What Lies Beneath? A Lesson for the Clinician. Intraoperative Frozen Section Appearance of Persistent Basal Cell Carcinoma after Apparent Cure with Imiquimod 5% Cream

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The Food and Drug Administration (FDA) has approved imiquimod 5% cream for the treatment of nonfacial superficial basal cell carcinoma (BCC), and it has increased in popularity as a nonsurgical approach for the treatment of BCC.[1] Its use for the treatment of superficial BCCs on the trunk, neck, and extremities has been documented in the dermatology and family physician literature.[2,3] Studies of imiquimod for nodular BCC, on the other hand, have demonstrated suboptimal cure rates according to both clinical and histologic criteria,[4] but little is known about the efficacy of imiquimod cream in the treatment of more extensive lesions, more aggressive BCC subtypes, or treatment in higher risk locations like the face, although the off-label practice of treating facial BCCs with imiquimod is not rare.[5,6]

We report a series of three patients who had persistent nodular or micronodular BCC on the face after apparent clearance with topical imiquimod therapy. In addition, we present the intraoperative frozen-section appearance of persistent tumor during Mohs micrographic surgery, which demonstrates the presence of BCC in the mid-dermis, with apparent clearance of tumor in the superficial dermis and epidermis.

Case Reports

Case 1

A 59-year-old woman presented to a referring physician with an asymptomatic, 7- × 6-mm erythematous papule located on the right upper lip. A shave biopsy performed showed micronodular BCC. The referring dermatologist recommended imiquimod therapy because the patient expressed her desire to minimize scarring. Imiquimod 5% cream was used three times per week for 6 weeks. A superficial surveillance biopsy of the area showed no tumor after the course of imiquimod. Over the following 11 months, the same location developed a lesion suspicious for recurrence, so a repeat biopsy was performed that demonstrated nodular and focally infiltrating BCC. The patient was referred to our surgery center for Mohs micrographic extirpation of the tumor. The first stage of Mohs surgery revealed the presence of

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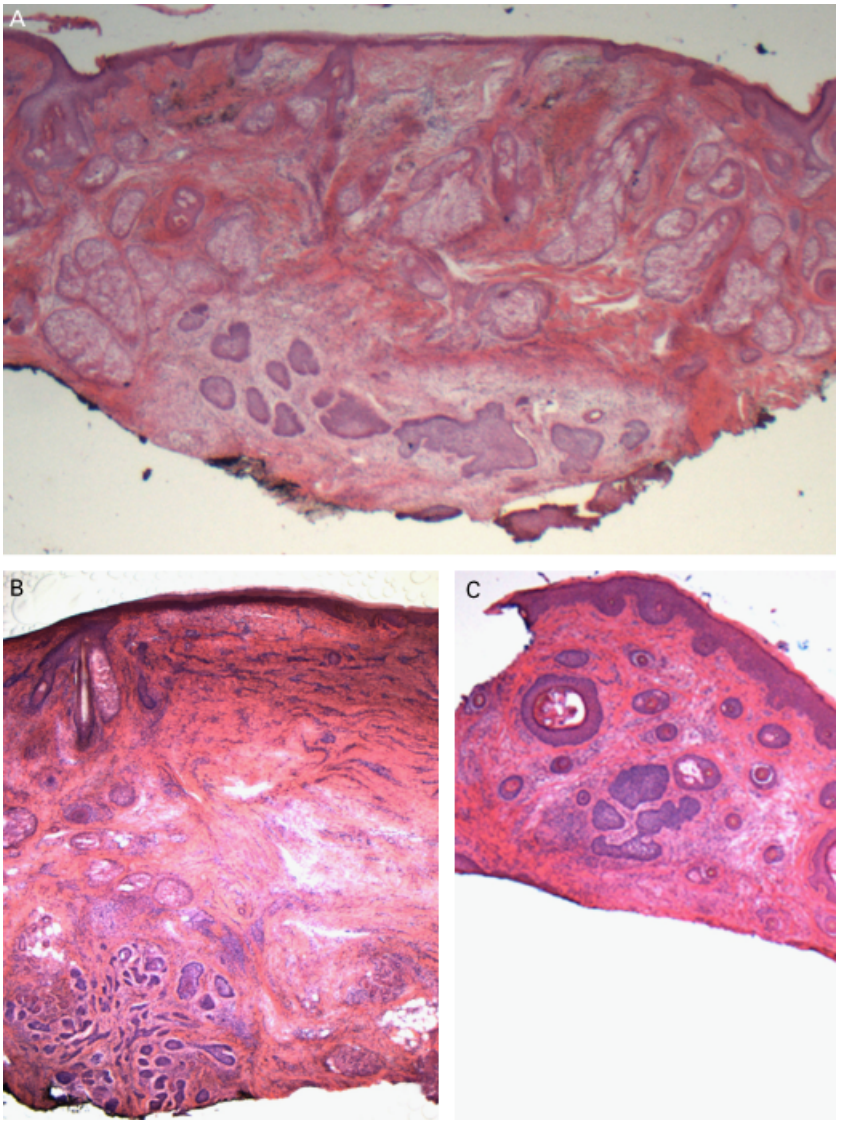

Figure 1. Intraoperative frozen sections. Pathology from Patient 1 (A), Patient 2 (B), and Patient 3 (C) demonstrating tumor in the mid-dermis with clearance of tumor from papillary dermis and overlying epidermis.

nodular BCC in the deep dermis without any evidence of tumor in the superficial dermis or epidermis in multiple sections examined (Figure 1A). The tumor was cleared in one additional Mohs stage.

Case 2

A 51-year-old woman was treated with imiquimod 5% cream five times weekly for 6 weeks for a nodular BCC on the right nasal sidewall. Several months later, she presented to a referring dermatologist and was found to have a 4- × 3-mm erythematous papule at the same site. A biopsy was performed that demonstrated nodular BCC, and she was referred to our surgery center for Mohs micrographic surgery. The tumor was extirpated in two stages. Histologic examination of multiple sections of the first stage demonstrated the presence of infiltrative and nodular BCC in the mid to deep dermis with clearance in the papillary dermis and no involvement of the epidermis (Figure 1B).

Case 3

A 29-year-old woman with a BCC on the right side of her nose presented for evaluation. She requested postponement of surgical treatment of the tumor because of an upcoming important life event, so treatment was initiated with imiquimod 5% cream three times weekly for 6 weeks. She returned after 10 weeks for surgical extirpation of residual tumor by Mohs micrographic surgery. Histologic examination of multiple sections of the first stage demonstrated nodular BCC in the mid-dermis without involvement of the overlying superficial dermis or epidermis (Figure 1C).

Discussion

Imiquimod was approved in 2004 for the treatment of primary, superficial BCCs smaller than 2 cm in size and limited to the trunk, neck, and extremities.[1] Cure rates with imiquimod for superficial BCCs have been reported to be as high as 80% to 90%, but these studies are not limited to facial lesions and have limited follow-up periods ranging from 6 weeks to 23 months.[7–9] Quirk and colleagues entered 157 patients with complete clearance of superficial BCC after imiquimod into a long-term follow-up study with a 2-year interim recurrence rate of 8.9%.[10] Similarly, 2-year interim results from an ongoing 5-year follow-up study in Europe report an initial clearance of 90% with a continued clearance of 79.4% at 2 years.[11]

Treatment of nodular BCCs with imiquimod 5% cream has been significantly less efficacious. Peris and colleagues conducted a 12-week open-label trial with imiquimod for the treatment of superficial and nodular BCCs on variable sites with a clearance rate of only 52.6% for nodular BCCs.[9] A phase III trial evaluating efficacy of imiquimod applied thrice weekly for 8 to 12 weeks to nodular BCCs found residual tumor in one-third of patients.[2] By comparison, surgical management of primary BCC with Mohs micrographic surgery had a 5-year recurrence rate of 0.7% for all subtypes and 1.6% for nodulocystic and micronodular subtypes in a large prospective series.[12] The superior cure rates seen with Mohs micrographic surgery may stem from the ability to histologically evaluate 100% of the margin in depth as well as periphery.[13,14]

The intraoperative frozen sections presented here suggest a potential reason for the limited treatment effectiveness and raise questions regarding the reliability of clinical monitoring while using imiquimod for nodular and other more aggressive forms of BCC. These representative sections, and others viewed during the surgical procedures, demonstrated persistent mid- or deep-dermal tumor without papillary-dermal or epidermal involvement. Furthermore, subsequent layers were found to be free of tumor. Such superficial clearance would mask deeper involvement and lead to clinically undetectable growth. This may be especially relevant in cases where there is poor patient follow-up or in facial tumors, where recurrences are more common.[15] Although the images presented here suggest superficial clearance of tumor, it is possible that such tumor was present in sections not examined. Histologic examination through the entirety of the Mohs tissue block in this patient population would be helpful to provide more definitive support of this phenomenon.

It is unclear what factors led to decreased efficacy and tumor persistence in the patients treated here and higher rates of recurrence in patients with nonsuperficial-type BCC. It is possible that limitations in penetration of the topical imiquimod cream may influence its ability to treat tumor cells that reside more deeply in the dermis. The presence of differing histologic subtypes has been hypothesized to be a cause of recurrent BCC elsewhere, and it is possible that such heterogeneity could lead to a variable response to imiquimod cream.[16,17] In two of the patients presented here, suboptimal regimens of imiquimod use (three times weekly vs FDA-approved five times weekly)[8] may have contributed to the persistence of tumor in the dermis, reinforcing

the need for adequate application if imiquimod is chosen as a treatment option.

In summary, we present a series of patients with persistent BCC after treatment with imiquimod in which superficial clearance of tumor may have been the basis for apparent clinical cure. These findings and recent studies demonstrating suboptimal efficacy in certain subtypes of BCC indicate potential limitations in imiquimod use outside of the indications currently approved by the FDA. Further study of the histologic findings of nonsuperficial subtype BCCs treated with imiquimod is warranted.

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