg vismodegib daily in patients with locally advanced or metastatic BCC. While this study is not yet complete, interim analysis of 499 patients was performed. Of the patients with locally advanced disease, 66.7% responded to the drug; Of 453 patients, 153 had complete responses, and 149 had partial responses. Partial response was defined as at least a 30% decrease in the sum diameters of target lesions. Those who did respond, the median time to best response was 2.6 months.

The optimal duration of treatment with vismodegib has not been defined. Studies have typically continued patients on vismodegib until they experienced intolerable side effects, progression of disease, complete cure, or the end of the study. In the interim analysis from the STEVIE trial, 80% of patients had discontinued treatment at clinical cutoff. The median duration of treatment was 36.4 weeks. The reasons for cessation included: adverse events (36%), progressive disease (14%), patient request to stop treatment (10%), investigator request, and death.

Drug intolerance can potentially present an obstacle in treatment of advanced basal cell carcinoma. Ninety-eight percent of patients from the STEVIE interim analysis experienced an adverse event. The most commonly reported side effects included muscle spasms, alopecia, dysgeusia, weight loss, asthenia, decreased appetite, aguesia, alopecia, nausea, and fatigue. Most of the adverse events were grade 1 or 2. Pretreatment counseling regarding possible medication side effects is essential.

For patients who are refractory to vismodegib or develop resistance, few treatment options exist. Sonidegib, another smoothened inhibitor, was approved by the FDA in 2015 for locally advanced BCC recurring after surgery or radiation therapy, and for patients who are poor candidates for surgery or radiation therapy. The BOLT study, a phase 2 trial of 230 patients with locally advanced BCC, found an objective response rate in approximately 35% of participants. The side effect profile is similar to that of vismodegib. A recent study was undertaken using sonidegib 800 mg daily in nine patients with advanced BCC previously resistant to treatment with vismodegib. The study did not find better outcomes with sonidegib. Of the nine patients, five experienced progressive disease, three remained stable, and one was not able to be evaluated. In the future, therapies with targets in the hedgehog pathway downstream of SMO may prove more beneficial for refractory or resistant cases.

**Conclusion**

Advanced basal cell carcinoma with intracranial invasion is rare. Once the tumor has infiltrated and destroyed the facial bones, treatment becomes extremely challenging. This case highlights the importance of closely monitoring patients who have a history of multiple recurrences, especially in high risk anatomic locations or with more aggressive histologic subtype. A detailed review of systems should be elicited at each follow-up visit. Based on the history and physical exam, imaging studies may be warranted to rule out progressive disease. Hedgehog pathway inhibitors should be considered in patients with unresectable disease.
References


