Recurrent and Metastatic Primary Cutaneous Mucinous Carcinoma After Excision and Mohs Micrographic Surgery

Christine C. Tam, MD; David M. Dare, BA; John J. DiGiovanni, BS; Allan C. Harrington, MD; April C. Deng, MD, PhD

Primary cutaneous mucinous carcinoma is a neoplasm of sweat gland origin. Optimal management guidelines have not been established for this rare tumor. It is treated most commonly by traditional excision and more recently by Mohs micrographic surgery in an effort to decrease its recurrence rate. We report a case of primary cutaneous mucinous carcinoma with multiple recurrences and metastases following 3 excisions and 2 Mohs procedures, highlighting the potential difficulty in treating this cancer and suggesting the need for a more effective treatment approach.
Cutis. 2011;87:245-248.

Primary cutaneous mucinous carcinoma, a rare neoplasm with sweat gland differentiation, can be locally aggressive with a high recurrence rate following standard excision.[1] Mohs micrographic surgery has been used to treat this neoplasm with encouraging results,[2-12] though follow-up has been limited. We present a case of primary cutaneous mucinous carcinoma that recurred locally 3 times after traditional excision as well as Mohs micrographic surgery. After a second Mohs procedure, the patient developed 2 regional metastases, one that occurred following wide excision with lymph node dissection.

Case Report

In 2003 a 51-year-old man presented to an outside clinic with a nodule on his left mid cheek. Biopsy results revealed a mucinous carcinoma and the tumor was excised. The tumor recurred later that year and was reexcised. The margin size of either excision was not available.

In December 2004 the patient presented to our clinic with a nodule in the same area. A punch biopsy specimen showed a mucinous carcinoma with islands of tumor cells floating in pools of mucin (Figure 1). The tumor cells were strongly positive for low-molecular-weight cytokeratin, weakly positive for cytokeratin 5/6, and negative for p63. The tumor was cleared following 2 stages of Mohs micrographic surgery. Systemic workup by the hematology/oncology department, including computed tomography of the head and neck, revealed no further malignancy.

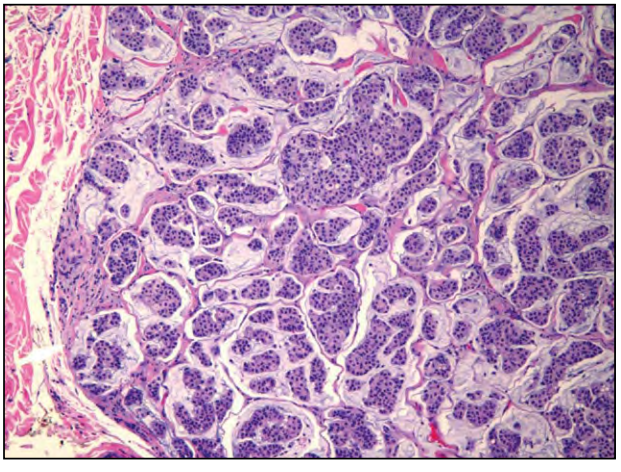

Figure 1. Section from nodule arising after second excision showing islands of tumor cells floating in pools of mucin (H&E, original magnification ×100).

Drs. Tam and Deng are from the Department of Dermatology, University of Maryland, Baltimore. Mr. Dare is from the University of Virginia School of Medicine, Charlottesville. Mr. DiGiovanni is from the Edward Via College of Osteopathic Medicine, Blacksburg, Virginia. Dr. Harrington is from the Department of Dermatology, Johns Hopkins University, Baltimore.
The authors report no conflict of interest.
Correspondence: Christine C. Tam, MD, 4869 Jones Dr, Fort Meade, MD 20755 (telias05@yahoo.com).

One and a half years after Mohs micrographic surgery, the patient developed a 2-cm nodule at his left lateral canthus, superior to the prior Mohs defect (Figure 2). A punch biopsy specimen confirmed a third recurrence of a mucinous carcinoma. An in situ component comprised of proliferating epithelium adherent to ductal walls with an intact peripheral myoepithelial layer was seen in multiple areas, confirming its primary cutaneous origin.

Computed tomography and magnetic resonance imaging showed no intraorbital extension of the tumor and no lymphadenopathy. The patient underwent a second Mohs procedure in May 2006 and the tumor was cleared in 2 stages. The patient was then referred to an otolaryngologist for resection of an additional margin of 2 mm adjacent to the eyelid margin and 4 mm around the remainder of the excision site to confirm a tumor-free plane. Serial section examination with hematoxylin and eosin staining and immunostaining with cytokeratin 7, pancytokeratin, and carcinoembryonic antigen revealed no residual tumor.

In November 2006, less than 1 year after his second Mohs procedure, the patient presented a fifth time with a 1.5-cm firm dermal nodule in the preauricular area, anterior to the tragus and 2.5 cm away from the Mohs surgical scar. Biopsy results confirmed a mucinous carcinoma. The patient was referred to an otolaryngologist for wide excision of the lesion and superficial parotidectomy, which revealed regional lymph node metastasis in 2 of 7 lymph nodes.

In July 2007 a 6-mm firm, mobile, subcutaneous nodule in the preauricular crease inferior to the tragus was noted. There was no palpable lymphadenopathy. A recurrence of the locally metastatic disease was confirmed by biopsy results demonstrating cords and nests of malignant epithelial calls in pools of mucin located in the deep dermis. An in situ component was not evident. Computed tomography of the head, neck, and chest revealed no evidence of further metastatic disease. A head and neck surgeon performed another wide excision with adjuvant postoperative radiation therapy. The patient had no evidence of recurrence or metastasis for 19 months before being lost to follow-up.

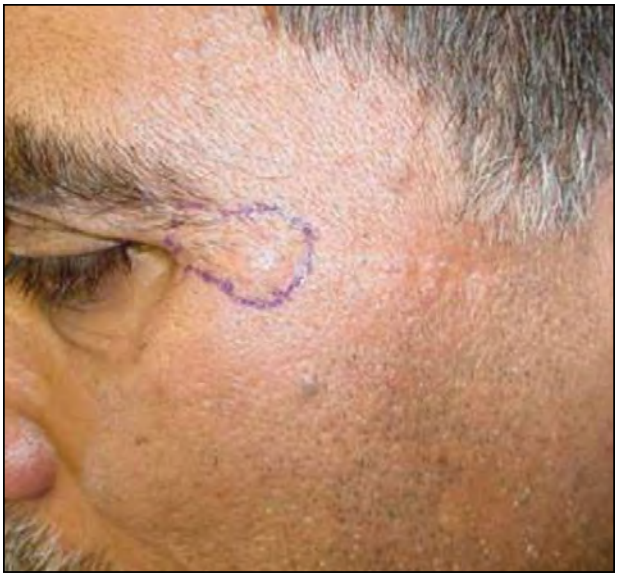

Figure 2. Left lateral canthus nodule arising after first Mohs procedure.

Comment

Primary cutaneous mucinous carcinoma is a rare neoplasm with sweat gland differentiation.[1] It typically presents in the sixth and seventh decades of life as a slowly growing, solitary, flesh-colored nodule on the head, especially the periorbital region, though its clinical appearance is variable.[1,13-16] Histology shows epithelial cells arranged in elongated cords, nests, cribriform masses, and ductlike structures floating in large pools of mucin separated by thin fibrovascular septa. The mucin stains positively with periodic acid–Schiff, colloidal iron, mucicarmine, and Alcian blue at a pH of 2.5.[1,13,17] The tumor cells show positive staining with S-100 protein; carcinoembryonic antigen; epithelial membrane antigen; and low-molecular-weight cytokeratins, including cytokeratin 7.[14,15,18] Estrogen- and progesterone-receptor positivity also has been demonstrated.[3,9,12,13,16,19] Cytokeratin 20 staining is almost always negative.[3,14,15,18]

The differential diagnosis for primary cutaneous mucinous carcinoma is broad. In particular, metastatic mucinous carcinoma to the skin originating in the breast, gastrointestinal tract, salivary gland, lacrimal gland, lung, gallbladder, pancreas, kidney, ovary, and prostate must be considered and ruled out. The presence of an in situ component bounded by basement membrane and myoepithelial cells is evidence for a primary cutaneous tumor.[14,15] Full clinical investigation to establish the origin of the tumor is essential if an in situ component is not evident.[14]

The local recurrence rate for primary cutaneous mucinous carcinoma is high, with reported rates of 21% to 43% after traditional surgical excision.[1,13,14] Multiple recurrences are not uncommon and may occur up to 9 years after initial presentation.[13,14,20] Locally aggressive behavior, including invasion into skeletal muscle,[1] bone,[20,21] sinuses,[20] and the orbit,[20-22] has led to aggressive surgical therapy such as vulvectomy,[15] craniofacial resection,[20,21] and orbital exenteration.[20-22] Recurrences tend to be more invasive.[2,20] There is an 11% metastatic rate to regional lymph nodes.[13] In-transit metastasis has been reported.[4]

Distant metastasis and death are rare.[13,23-25] Local excision has been the mainstay of treatment. Reported excision margins vary widely from 0.2 to 2 cm.[5,26-29] Even with wide margins, recurrences have been reported.[20,23,25]

According to a PubMed search of articles indexed for MEDLINE using the terms *primary cutaneous mucinous carcinoma*, *primary mucinous carcinoma*, *primary cutaneous sweat gland carcinoma*, *mucinous eccrine carcinoma*, and *cutaneous mucinous carcinoma*, all along with *Mohs surgery*, Mohs micrographic surgery has been performed for this tumor in 15 reported cases. In these cases, all final margins were clear and no additional permanent sections were removed.[2-12] Twelve of these cases showed no tumor recurrence for 1 to 5 years.[3-7,9-12] Of the 3 cases that recurred, 1 patient developed metastasis and died[8]; however, as stated in a letter to the editor by Bang et al,[30] this case was likely a metastatic mucinous carcinoma to the skin and not a primary cutaneous neoplasm due to its clinical behavior and histological and histochemical properties. In the other 2 cases of recurrence,[2] the patients underwent a second Mohs procedure, one with adjuvant postoperative radiation therapy, and were free of recurrence after 7 and 8 months. The authors suggested that an extra 5- to 6-mm margin after achieving clear margins with Mohs micrographic surgery may be prudent.[2] One case, free of recurrence for 3 years, employed rapid immunohistochemical staining of frozen sections using low-molecular-weight cytokeratin to enhance margin control. Immunostaining revealed a tumor in frozen sections that were equivocal or negative using hematoxylin and eosin staining.[6]

Discounting 1 Mohs treatment failure due to its probable noncutaneous origin,[8] our case brings the local recurrence rate of primary cutaneous mucinous carcinoma after Mohs micrographic surgery to 20% (3 of 15 cases) and, to our knowledge, is the first report of regional metastasis following Mohs micrographic surgery. This recurrence rate is comparable with standard excision and suggests the need for a different treatment approach for this neoplasm. The recurrent tumors in our case and in other reported cases[2,20] were more aggressive and difficult to treat, increasing the importance of completely clearing the primary tumor at the outset.

Treatment failure with standard excision may result from incomplete margin evaluation using the bread loafing technique. Although Mohs micrographic surgery allows for complete margin evaluation, increased difficulty interpreting frozen sections compared to permanent paraffin-embedded sections may contribute to some Mohs treatment failures. Mohs micrographic surgery in conjunction with rapid immunohistochemical staining may enhance margin control with frozen sections. Taking an additional margin after clearance with frozen sections to confirm a tumor-free plane also may be helpful. Another alternative is to perform slow Mohs utilizing Mohs mapping techniques with paraffin-embedded sections to allow for permanent section histologic evaluation of the entire surgical margin. To decrease the recurrence rate, adjuvant postoperative radiation therapy also may be considered, though the reported cases treated in this manner are few and without a clear improvement in outcome.[2,31] In 1 case utilizing this approach, the tumor recurred[2]; in 2 other cases, the patients have been free of recurrence for 7 months and 4 years.[2,31] Our patient received postoperative radiation therapy for his recurrent metastatic lesion and had been free of disease for 19 months before being lost to follow-up. When primary radiation therapy has been used to treat metastatic lesions, however, it has not been beneficial.[24,25]

Conclusion

Primary cutaneous mucinous carcinoma continues to have a high recurrence rate despite Mohs micrographic surgery, though the number of cases is still small. Potential interventions to increase the rate of surgical cure using the Mohs technique include adding immunohistochemical stains to frozen sections, taking an additional margin after clearance with frozen sections, and using paraffin-embedded sections. Further study is needed to determine if these or other treatment interventions would lead to better overall outcomes.

ADDENDUM

After the manuscript was accepted for publication, 5 cases of primary cutaneous mucinous carcinoma treated with Mohs micrographic surgery were reported.[32] No rapid immunohistochemical staining of frozen sections was performed and no additional permanent sections were taken. The patients did not receive adjuvant radiation therapy. Four of 5 patients were cleared after Mohs micrographic surgery and remained disease free at 3 months to 4 years of follow-up. One patient had positive margins of resection; this patient developed 2 recurrences, which were both surgically excised.[32]

REFERENCES

1. Mendoza S, Helwig EB. Mucinous (adenocystic) carcinoma of the skin. *Arch Dermatol*. 1971;103:68-78.
2. Durairaj VD, Hink EM, Kahook MY, et al. Mucinous eccrine adenocarcinoma of the periocular region. *Ophthal Plast Reconstr Surg*. 2006;22:30-35.

3. Cecchi R, Rapicano V. Primary cutaneous mucinous carcinoma: report of two cases treated with Mohs' micrographic surgery. *Australas J Dermatol*. 2006;47:192-194.
4. Tannous ZS, Avram MM, Zembowicz A, et al. Treatment of synchronous mucinous carcinoma and endocrine mucin-producing sweat gland carcinoma with Mohs' micrographic surgery. *Dermatol Surg*. 2005;31:364-367.
5. Cabell CE, Helm KF, Sakol PJ, et al. Primary mucinous carcinoma in a 54-year-old man. *J Am Acad Dermatol*. 2003;49:941-943.
6. Marra DE, Schanbacher CF, Torres A. Mohs micrographic surgery of primary cutaneous mucinous carcinoma using immunohistochemistry for margin control. *Dermatol Surg*. 2004;30:799-802.
7. Bindra M, Keegan DJ, Guenther T, et al. Primary cutaneous mucinous carcinoma of the eyelid in a young male. *Orbit*. 2005;24:211-214.
8. Jih MH, Friedman PM, Kimyai-Asadi A, et al. A rare case of fatal primary cutaneous mucinous carcinoma of the scalp with multiple in-transit and pulmonary metastases. *J Am Acad Dermatol*. 2005;52(5, suppl 1):76-80.
9. Bertagnoli R, Cook DL, Goldman GD. Bilateral primary mucinous carcinoma of the eyelid treated with Mohs surgery. *Dermatol Surg*. 1999;25:566-568.
10. Weber PJ, Hevia O, Gretzula JC, et al. Primary mucinous carcinoma. *J Dermatol Surg Oncol*. 1988;14:170-172.
11. Ortiz KJ, Gaughan MD, Bang RH, et al. A case of primary mucinous carcinoma of the scalp treated with mohs surgery. *Dermatol Surg*. 2002;28:751-754.
12. Snow SN, Reizner GT. Mucinous eccrine carcinoma of the eyelid. *Cancer*. 1992;70:2099-2104.
13. Wright JD, Font RL. Mucinous sweat gland adenocarcinoma of eyelid: a clinicopathologic study of 21 cases with histochemical and electron microscopic observations. *Cancer*. 1979;44:1757-1768.
14. Kazakov DV, Suster S, LeBoit PE, et al. Mucinous carcinoma of the skin, primary, and secondary: a clinicopathologic study of 63 cases with emphasis on the morphologic spectrum of primary cutaneous forms: homologies with mucinous lesions in the breast. *Am J Surg Pathol*. 2005;29:764-782.
15. Qureshi HS, Salama ME, Chitale D, et al. Primary cutaneous mucinous carcinoma: presence of myoepithelial cells as a clue to the cutaneous origin. *Am J Dermatopathol*. 2004;26:353-358.
16. Hanby AM, McKee P, Jeffery M, et al. Primary mucinous carcinomas of the skin express TFF1, TFF3, estrogen receptor, and progesterone receptors. *Am J Surg Pathol*. 1998;22:1125-1131.
17. Headington JT. Primary mucinous carcinoma of skin: histochemistry and electron microscopy. *Cancer*. 1977;39:1055-1063.
18. Bellezza G, Sidoni A, Bucciarelli E. Primary mucinous carcinoma of the skin. *Am J Dermatopathol*. 2000;22:166-170.
19. Kwatra KS, Prabhakar BR, Jain S. Oestrogen and progesterone receptors in primary mucinous carcinoma of skin. *Australas J Dermatol*. 2005;46:246-249.
20. Tanaka A, Hatoko M, Kuwahara M, et al. Recurrent mucinous carcinoma of the skin invading to the frontal skull base. *Br J Dermatol*. 2000;143:458-459.
21. Andrews TM, Gluckman JL, Weiss MA. Primary mucinous adenocarcinoma of the eyelid. *Head Neck*. 1992;14:303-307.
22. Holds JB, Haines JH, Mamalis N, et al. Mucinous adenocarcinoma of the orbit arising from a stable, benign-appearing eyelid nodule. *Ophthalmic Surg*. 1990;21:163-166.
23. Ajithkumar TV, Nileena N, Abraham EK, et al. Bone marrow relapse in primary mucinous carcinoma of skin. *Am J Clin Oncol*. 1999;22:303-304.
24. Yeung KY, Stinson JC. Mucinous (adenocystic) carcinoma of sweat glands with widespread metastasis. case report with ultrastructural study. *Cancer*. 1977;39:2556-2562.
25. Rao KV, Tikku I, Kapur BM, et al. Invasive primary mucinous carcinoma of the skin. *Int Surg*. 1978;63:168-170.
26. Grossman JR, Izuno GT. Primary mucinous (adenocystic) carcinoma of the skin. *Arch Dermatol*. 1974;110:274-276.
27. Karimipour DJ, Johnson TM, Kang S, et al. Mucinous carcinoma of the skin. *J Am Acad Dermatol*. 1997;36(2, pt 2):323-326.
28. Abe S, Matsumoto Y, Fujita T. Primary mucinous carcinoma of the skin. *Plast Reconstr Surg*. 1997;99:1160-1164.
29. Fukamizu H, Tomita K, Inoue K, et al. Primary mucinous carcinoma of the skin. *J Dermatol Surg Oncol*. 1993;19:625-628.
30. Bang RH, Bang R, Padilla RS. Case of fatal cutaneous mucinous carcinoma of the scalp with multiple in-transit and pulmonary metastases unlikely to have been of primary cutaneous origin [letter]. *J Am Acad Dermatol*. 2006;55:726-727.
31. Breier F, Clabian M, Pokieser W, et al. Primary mucinous carcinoma of the scalp. *Dermatology*. 2000;200:250-253.
32. Zhang Q, Wojno TH, Fitch SD, et al. Mucinous eccrine adenocarcinoma of the eyelid: report of 6 cases. *Can J Ophthalmol*. 2010;45:76-78.