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Primary Cutaneous Cribriform Apocrine Carcinoma

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 Study Design A
 Data Collection B
 Statistical Analysis C
 Data Interpretation D
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ABCDEF 1 **Michelle Boettler**
 BCDE 1 **Martha A. Hickmann**
 ABDEF 2,3,4 **Jeffrey B. Travers**

1 Dayton Skin Care Specialists, Dayton, OH, U.S.A.
 2 Department of Pharmacology and Toxicology, Boonshoft School of Medicine, Wright State University, Dayton, OH, U.S.A.
 3 Department of Dermatology, Boonshoft School of Medicine, Wright State University, Dayton, OH, U.S.A.
 4 Dayton VA Medical Center, Dayton, OH, U.S.A.

Corresponding Author: Jeffrey B. Travers, e-mail: Jeffrey.travers@wright.edu

Conflict of interest: None declared

Patient: Male, 56-year-old
Final Diagnosis: Apocrine carcinoma
Symptoms: Lesion on skin
Medication: —
Clinical Procedure: —
Specialty: Dermatology

Objective: Rare disease

Background: Primary cutaneous cribriform apocrine carcinoma is a histopathological variant of apocrine adenocarcinoma (AA) of the skin, which is a rare, low-grade malignancy. While low-grade in nature, cutaneous cribriform apocrine carcinoma can mimic a metastatic manifestation of a visceral or breast malignancy, and is important to distinguish as primary through clinical history, histology, and immunohistochemical studies, if indicated.

Case Report: A 56-year-old man with past medical history remarkable for basal cell carcinoma and hypertension presented with a 12-month history of a slowly enlarging, asymptomatic nodule on his right anterior medial lower leg. Physical examination revealed a 12×9 mm indurated and erythematous nodule with no other masses or lymphadenopathy detected. Histology demonstrated a well-circumscribed proliferation of epithelial cells in fibrosing granulation tissue-like stroma having the delicate cross-bridging of a cribriform carcinoma. Immunohistochemical studies were significant for positive high-molecular-weight keratin and cytokeratin, focal positivity for carcinoembryonic antigen (CEA) and S100, with negative results for prostate-specific antigen (PSA) and cytokeratin 20.

Conclusions: Clinicians should maintain a high index of suspicion for metastasis when cutaneous cribriform apocrine carcinoma is diagnosed. The use of clinical history and appropriate laboratory workup with parameters such as age and sex can guide workup. After a wider excision with clear margins, follow-up for evidence of recurrence or metastasis is recommended, as the limited number of reported cases suggests that this assumption cannot be made with certainty.

MeSH Keywords: Adenocarcinoma • Apocrine Glands • Dermatologic Surgical Procedures

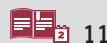
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Background

Primary cutaneous cribriform apocrine carcinoma is a histopathological variant of apocrine adenocarcinoma (AA) of the skin, which is a rare low-grade malignancy [1]. This usually well-circumscribed firm nodule has distinct histopathological features, including a diffuse cribriform pattern similar to a sieve in appearance, interconnected aggregations of neoplastic epithelial cells, periodic acid-Schiff-positive basement membrane-like substance, and pleomorphic nuclei [2]. Focal decapitation luminal secretion can often be found, indicating apocrine differentiation. While low-grade in nature, cutaneous cribriform apocrine carcinoma can mimic a metastatic manifestation of a visceral or breast malignancy and is important to distinguish as primary through clinical history, histology, and immunohistochemical (IHC) studies, if indicated. We present a case of this rare neoplasm and provide a suggested systemic workup based upon the literature.

Case Report

A 56-year old male presented with a 12-month history of a slowly enlarging, asymptomatic nodule on his right anterior medial lower leg. His medical history was remarkable for basal cell carcinoma and hypertension. His only medication consisted of hydrochlorothiazide. Physical examination revealed a 12×9 mm indurated and erythematous nodule involving the medial right lower leg (**Figure 1**). His physical examination was normal, with no other masses nor lymphadenopathy detected. A shave biopsy was performed, and the pathologic diagnosis was papillary eccrine adenoma. However, histologically, the lesion was not seen in its entirety, and an excision was performed, demonstrating a well-circumscribed proliferation of epithelial cells in fibrosing granulation tissue-like stroma, having the delicate cross-bridging of a cribriform carcinoma (**Figure 2**). The strands traversing the lumens had nuclei, whose long axes were in the same directions as the strands rather than perpendicular, which would be present in other forms of adenocarcinoma. Immunohistochemical studies were significant for positive high-molecular-weight keratin and cytokeratin, focal positivity for carcinoembryonic antigen (CEA) and S100, with negative results for prostate-specific antigen (PSA) and cytokeratin 20, providing further support for the diagnosis of cribriform carcinoma (**Figure 3**). The patient underwent a more extensive excision with a 3-mm clinical margin, resulting in clear histopathology margins. A sentinel lymph node biopsy was declined as well as any further invasive studies. Screening colonoscopy was up-to-date. His postoperative course was unremarkable, and he showed no evidence of local recurrence or metastasis at 6-month follow-up.



Figure 1. Asymptomatic lesion on the lower leg.

Discussion

Primary cutaneous cribriform apocrine carcinoma is a rare malignancy of the apocrine sweat gland. This neoplasm appears to be more common in females, with 1 study of 26 patients demonstrating a 2.7: 1 ratio, and often presents on the upper and lower extremities of adults [3]. There are no reported cases of local recurrence, metastasis, or disease-related mortality following complete excision [4]. Excision with variable margins of 1 to 2 cm has been the mainstay of treatment [2]. Of note, apocrine carcinomas that are not differentiated by histopathology have no clear sex predilection and have a presentation that most commonly reflects the normal distribution of apocrine glands, with the axillae being the most common. In addition, in up to 50% of cases of AA not differentiated by histopathology, lymph node metastases are present [5]. There are limited reports in the literature of primary cutaneous cribriform apocrine carcinoma, but this histopathological variant behaves distinctly from other apocrine carcinomas, as it is indolent.

Diagnosis primarily relies on histopathology and IHC. IHC staining of cytokeratins AE1/3 [1,3,6–8], MNF116 [1,3,6], Cam5.2

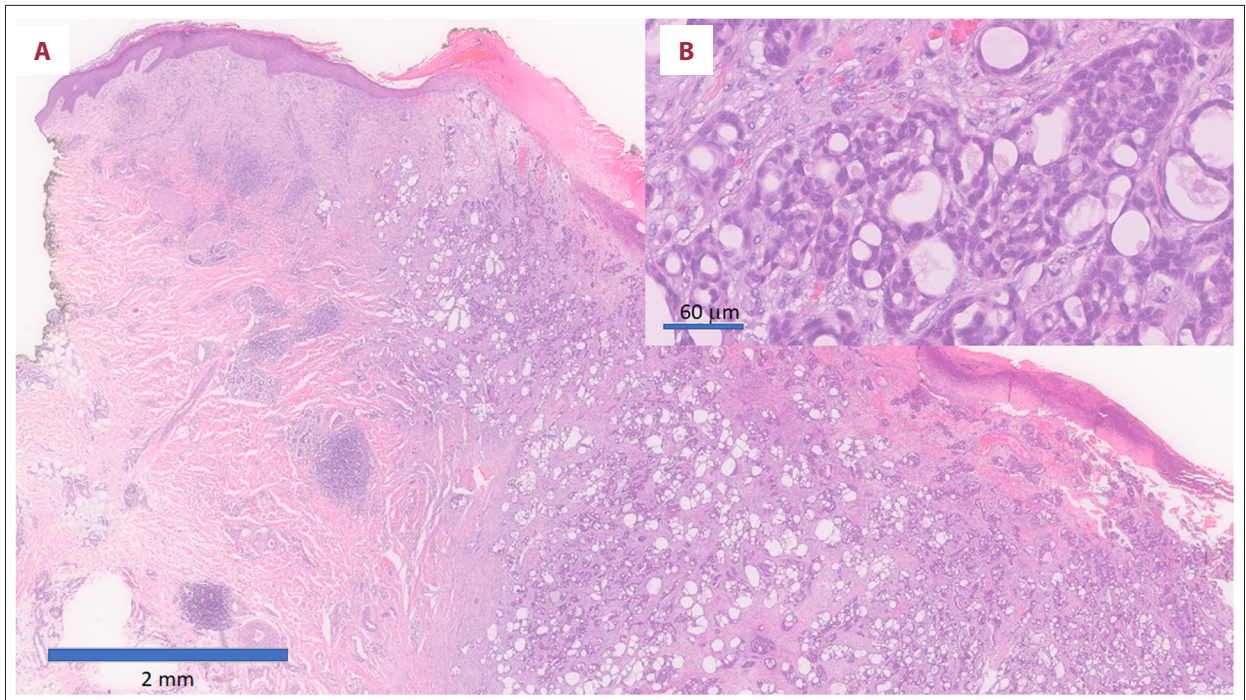


Figure 2. Histopathologic features of primary cutaneous cribriform carcinoma. (A) Low-power H&E staining revealing a well-circumscribed, non-encapsulated dermal neoplasm. (B) Higher magnification reveals cellular aggregations of neoplastic cells with round or oval enlarged pleomorphic hyperchromatic basophilic nuclei. Interconnected ducts with secretions resulting in a cribriform pattern are noted.

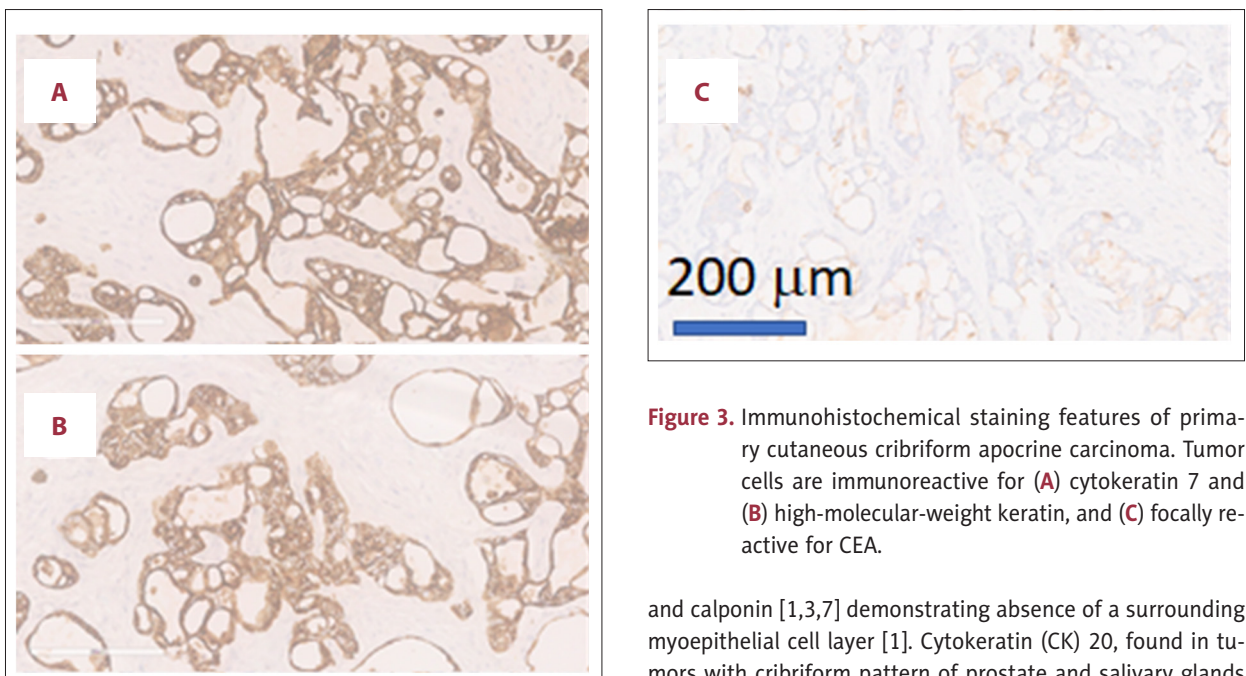


Figure 3. Immunohistochemical staining features of primary cutaneous cribriform apocrine carcinoma. Tumor cells are immunoreactive for (A) cytokeratin 7 and (B) high-molecular-weight keratin, and (C) focally reactive for CEA.

[1,3,6–8], cytokeratin 7 [1–3,6–8] are the most commonly reported in the literature. Epithelial membrane antigen (EMA) and CEA show luminal differentiation [1,3,6,7]. IHC staining should be negative for smooth-muscle antigen (SMA) [1,3,6–8]

and calponin [1,3,7] demonstrating absence of a surrounding myoepithelial cell layer [1]. Cytokeratin (CK) 20, found in tumors with cribriform pattern of prostate and salivary glands [2,3], and gross cystic disease fluid protein 15 (GCDFFP-15), found in breast carcinomas [3,6,8], are negative in primary cutaneous cribriform apocrine carcinomas. Negativity for CK 20 staining is also important, as it excludes Merkel cell carcinoma. Of note, 2 sources reported S100 should be negative in

primary cutaneous cribriform apocrine carcinoma [6,7]; however, the articles by Flux, Fernandez, and Arps [1,8,9] reported S100 staining is positive, and our case coincides with this IHC presentation of patchy positivity in tumor cells.

There is currently no consensus on additional workup of cutaneous cribriform apocrine carcinoma for determining primary versus secondary localization to the skin. Given the wide biologic spectrum of cribriform carcinomas that directs clinical prognosis and treatment, differentiating local versus metastatic disease is important. IHC has limited value aside from providing orientation details, but there is not currently an IHC panel to completely differentiate a primary carcinoma and metastatic disease. Immunohistochemical stains such as BRST-2, ER, PR, CK20, CDX-2, PSA, and PAX-8 can be useful in supporting the diagnosis of metastasis and determining the site of origin [9]. Clinical history provides the best information in determining metastasis [8]. Other primary carcinomas with a cribriform pattern can originate from the prostate, lung, breast, stomach, colon, thyroid, salivary glands, vulva, uterus, ovaries, and skin [8–10]. Historically, a myriad of clinical studies, including breast palpation, mammography, rectal examination, salivary gland palpation, chest x-ray, abdominal ultrasonography, and sentinel lymph node biopsy, have been performed when cribriform carcinoma was diagnosed histologically [2,7–9]. Laboratory values for serum PSA, prostate acid phosphatase, CEA, antigen

CA 15.3, and alpha-fetoprotein can be useful in appropriate patients [2,8]. Arps remarked that close inspection of microscopy would likely divulge features divergent from primary cutaneous cribriform apocrine carcinoma, such as a cribriform appearance without thread-like intraluminal bridges, the presence of high-grade cytomorphology, or dirty necrosis [9].

Conclusions

Clinicians should maintain a high index of suspicion for metastasis when cutaneous cribriform apocrine carcinoma is diagnosed. The use of clinical history and appropriate laboratory workup with parameters such as age and sex can guide workup. After a wider excision with clear margins, follow-up for evidence of recurrence or metastasis is recommended. Although primary cutaneous cribriform apocrine carcinoma has an overall favorable prognosis, the limited number of reported cases since the first reported by Requena and colleagues [11] in 1998 suggests that this assumption cannot be made with certainty, and long-term follow-up for evidence of recurrence or metastasis is recommended.

Conflict of interest

None.

References:

1. Flux K, Brenn T: Cutaneous sweat gland carcinomas with basaloid differentiation: An update with emphasis on differential diagnoses. *Clin Lab Med*, 2017; 37(3): 587–601
2. Adamski H, Le Lan J, Chevrier S et al: Primary cutaneous cribriform carcinoma: A rare apocrine tumour. *J Cutan Pathol*, 2005; 32(8): 577–80
3. Rütten A, Kutzner H, Mentzel T et al: Primary cutaneous cribriform apocrine carcinoma: A clinicopathologic and immunohistochemical study of 26 cases of an under-recognized cutaneous adnexal neoplasm. *J Am Acad Dermatol*, 2009; 61(4): 644–51
4. Brenn T: Do not break a sweat: Avoiding pitfalls in the diagnosis of sweat gland tumors. *Mod Pathol*, 2020; 33: 25–41
5. Cardoso JC, Calonje E: Malignant sweat gland tumours: An update. *Histopathology*, 2015; 67(5): 589–606
6. Llamas-Velasco M, Pérez-González YC, Daudén E, Rütten A: GATA3 staining in primary cutaneous apocrine cribriform carcinoma: Usefulness to differentiate it from breast cancer metastasis. *J Cutan Pathol*, 2018; 45(5): 348–51
7. Wu JD, Changchien CH, Liao KS: Primary cutaneous cribriform apocrine carcinoma: Case report and literature review. *Indian J Dermatol Venereol Leprol*, 2018; 84(5): 569–72
8. Fernandez-Flores A, Pol A, Juanes F et al: Immunohistochemical phenotype of cutaneous cribriform carcinoma with a panel of 15 antibodies. *Med Mol Morphol*, 2007; 40: 212–17
9. Arps DP, Chan MP, Patel RM, Andea AA: Primary cutaneous cribriform carcinoma: Report of six cases with clinicopathologic data and immunohistochemical profile. *J Cutan Pathol*, 2015; 42(6): 379–87
10. Branca G, Ieni A, Barresi V et al: An updated review of cribriform carcinomas with emphasis on histopathological diagnosis and prognostic significance. *Oncol Rev*, 2017; 11(1): 317
11. Requena L, Kiryu H, Ackerman AB: *Neoplasms with apocrine differentiation*. Philadelphia, Lippencott-Raven, 1998