Multiple recurrent squamous cell carcinomas and utility of anticytokeratin immunohistochemistry

Michael W. Pelster, MD,[a] Sapna M. Amin, MD,[b] and Simon Yoo, MD[a]
Chicago, Illinois

Key words: aggressive; dermatologic surgery; immunohistochemistry; Mohs surgery; nonmelanoma skin cancer; recurrent; squamous cell carcinoma.

INTRODUCTION

Mohs micrographic surgery remains the gold standard for the treatment of cutaneous squamous cell carcinomas (SCCs) of the head and neck. However, for recurrent or aggressive SCCs, it can be challenging at times to ensure complete margin control on hematoxylin and eosin (H&E) frozen sections alone. The authors present a case of multiple recurrent SCC that was ultimately found to have occult foci of tumor identifiable only by anticytokeratin immunohistochemistry (IHC). Although a large volume of literature addresses the topic of IHC for melanocytic neoplasms treated by traditional Mohs and "slow Mohs," there is a relative paucity of commentary on its use in SCCs.[1] This unusual case highlights the importance of anticytokeratin IHC for SCCs, especially in tumors that are recurrent or have aggressive or atypical cytomorphology.

Abbreviations used:

AE1/AE3:	anti-pan cytokeratin 1/3
ART:	adjuvant radiation therapy
H&E:	hematoxylin and eosin
IHC:	immunohistochemistry
SCC:	squamous cell carcinoma

CASE REPORT

A 63-year-old woman with a medical history significant for 2 basal cell carcinomas, follicular lymphoma, and breast cancer presented for evaluation of an 8-mm infiltrative erythematous papule on the left lateral cheek near the angle of the mandible. There was no nerve pain, pruritus, or other clinical indicator of perineural invasion. A biopsy of the lesion found a well-differentiated invasive SCC (Fig 1), which was excised via the Mohs technique and repaired with a small advancement flap.

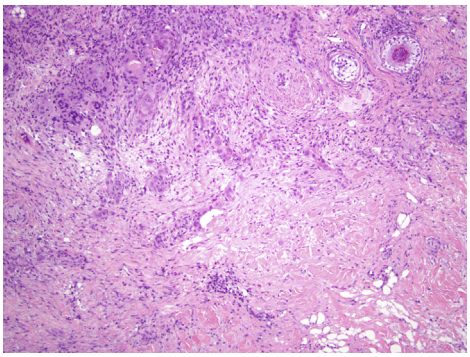

Fig 1. Original biopsy shows SCC infiltrating into the papillary dermis. (H&E stain; original magnification: ×10.)

Fifteen months later, the patient presented for evaluation of an infiltrative, scaly, telangiectatic 1-cm plaque immediately superior to and abutting the scar from the prior Mohs procedure without regional lymphadenopathy. Biopsy of the lesion found well-differentiated and invasive SCC in a background of scar and repair changes. The pathologists noted in their report that the specimen had architectural and

From the Departments of Dermatology[a] and Dermatopathology,[b] Feinberg School of Medicine, Northwestern University.

Funding sources: None.

Conflicts of interest: Dr. Yoo has been a consultant and on the advisory board for Genentech and the advisory board for Abbvie. Drs. Pelster and Amin have no conflicts to disclose.

Correspondence to: Michael W. Pelster, MD, Dermatology Resident, Department of Dermatology, Feinberg School of Medicine, Northwestern University, 676 N St Clair St, Suite 1600, Chicago, IL 60611. E-mail: michael.w.pelster@gmail.com.

JAAD Case Reports 2016;2:346-9.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2016.06.009

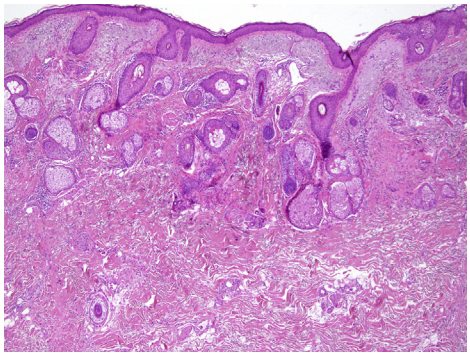

Fig 2. Permanent sections of the Mohs layer did not show SCC. (H&E stain; original magnification: ×4.)

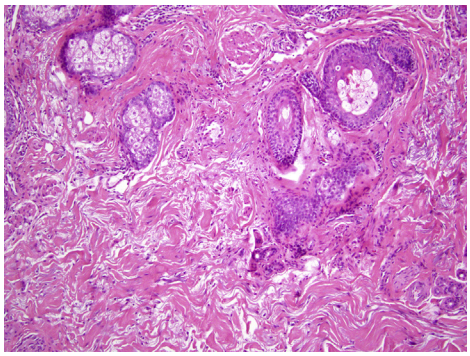

Fig 3. Permanent sections of the Mohs layer did not show SCC. (H&E stain; original magnification: ×20.)

cytological features consistent with an aggressive tumor, specifically noting marked nuclear pleomorphism and an infiltrative growth pattern. The tumor was re-excised using the Mohs technique. Given the aggressive histopathologic appearance, referral was also made to the radiation oncology department. Although recommended at that time to undergo a dedicated planning computed tomography scan in anticipation of adjuvant radiation, the patient declined both the computed tomography scan and the adjuvant radiation.

Two years later, the patient was again found to have a lesion suspicious for recurrence—this time a 7-mm firm, tender, erythematous papule within the scar. There was no regional lymphadenopathy. Biopsy and subsequent histopathologic examination found well-differentiated and invasive SCC at the site, with aggressive features as before, including marked nuclear pleomorphism and a highly infiltrative growth pattern. For this second recurrence, the patient was again treated with Mohs micrographic surgery, which was thought to be clear after 3 stages and closed with an advancement flap.

Eight months later, the patient noted a small area of ulceration within the inferior portion of the scar.

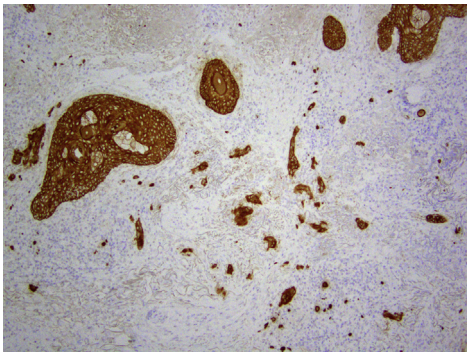

Fig 4. IHC using AE1/AE3 shows irregular infiltrating strands of SCC and scattered single atypical cells. (AE1/AE3 stain; original magnification: ×20.)

Rebiopsy found well-differentiated SCC again. At that time, a dedicated computed tomography scan of the face and neck/larynx with contrast found no radiographic evidence of tumor or lymphadenopathy. The patient subsequently underwent her fourth Mohs procedure, which was thought to be clear after 2 stages. However, this time, the final stages were sent for formalin-embedded permanent sections to be read by a dermatopathologist prior to definitive closure (Figs 2 and 3). This action was done because of the multiple recurrences of the tumor and an inflammatory infiltrate noted on frozen section potentially obscuring occult foci of tumor, a feature that had not been noted during any of the patient's previous Mohs procedures. On histopathologic examination, no residual SCC was identified on H&E, so the defect was then closed as planned. Given the unusual circumstances of the case and development of additional nonmelanoma skin cancers at other sites over the same period, the patient was started on acitretin. She was also evaluated by radiation oncology for a second time, but the patient remained reluctant to undergo any radiation therapy.

One year later, the patient had a suspicious lesion at the same site, and rebiopsy found well-differentiated invasive SCC again. At this time, given the unusual nature of the case, anticytokeratin staining (AE1/AE3) was performed on the block sent for frozen section from the most recent Mohs procedure 1 year prior. Despite no residual SCC identified on H&E by an experienced dermatopathologist, AE1/AE3 staining found a minute focus of infiltrating cells in the papillary dermis suspicious for residual SCC (Fig 4). Given the apparent impossibility of fully characterizing the tumor on H&E and its multiple recurrences, Mohs was no longer felt to be an appropriate treatment modality. The patient then was sent to the otolaryngology department for a wide local excision with parotidectomy and

dissection of the left side of the neck. Pathology findings showed residual SCC invading to a maximum depth of 4 mm and a maximum width of 1.5 cm. There was no invasion of the subcutaneous fat or into the parotid capsule. Eight lymph nodes, including 6 from the neck and 2 intraparotid nodes, were negative for malignancy. She was again referred to the radiation oncology department, who discussed with her the pros and cons of adjuvant radiation therapy versus close observation. The patient elected observation, and she has had no evidence of recurrence at the site after an additional 26 months of follow-up.

DISCUSSION

Mohs micrographic surgery as it is customarily practiced relies on accurate identification of tumor extension on frozen sections stained with H&E. However, as illustrated by this case, there are certain circumstances in which tumor characteristics preclude obtaining complete margin control on H&E alone. One study using rapid staining for AE1 found hidden foci of SCC in 8 of 20 (40%) of the extensive, aggressive, or recurrent SCCs analyzed.[2] In our patient's case, there is also a known association between concomitant non-Hodgkin's lymphomas, such as follicular lymphoma, and a dramatically increased risk for SCC.[3] It is possible that the patient's underlying immune dysregulation secondary to her lymphoid neoplasm may have also contributed to the aggressive behavior of the tumor and subsequent difficulty in histologic detection.

Several stains are available that are useful for highlighting squamous cell carcinoma, including AE1/AE3 (a broad-spectrum anticytokeratin stain), anticytokeratin 14, MNF116 (a collection of monoclonal antibodies to cytokeratins 5, 6, 8, 17, and 19), and p63.[4] Despite the utility of these stains in certain clinical situations, according to a 2001 survey only 13 of 108 (12%) of American College of Mohs Surgery laboratories were using real-time IHC, of which only some reported using anticytokeratin stains.[5] However, recent advances, including a new validated 19-minute staining protocol for AE1/AE3, the most commonly used anticytokeratin stain, have mitigated some of the concerns related to increased processing times and higher costs.[6] Of note, it is permissible to send Mohs stages for paraffin-embedded permanent sections in specific circumstances. According to the American Academy of Dermatology position statement on the topic, these include scenarios in which a tumor has aggressive histologic features or there is difficulty in ensuring accurate margin control.[7]

Adjuvant radiation therapy (ART) after surgical excisions of SCCs is a controversial topic. Although there are no clear consensus guidelines on when to use postsurgical ART, both the National Comprehensive Cancer Network and the American College of Radiology recommend ART in the setting of significant perineural invasion, which was not present in our case.[8,9] However, ART is also generally considered in the setting of lymph node involvement, invasion of the cranium, or, as in our case, when there are several high-risk features or multiple recurrences.[10] Importantly, in high-risk SCC, analysis of the central debulking from the Mohs procedure can be particularly useful before referral for adjuvant radiation, as it can offer further information regarding depth of invasion, perineural invasion, and other high-risk features potentially not identified in the original biopsy.

This case shows 2 major teaching points. First, it is extremely important to remain cognizant of the high-risk features of cutaneous SCCs, which, in this case, include concurrent hematologic malignancy, aggressive histologic features, and recurrent status. It is especially vital in these cases to ensure accurate margin control, strategies for which could include review of the original biopsy by the surgeon, careful analysis of the debulking specimen to familiarize oneself with the particular histopathology of a given tumor, or the use of immunohistochemistry. Second, this report illustrates the particular benefits of anticytokeratin IHC for patients with recurrent and aggressive SCCs and in those with underlying immune dysregulation, either with rapid staining protocols if available or, if not, on permanent sections using the slow Mohs technique. In cases such as this one, IHC can serve as a valuable tool to minimize excess morbidity in the management of squamous cell carcinoma.

REFERENCES

1. Miller CJ, Sobanko JF, Zhu X, Nunnciato T, Urban CR. Special stains in Mohs surgery. *Dermatol Clin*. 2011;29:273-286.
2. Zachary CB, Rest EB, Furlong SM, Arcedo PN, McGeorge BC, Kist DA. Rapid cytokeratin stains enhance the sensitivity of Mohs micrographic surgery for squamous cell carcinoma. *J Dermatol Surg Oncol*. 1994;20:530-535.
3. Cherpelis BS, Turner L, Ladd S, Glass LF, Fenske NA. Innovative 19-minute rapid cytokeratin immunostaining of nonmelanoma skin cancer in Mohs micrographic surgery. *Dermatol Surg*. 2009;35:1050-1056.
4. Stranahan D, Cherpelis BS, Glass LF, Ladd S, Fenske NA. Immunohistochemical stains in Mohs surgery: a review. *Dermatol Surg*. 2009;35:1023-1034.
5. Robinson JK. Current histologic preparation methods for Mohs micrographic surgery. *Dermatol Surg*. 2001;27:555-560.
6. Levi F, Randibison L, Te VC, La Vecchia C. Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br J Cancer*. 1996;74:1847-1850.

7. American Academy of Dermatology Position Statement on Appropriate Use of Paraffin Sections with Mohs Micrographic Surgery. Available from: https://www.aad.org/Forms/Policies/Uploads/PS/PS%20Appropriate%20Uses%20of%20Paraffin%20Sections%20in%20Association%20with%20Mohs%20Micrographic%20Surgery.pdf. Accessed May 1, 2016.
8. National Comprehensive Cancer Network Guidelines®—Squamous Cell Skin Cancer. Available from: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed May 3, 2016.
9. Koyfman SA, Cooper JS, Beitler JJ, et al. ACR appropriateness criteria® aggressive nonmelanomatous skin cancer of the head and neck. *Head Neck*. 2016;38(2):175-182.
10. LeBoeuf NR, Schmults CD. Update on the management of high-risk squamous cell carcinoma. *Semin Cutan Med Surg*. 2011;30:26-34.