Cutaneous Adnexal Carcinoma With Apocrine Differentiation

Vikram Prasad, MD; Wynn H. Kao, MD, PhD; Grace F. Kao, MD

PRACTICE **POINTS**

- Despite advances in immunohistochemical analysis, differentiating between primary apocrine carcinoma and metastatic breast carcinoma remains largely dependent on the clinical course of the patient.
- Treatment of apocrine carcinoma typically involves local excision with clear margins with or without lymph node dissection.

Primary cutaneous apocrine carcinomas are uncommon malignant neoplasms that can be difficult, if not impossible, to distinguish histologically from metastatic breast carcinomas. We present the case of a 71-year-old man with a 5-year history of extensive ulcerated plaques on the posterior neck and posterior scalp. Biopsy revealed a poorly differentiated infiltrating adenocarcinoma consistent with either primary cutaneous apocrine carcinoma or occult metastatic breast carcinoma. Immunohistochemical analysis demonstrated positive staining for cytokeratin (CK) 7, estrogen receptor, and progesterone receptor, and negative staining for p63, podoplanin, CK20, and thyroid transcription factor 1. Extensive radiologic imaging studies showed no evidence of occult breast or other internal malignancies. Based on the indolent clinical course, lack of evidence for an internal primary site, and immunohistochemical staining, the lesion was determined to be consistent with a cutaneous neoplasm with features of apocrine differentiation. This case highlights the distinction between apocrine carcinoma and other primary adnexal carcinomas for which p63 and D2-40 have been reported to be sensitive and specific markers but are negative in apocrine carcinomas.

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Differentiation between a primary adnexal carcinoma and a metastatic carcinoma to the skin is a challenging yet critical task for dermatologists and pathologists. Carcinomas that have metastasized to the skin are a sign of widespread systemic involvement and poor prognosis, while primary adnexal carcinomas tend to progress with an indolent clinical course. Although many patients with cutaneous metastases from an internal primary neoplasm can expect a median survival of no more than 12 months,[1] patients with primary adnexal carcinomas are reported to have a 5-year survival rate of 95.5% for localized disease and 85% with spread to regional lymph nodes.[2] We report a case of multiple cutaneous neoplasms of unknown primary origin in a 71-year-old man and describe our approach to identification of the possible primary site as well as management of the disease.

Case Report

A 71-year-old man initially presented to his primary physician for evaluation of a mass on the left side of the neck of 3 months' duration. On physical

Drs. Prasad and WH Kao are from the Department of Dermatology, The George Washington University School of Medicine, Washington, DC. Dr. GF Kao is from the Department of Dermatology, University of Maryland School of Medicine, Baltimore.
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Correspondence: Vikram Prasad, MD, 2150 Pennsylvania Ave NW, Washington, DC 20037 (vprasad@gwmail.gwu.edu).

examination, a firm 2.5×3.0-cm nodule was noted at the anterior border of the trapezius muscle. Palpation of the thyroid revealed an additional right-sided nodule. The submandibular and parotid glands were unremarkable to palpation. The patient was referred to general surgery for biopsy, which revealed an infiltrating, moderately differentiated adenocarcinoma with extensive lymphatic permeation. Immunohistochemical staining for cytokeratin (CK) 7 was positive, while CK20 and thyroid transcription factor 1 were negative. A positron emission tomography/computed tomography (CT) fusion scan demonstrated 3 areas of enhanced uptake: one in the right side of the thyroid, a second corresponding to the mass on the left side of the neck at the level of the trapezius muscle, and a third in the left masseter muscle. Surgical excision with negative margins with possible chemotherapy was recommended; however, the patient declined treatment and was lost to follow-up until 2 years later when he presented to his primary physician with an additional lesion on his scalp.

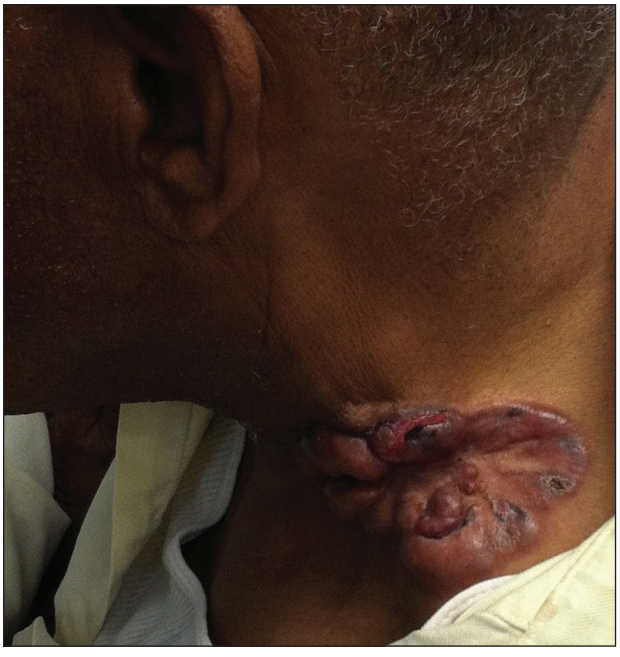

Figure 1. Indurated ulcerated plaque on the left side of the lateral neck 5 years after initial presentation.

Four years after the biopsy, the patient presented to the dermatology department with additional tumor nodules including a 4-cm, annular, indurated, focally eroded plaque on the left side of the lateral neck (Figure 1); 3 separate 1-cm nodules on the right side of the lateral neck; and an ulcerated, crusted, 10×8-cm plaque on the posterior aspect of the scalp. Despite the extensive lesions, the patient remained in good health and reported no recent weight loss or signs or symptoms of systemic involvement. The posterior scalp lesion, which developed 2 years after the initial appearance of the mass on the neck and was thought to represent a possible metastasis of the tumor, was biopsied and showed diffuse infiltration of the dermis by poorly differentiated tumor cells with vacuolated cytoplasm arranged in nests and cords and sometimes in a single-file arrangement (Figure 2). A CT scan demonstrated pretracheal lymphadenopathy as well as small intraparenchymal and subpleural pulmonary nodules throughout both lung fields.

Another scalp biopsy was taken. Tumor cells were negative on mucicarmine staining. Additional immunohistochemical staining, including a periodic acid–Schiff stain with diastase digestion for epithelial mucin revealed minimal luminal positivity. Immunostaining was positive for CK7, carcinoembryonic antigen, CD15, estrogen receptor, progesterone receptor, gross cystic disease fluid protein 15 (GCDFP-15), and mammaglobin, and negative for CK20, podoplanin, thyroid transcription factor 1, S-100 protein, p63, and prostate specific antigen. *ERBB2* (formerly *HER2/neu*) staining was negative according to fluorescence in situ hybridization analysis. Tumor cells showed a Ki-67 nuclear proliferation

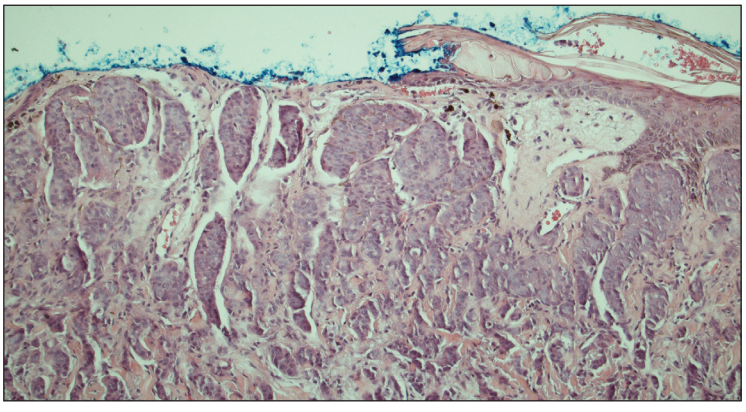

Figure 2. Histopathology of a posterior scalp lesion demonstrated irregular nests and confluent islands of undifferentiated tumor cells infiltrating the upper dermis, approaching but not connected to the epidermis, along with rounded to ovoid nuclei and abundant eosinophilic cytoplasm (H&E, original magnification ×100).

index of greater than 50%, indicating progression to aggressive carcinoma.

Based on the histological and immunochemical studies, the differential diagnosis included primary cutaneous apocrine carcinoma versus breast carcinoma; however, the prolonged clinical progression of these lesions favored a primary cutaneous adnexal tumor over a metastatic adenocarcinoma. Nevertheless, despite the initially indolent growth of the lesions over the first 5 years, the Ki-67 proliferation index and presence of widespread metastases on the posterior scalp indicated progression to an aggressive carcinoma. Chemotherapy was recommended as the treatment of choice. At his most recent follow-up visit 4 months later, the patient chose to begin treatment with tamoxifen and refused other treatment options.

Comment

The distinction between primary adnexal and metastatic adenocarcinomas of the skin is challenging both clinically and histologically. Some pathologists have argued that metastatic breast carcinomas and primary cutaneous apocrine carcinomas are essentially indistinguishable.[3] Patients with cutaneous metastases, which occur in approximately 5.3% of all malignancies,[4] typically can expect survival of no more than 12 months from the time of detection.[1] In contrast, primary apocrine carcinomas of the skin, though much less common, carry a remarkably better prognosis, with 5-year relative survival rates of 95.5% and 85.5% reported for patients with localized disease and spread to regional lymph nodes, respectively.[2]

Fewer than 100 cases of primary cutaneous adnexal (apocrine) carcinomas have been reported overall, with the earliest known report dating back to 1944.[5] According to the literature, primary apocrine carcinomas were diagnosed at a median age of 66 years and were slightly more common in females than males.[2,6] Apocrine carcinomas were seen most frequently on the head, neck, and trunk,[2] generally presenting in the form of asymptomatic nodules or plaques of 2 to 3 cm in size, with gradual progression occurring over months to years.[6] Approximately 40% of patients have been reported with positive regional lymph nodes at diagnosis. Treatment of apocrine carcinoma typically has involved local excision with clear margins with or without lymph node dissection. Chemotherapy and radiation therapy have shown no proven benefit.[7]

Currently, there is no standardized approach to evaluating patients with possible cutaneous metastasis versus primary cutaneous adnexal carcinomas. Imaging studies such as mammography and abdominal CT typically reveal an internal primary cancer in one-third of patients. However, additional studies such as gastrointestinal radiography, chest and pelvic CT, barium enema, and intravenous pyelogram have shown to be of limited value.[8] Although specificity and sensitivity of immunohistochemistry is limited, a number of immunomarkers, including CK7 and CK20, are routinely studied to narrow the differential diagnosis of a cutaneous neoplasm of unclear origin. Urothelial, gastric, colorectal, and pancreatic carcinomas generally are positive for CK20; CK7-positive adenocarcinomas include salivary, non–small cell lung, breast, ovarian, pancreatic, endometrial, and transitional cell adenocarcinomas. Carcinomas negative for both CK7 and CK20 include colorectal, hepatocellular, renal cell, prostate, and squamous cell carcinoma of the lung.

The presence of positive staining for estrogen and progesterone receptors as well as GCDFP-15 and mammaglobin raised the possibility of primary breast adenocarcinoma in our patient, but given that these markers can be positive in primary cutaneous adnexal tumors, immunohistochemistry results were not able to provide a definitive primary site. The overall staining pattern was nearly identical to 26 cases of primary cutaneous cribriform apocrine carcinoma, which was found to be positive for CK7 and carcinoembryonic antigen, and negative for CK20 and S-100. The only difference was in GCDFP-15 staining, which was positive in our case and negative in the cases of cribriform apocrine carcinoma.[9] Histologic features favoring a primary apocrine origin include normal apocrine glands in the vicinity, glandular structures with decapitation secretion high in the dermis, and intracytoplasmic iron granules.[10] Additionally, positive estrogen receptor staining appears to be much more common in apocrine carcinomas (5/10) than in eccrine carcinomas (1/7).[11]

A number of other markers have been investigated for possible diagnostic utility for distinction between primary adnexal carcinomas and metastatic adenocarcinomas. The nuclear transcription factor p63, which plays a role in keratinocyte differentiation, is preferentially expressed in a number of primary adnexal carcinomas and is purported to be the most sensitive marker overall, with a sensitivity of 78% to 91%.[12-14] However, p63 has shown incomplete specificity for primary adnexal neoplasms, having been reported as positive in 11% to 22% of adenocarcinomas metastatic to skin.[15-18] Nestin and CK15, which are expressed in hair follicle progenitor cells, also are potential specific markers for some primary adnexal lesions, specifically eccrine carcinoma, porocarcinoma, hidradenocarcinoma, and microcystic

adnexal carcinoma; however, in one report, none of the apocrine carcinomas were positive for p63, cytokeratin 15, or D2-40.[19] Thus, while markers for some primary adnexal neoplasms are emerging, specific tests at the immunohistochemical level for the apocrine carcinoma subgroup are still lacking.

Conclusion

In summary, a conclusive distinction between primary cutaneous apocrine carcinoma and metastatic adenocarcinoma to the skin remains challenging. Although new markers provide more specificity and sensitivity for neoplasms of eccrine origin, these markers do not appear to differentiate between primary apocrine carcinoma and metastatic breast carcinoma. In this case, as in other recent reports, diagnosis remained dependent on the clinical course of the patient. Although considerable progress has been made regarding immunohistochemical analysis of these cases, additional markers, especially ones more specific for primary skin cancers with apocrine differentiation, are still needed.

REFERENCES

1. Nashan D, Müller ML, Braun-Falco M, et al. Cutaneous metastases of visceral tumours: a review. *J Cancer Res Clin Oncol*. 2009;135:1-14.
2. Blake PW, Bradford PT, Devesa SS, et al. Cutaneous appendageal carcinoma incidence and survival patterns in the United States: a population-based study. *Arch Dermatol*. 2010;146:625-632.
3. Fernandez-Flores A. The elusive differential diagnosis of cutaneous apocrine adenocarcinoma vs. metastasis: the current role of clinical correlation. *Acta Dermatovenerol Alp Pannonica Adriat*. 2009;18:141-142.
4. Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma. A retrospective study of 7316 cancer patients. *J Am Acad Dermatol*. 1990;22:19-26.
5. Horn RC. Malignant papillary cystadenoma of sweat glands with metastases to the regional lymph nodes. *Surgery*. 1944;16:348-355.
6. Pucevich B, Catinchi-Jaime S, Ho J, et al. Invasive primary ductal apocrine adenocarcinoma of axilla: a case report with immunohistochemical profiling and a review of literature. *Dermatol Online J*. 2008;14:5.
7. Vasilakaki T, Skafida E, Moustou E, et al. Primary cutaneous apocrine carcinoma of sweat glands: a rare case report [published online December 17, 2011]. *Case Rep Oncol*. 2011;4:597-601.
8. Hainsworth JD, Greco FA. Treatment of patients with cancer of an unknown primary site. *N Engl J Med*. 1993;329:257-263.
9. Rutten A, Kutzner H, Mentzel T, et al. Primary cutaneous cribriform apocrine carcinoma: a clinicopathologic and immunohistochemical study of 26 cases of an underrecognized cutaneous adnexal neoplasm. *J Am Acad Dermatol*. 2009;61:644-651.
10. Elder DE, Elenitsas R, Johnson BL Jr, et al, eds. *Lever's Histopathology of the Skin*. 10th ed. Philadelphia, PA: Lippincott, Williams, and Wilkins; 2009.
11. Le LP, Dias-Santagata D, Pawlak AC, et al. Apocrine-eccrine carcinomas: molecular and immunohistochemical analyses. *PLoS One*. 2012;7:e47290.
12. Levrero M, De Laurenzi V, Costanzo A, et al. The p53/p63/p73 family of transcription factors: overlapping and distinct functions. *J Cell Sci*. 2000;113:1661-1670.
13. Pellegrini G, Dellambra E, Golisano O, et al. p63 identifies keratinocyte stem cells. *Proc Natl Acad Sci U S A*. 2001;98:3156-3161.
14. Reis-Filho JS, Torio B, Albergaria A, et al. p63 expression in normal skin and usual cutaneous carcinomas. *J Cutan Pathol*. 2002;29:517-523.
15. Sariya D, Ruth K, Adams-McDonnell R, et al. Clinicopathologic correlation of cutaneous metastases: experience from a cancer center. *Arch Dermatol*. 2007;143:613-620.
16. Liang H, Wu H, Giorgadze TA, et al. Podoplanin is a highly sensitive and specific marker to distinguish primary skin adnexal carcinomas from adenocarcinomas metastatic to skin. *Am J Surg Pathol*. 2007;31:304-310.
17. Kanitakis J, Chouvet B. Expression of p63 in cutaneous metastases. *Am J Clin Pathol*. 2007;128:753-758.
18. Qureshi HS, Ormsby AH, Lee MW, et al. The diagnostic utility of p63, CK5/6, CK 7, and CK 20 in distinguishing primary cutaneous adnexal neoplasms from metastatic carcinomas. *J Cutan Pathol*. 2004;31:145-152.
19. Mahalingam M, Nguyen LP, Richards JE, et al. The diagnostic utility of immunohistochemistry in distinguishing primary skin adnexal carcinomas from metastatic adenocarcinoma to skin: an immunohistochemical reappraisal using cytokeratin 15, nestin, p63, D2-40, and calretinin. *Mod Pathol*. 2010;23:713-719.