Two Different Scenarios of Squamous Cell Carcinoma Within Advanced Basal Cell Carcinomas Cases Illustrating the Importance of Serial Biopsy During Vismodegib Usage

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Vismodegib is a Hedgehog signaling pathway inhibitor recently approved by the US Food and Drug Administration for advanced basal cell carcinoma (BCC). In animal models, decreased Hedgehog signaling has been shown to predispose to squamous cell carcinoma (SCC). Recently, 4 cases of vismodegib-associated SCC at sites distant to the BCC have been reported. Herein, we report a clinically important phenomenon of SCCs within the tumor bed of locally advanced basal cell carcinoma, spindle cell subtype. In both cases, the squamous cell carcinomas were surgically resected.

OBSERVATIONS The first case is that of a patient with locally advanced basal cell carcinoma responsive to vismodegib but with an enlarging papule within the tumor bed. On biopsy, this papule was an invasive acantholytic squamous cell carcinoma. The second case is that of a patient with Gorlin syndrome with a locally advanced basal cell carcinoma that was stable while the patient was receiving therapy with vismodegib for 2.5 years but subsequently increased in size. Biopsy specimens from this tumor showed invasive squamous cell carcinoma, spindle cell subtype. In both cases, the squamous cell carcinomas were surgically resected.

CONCLUSIONS AND RELEVANCE These cases highlight the importance of repeated biopsy in locally advanced basal cell carcinomas in 2 clinical situations: (1) when an area within the tumor responds differentially to vismodegib, and (2) when a tumor stops being suppressed by vismodegib. Timely diagnosis of non-basal cell histologic characteristics is critical to institution of effective therapy.

IMPORTANCE Vismodegib is a Hedgehog signaling pathway inhibitor recently approved by the US Food and Drug Administration for advanced basal cell carcinoma. We present 2 cases of clinically significant squamous cell carcinoma within the tumor bed of locally advanced basal cell carcinoma found during vismodegib treatment.

Case 1
A woman in her 60s with no history of SCCs presented with a 2.8 × 3.4-cm ulcerated plaque involving the right medial canthus, upper eyelid, lacrimal duct opening, and nasal sidewall (Figure 1A). Owing to the extent of the tumor, 2 biopsy specimens were taken, 1 from the superior aspect of the tumor on the upper eyelid and 1 from the inferior aspect of the tumor on the cheek. Both biopsy specimens demonstrated infiltrative and nodular BCC with focal nonneoplastic epithelial hyperplasia (Figure 1B). A computed tomographic (CT) scan demonstrated erosion of the right nasal bone by tumor. The patient was referred for Mohs surgery but opted to pursue medical therapy with vismodegib owing to concern about surgical morbidity from the periocular location, lacrimal duct involvement, and invasion into nasal bone.

The patient started therapy with vismodegib, 150 mg daily, with dramatic tumor shrinkage. After 4 months of vismodegib, the patient reported enlargement of a discrete 0.5 × 0.7-cm hyperkeratotic papule within the prior BCC tumor bed (Figure 1C). Comparison with a pretreatment photograph showed that this papule was likely present, but smaller, prior to vismodegib treatment. A biopsy of the papule showed invasive acantholytic SCC and no abnormal basaloid cells (Figure 1D). The SCC was resected with Mohs surgery that re-
required only 1 stage. The patient continued therapy with vismodegib during and after Mohs surgery, with subsequent complete response of the surrounding BCC.

**Case 2**

A woman in her 40s with Gorlin syndrome presented with a 15-cm, locally advanced, nodular BCC on the vertex of her scalp extending to the dura (Figure 2A and B). The BCC had previously been treated with photodynamic therapy and radiation, with disease recurrence. Owing to the advanced nature of her scalp BCC, she was started on therapy with vismodegib, 150 mg daily. The scalp BCC shrank to 11 cm after 3 months of treatment with vismodegib. She continued to receive vismodegib over the next 2.5 years with stable scalp disease until a head magnetic resonance imaging (MRI) scan demonstrated tumor progression. Owing to the size of the tumor, 2 areas of the same tumor were biopsied (Figure 2C). Both biopsy specimens showed an atypical pleomorphic spindle cell proliferation (Figure 2D). Immunohistochemical analysis was performed with positive staining for cytokeratin (CK) 5/6 (Figure 3A) and p63, supporting a diagnosis of keratinocytic neoplasm and ruling out atypical fibroxanthoma. Immunohistochemical staining of tumor cells showed that the cells did not stain with antibodies to CD10 (Figure 3B) and CD68 (Figure 3C), further ruling out a diagnosis of atypical fibroxanthoma; Sox-10 and S-100, ruling out melanoma; and smooth muscle actin (Figure 3D); and desmin, ruling out leiomyosarcoma. Taken together, these immunohistochemical findings support the diagnosis of invasive SCC, spindle cell subtype. There were no abnormal basaloid cells in the biopsy specimens.

After consultation with the Stanford multidisciplinary head and neck tumor board, the patient underwent surgical resection of the scalp tumor, including removal of portions of the calvarium and dura. Frozen sections demonstrated discontinuous distribution of spindled cells with significant atypia and mitoses. These areas were interspersed with nodular and infiltrative BCC. Some of the spindled cells stained positive with an antibody cocktail for CK AE1/AE3/CAM5.2, whereas areas of transition between spindle and basaloid cells did not stain, consistent with dedifferentiation of a predominantly BCC tumor into discontinuous areas of spindle cell SCC (Figure 3E).

**Discussion**

These cases illustrate 2 different scenarios of SCCs within advanced BCCs during the course of vismodegib usage. Case 1 is likely that of a collision tumor of an SCC and BCC, which did not become apparent until the BCC regressed while the patient was receiving vismodegib and the SCC did not. Case 2 is
likely that of a BCC that dedifferentiated focally either before or during vismodegib therapy, particularly because Figure 3E shows a continuous transition from basaloid cells to spindle cells that are CK AE1/AE3/CAM 5.2 positive, without a clear border separating the 2. This second case prompted a biopsy after initial tumor shrinkage (likely of basaloid areas but not dedifferentiated areas) because it subsequently began to grow.

While there are no published data on the average time frame in which responses of locally advanced BCCs to vismodegib are detectable on clinical examination, our experience in treating dozens of patients has been that partial responses with tumor shrinkage are visible by 3 months. Hence, new or persistent ulcerations, nodules, or erythema in the locally advanced BCC tumor bed should prompt a biopsy after this time.

These cases highlight the importance of repeated biopsy in locally advanced BCCs in 2 clinical situations: (1) when an area within the tumor responds differentially to vismodegib and (2) when vismodegib stops suppressing tumor progression. Without repeated biopsies, these areas of tumor resistance might be incorrectly assumed to be BCC histo-
logic characteristics; only a biopsy can lead to a correct and timely diagnosis of non-BCC histologic characteristics. Accurate diagnosis is critical to institution of potentially more effective therapy, such as surgical resection (as in these cases), chemotherapies specific for SCC (eg, capecitabine, cetuximab, erlotinib), or radiation.

Conclusions

Squamous cell carcinomas associated with vismodegib have been reported in sites separate from the advanced BCC being treated. In the clinical setting, new, growing lesions at a distant site would likely trigger a decision to biopsy owing to their location separate from the known advanced BCC. Our cases illustrate the need to rebiopsy the same tumor if the tumor (or portions of the tumor) grows after previous shrinkage while the patient is receiving vismodegib therapy.

The exact biologic mechanisms behind the 2 cases presented herein are intriguing but beyond the scope of this report. For instance, we speculate that the first case could be either (1) a collision tumor with the SCC present within the original locally advanced BCC, and/or (2) the SCC could arise owing to chronic inflammation from the larger BCC (akin to Marjolin ulcer). In the second case, we hypothesize that the SCC evolved from the BCC under the selection pressure of vismodegib, which favored the growth of cells resistant to vismodegib. Another explanation could be sampling error on the initial biopsy of a large BCC with preexisting areas of dedifferentiation, with regression of the basaloid cells on vismodegib favoring detection of the SCC on biopsy. Definitive proof of these alternative hypotheses would require mutational analysis of single tumor cells.

Finally, the existence of basosquamous tumors as a single entity continues to be debated, with theories including (1) collision between BCC and SCCs or (2) dedifferentiation of BCC into SCC. Our 2 cases illustrate that both may exist. Smoothened inhibition via vismodegib offers a unique opportunity to explore these possibilities in human keratinocytic tumors.