BRAF/MEK inhibitor-induced remission of primary cutaneous myoepithelial carcinoma after local recurrence

Jacqueline Guidry, MD,[a] Karl Lewis, MD,[b] and Mariah Brown, MD[a]
Aurora, Colorado

Key words: BRAF inhibitor; cobimetinib; cutaneous myoepithelial carcinoma; myoepithelial carcinoma; MEK inhibitor; vemurafenib.

INTRODUCTION

Cutaneous myoepithelial carcinoma (MEC), also referred to as malignant myoepithelial tumor of the skin, is an extraordinarily rare diagnosis, with fewer than 15 cases reported in the scientific literature.[1-4] These tumors are aggressive, and surgical excision with clear margins is the treatment of choice.[2,3] However, postsurgical local recurrence and metastases occur in up to 30% and 15% of cases, respectively.[1] Additional therapeutic options are limited; traditional chemotherapy and/or radiation have been described with variable and often disappointing results.[2] Novel treatment modalities are needed for patients who develop local or metastatic disease. We describe a patient with extensive MEC on the lower portion of the left lower extremity complicated by local recurrence who had a complete response to small-molecule therapy with combined BRAF/MEK inhibition.

Abbreviations used:

MEC: myoepithelial carcinoma
PET: positron emission tomography

CASE REPORT

A 65-year-old woman presented to an outside dermatologist with a rapidly growing papule on the left ankle for 1 month. Results of punch biopsy of the lesion were inconclusive but favored a melanocytic lesion. An excisional biopsy was performed 1 month later; the results of pathologic analysis were consistent with MEC involving the deep and peripheral margins (Figs 1-3). Positron emission tomography (PET) scan showed postbiopsy changes on the left ankle only. Two months after diagnosis, wide local excision was performed with sentinel lymph node biopsy of the left inguinal node. Pathologic analysis showed residual MEC to a depth of 1.8 cm with positive deep margin. Sentinel lymph node biopsy results were negative. Three months after diagnosis, repeat excision results were negative for residual disease.

The patient was stable for 10 months until a PET scan showed evidence of local recurrence. Repeat excision had positive margins, and further surgical treatment was not feasible due to the extent of involvement and complications with wound healing. The patient was referred to the radiation oncology department and completed 5500 cGy in 22 fractions to the site 4 months after the recurrence.

A follow-up PET scan was done 2 months after radiation completion and showed areas of increased uptake at the site of surgery. It was unclear if this represented reactive changes or residual disease. Repeat PET scan 4 months later (11 months after recurrence) showed enlarged, persistent areas of uptake and new areas of disease consistent with local recurrence. Our patient was evaluated by a surgical oncologist, with planned amputation of the leg.

The treatment options for recurrent MEC no longer amenable to excision are anecdotal and limited in success. Although MEC does not have a known associated genetic mutation, broad

From the Departments of Dermatology[a] and Cutaneous Oncology, University of Colorado, Aurora.[b]
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Mariah Brown, MD, 1665 Aurora Ct, Mail Stop F703, Aurora, CO 80045. E-mail: Mariah.brown@ucdenver.edu.
JAAD Case Reports 2020;6:783-6.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.07.023

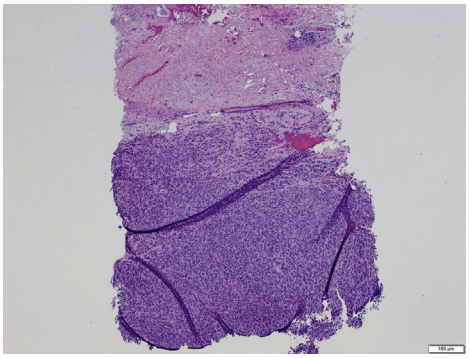

Fig 1. H&E-stained slide at × 4 original magnification of the excised tumor. At high power, a dense basophilic tumor located in the deep dermis and subcutis is visible. The tumor is not well circumscribed, and at the edges, tumor cells are infiltrating into the surrounding dermis.

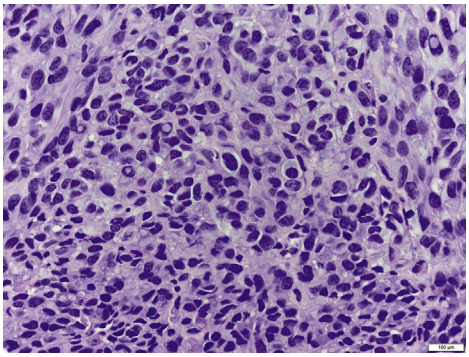

Fig 2. H&E-stained slide at × 40 original magnification of the excised tumor. The tumor has a dense population of pleomorphic, basophilic cells that are predominantly epithelioid. Occasional spindled cells are seen. Nuclear irregularities (coarse chromatin, prominent nucleoli, mitoses) are seen in several cells.

molecular testing of the tumor tissue was done with the hope of elucidating a potential target mutation to guide systemic treatment and avoid amputation. The chosen test analyzes cancer specimens for 4 main classes of genomic alterations and biomarkers known to be relevant in solid tumors, sarcomas, and hematologic malignancies. The patient's tumor was positive for a BRAF V600E mutation, a common mutation seen in malignant melanoma.

One year after recurrence, the patient began taking vemurafenib, a BRAF inhibitor, and cobimetinib, a MEK inhibitor. Because of several complications (wound infection, recurrent upper respiratory infections, and poor tolerability), the treatment was given intermittently. Repeat PET scan after 2 months of treatment showed nearly complete resolution of her hypermetabolic nodules. Vemurafenib-cobimetinib therapy was

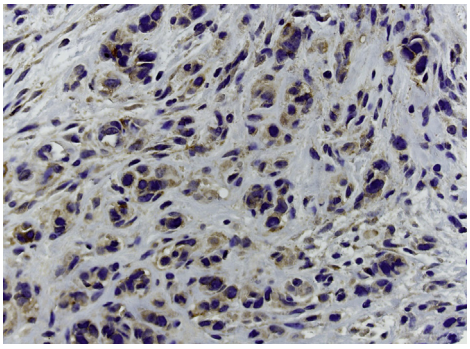

Fig 3. Positive staining for epithelial membrane antigen at × 40 original magnification. The lesion also stained positive for KBA62 and S100. Staining for CD34, CD45, CD56, Mart-1, HMB45, CK20, chromogranin, synaptophysin, desmin, p63, and pancytokeratin was performed, and results were negative. Because of their bidirectional differentiation, myoepithelial cells coexpress epithelial and muscle-specific immunohistochemical markers, typically keratin or epithelial membrane antigen and S-100.

discontinued after 5 months because of poor tolerability. Results of scouting biopsies 1 month after treatment discontinuation were negative for disease. Fifteen months after stopping vemurafenib and cobimetinib, a repeat PET scan had no evidence of disease. At the patient's last visit, 18 months after treatment discontinuation, she had no evidence of clinical recurrence (Fig 4).

DISCUSSION

Cutaneous MEC is an aggressive malignancy with high risk of metastases and local recurrence.[2] Postsurgical local recurrence and metastases have been reported in up to 30% and 15% of cases, respectively; however, the true metastatic and recurrence potential is difficult to estimate given the rarity of this tumor.[1] Although surgical removal with clear margins is the treatment of choice, this can be impractical in some cases, such as for the patient described here.

MEC is a rare malignancy that most commonly occurs in the salivary glands.[1] Cutaneous MEC is an even rarer entity that has been most commonly reported on the head and neck and the lower extremities.[1-4] Reported cases suggest that MEC has a slight female predominance with a bimodal age distribution (before adulthood or after the fifth to sixth decades).[2-4]

Myoepithelial cells are ectoderm-derived, specialized basal epithelial cells located in the salivary glands, respiratory tract, breast, and sweat glands, although they can also express mesenchymal characteristics due to bidirectional differentiation.[2,4] Normal myoepithelial cells are spindle shaped and

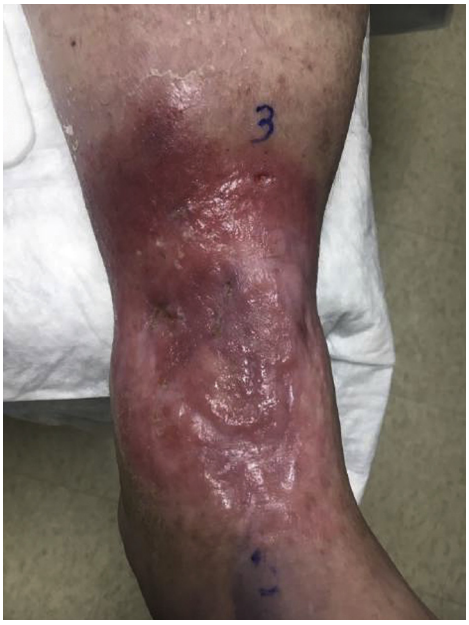

Fig 4. Clinical photograph of the patient's left ankle with no evidence of clinical recurrence. Because of difficulty in healing, the patient has a large atrophic scar, but the appearance has been stable over many months. Clinical signs of recurrence include new nodularity or ulceration, which are not seen in this photo.

located around the eccrine and apocrine glands, where they assist with delivery of secretory products.[2] In tumor form, myoepithelial cells show several morphologies, including spindled, hyaline, epithelioid, and clear cell, and their proliferation can lead to either benign myoepitheliomas or malignant MEC.[1-3]

MEC can be difficult to diagnosis histologically because of these variations in cell morphology, as well as similarity in histologic appearance and immunohistochemical staining to their benign counterpart.[1,4] Histologic features that favor MEC include infiltrative growth pattern, angiolymphatic or perineural invasion, nuclear atypia (pleomorphism, coarse chromatin, prominent nucleoli), and a high number of mitoses.[1,3] High mitotic rate is thought to predict a higher chance of local recurrence and/or metastasis.[2,3]

Because of their bidirectional differentiation, myoepithelial cells coexpress epithelial and muscle-specific immunohistochemical markers, typically keratin or epithelial membrane antigen and S-100.[3] Frost et al published a detailed table of immunohistochemical test positivity in myoepithelioma versus MEC.[2] The histopathologic differential diagnosis also includes extraskeletal myxoid chondrosarcoma, ossifying fibromyxoid tumor of soft parts, and extra-axial soft-tissue chordoma.[3]

Clinical size and appearance of these tumors also varies. Tumor sizes range from 0.7 to 7 cm, and most frequently, a soft dermal or subcutaneous nodule with or without ulceration is described.[1-4] No clear guidelines exist for systemic workup, but PET scan and sentinel lymph node biopsy are considered advisable given the tumor's high metastatic potential. Some researchers have advocated for lymph node dissection in every patient.[1] If localized, the treatment of choice is surgical removal with clear margins.[1] Most reports in the literature describe surgical treatment as wide local excision; however, no clear recommendation has been made for surgical margins. Although Mohs surgery has been reported for treatment of a recurrent myoepithelioma, it has not been described for MEC.[5]

There is no defined treatment algorithm in the setting of inoperable tumors, incompletely removed tumors, or metastatic disease. Treatment modalities reported include chemotherapy (systemic and isolated limb infusion) and radiation therapy.[1,2] The efficacy of these therapies is variable and often ineffective. Systemic chemotherapy alone is inadequate but may be reasonable when used in combination with surgical removal and may be more beneficial in pediatric patients.[2,3] Fitzgerald et al[1] reported the successful use of preoperative radiation to shrink tumor size. Radiation monotherapy for recurrent or metastatic MEC has been performed without significant benefit,[2] as in our patient.

Given the limited therapeutic options for inoperable or metastatic disease, we suggest genetic testing to identify potentially effective systemic therapies. The increasing availability of genomic profiling for tumors may allow for the identification of targeted systemic therapy for rare and aggressive cutaneous tumors, such as in this case. There is very little to no information available about the frequency of mutations in MEC. Broad molecular testing can detect mutations based on biomarkers known to be relevant in other tumor types and may elucidate additional treatment options, including currently available targeted therapies. Our patient's tumor had a BRAF V600E mutation and responded to combined BRAF/MEK inhibitor therapy.

The authors would like to thank Matthew Mahlberg, MD, referring physician, and Lori Prok, MD, dermatopathologist, for their assistance with this case report.

REFERENCES

1. Fitzgerald MJ, Busam K, Athanasian E, Brady MS. Myoepithelial carcinoma of the extremity: response to isolated limb infusion. *J Surg Oncol*. 2015;112:510-513.

2. Frost MW, Steiniche T, Damsgaard TE, Stolle LB. Primary cutaneous myoepithelial carcinoma: a case report and review of the literature. *APMIS*. 2013;122:369-379.
3. Johnson GE, Stevens K, Morrison AO, et al. Cutaneous myoepithelial carcinoma with disseminated metastases. *Cutis*. 2017; 99:e19-e26.
4. Yokose C, Asai J, Kan S, et al. Myoepithelial carcinoma on the right shoulder: case report with published work review. *J Dermatol*. 2016;43:1083-1087.
5. Miller TD, McCalmont T, Tope WD. Recurrent cutaneous myoepithelioma treated using Mohs micrographic surgery: case report and review of the literature. *Dermatol Surg*. 2009;35:139-143.