Case Letter

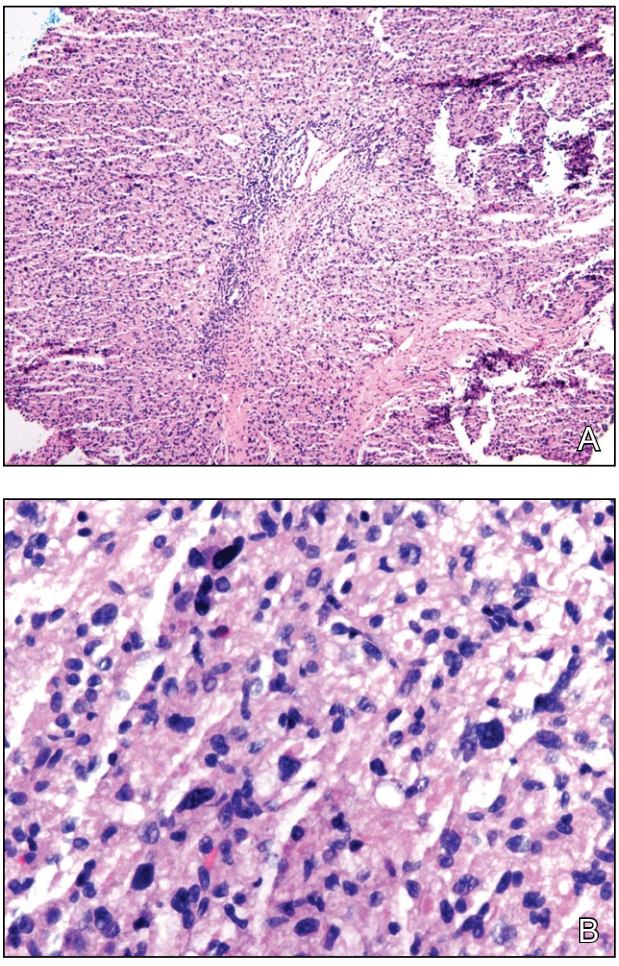
Cutaneous Metastasis of a Perivascular Epithelioid Cell Tumor

To the Editor:

A 67-year-old man presented for evaluation of a 3-mm subcutaneous nodule on the right side of the forehead. The lesion had appeared 3 months prior to presentation and remained stable in size. Two years prior to presentation, the patient had been diagnosed with perivascular epithelioid cell tumor (PEComa) by fine-needle aspiration of the right adrenal gland at which time metastatic disease demonstrated involvement of the bilateral adrenal glands, lung, and soft tissue. He received a course of sirolimus therapy, which was discontinued within a few weeks of therapy due to development of constitutional symptoms. A biopsy of the forehead lesion was performed and demonstrated sheets of pleomorphic cells with atypical nuclei as well as eosinophilic and granular cytoplasm with mitotic figures (Figure). There was immunopositivity for smooth muscle actin, desmin, and human melanoma black 45 (HMB-45). No immunoreactivity was demonstrated for S-100 or melan-A.

This case is a unique report of cutaneous metastasis from a PEComa. The PEComa family of related mesenchymal neoplasms includes angiomyolipoma (AML); lymphangioleiomyomatosis (LAM); clear-cell "sugar" tumor of the lung; and a subset of rare, morphologically and immunophenotypically similar, visceral, intra-abdominal, and soft tissue/bone tumors.[1] This concept of a spectrum of neoplasms was first advanced in 1992 by Bonetti et al[2] when the authors noted histologically and immunohistochemically distinctive perivascular epithelioid cells characterized by both melanocytic and smooth muscle differentiation.

There is no known normal cellular counterpart to these perivascular epithelioid cells; however, the presence of melanosome proteins in these tumors suggests that the cells may be derived from the neural crest.[3] There is a distinct overall female predominance of PEComas (female to male ratio is 7 to 1) with a median age of presentation of 38 years.[4] Although



Hematoxylin and eosin–stained sections showed pleomorphic cells with eosinophilic cytoplasm (A)(original magnification ×10). Higher magnification illustrated atypical nuclei and mitotic figures (B)(original magnification ×60).

Drs. Wu and Silvers are from the Department of Dermatology, Columbia University Medical Center, New York, New York. Dr. Silvers also is from the Department of Pathology. Dr. Wu also is from the Department of Medicine, Division of Dermatology, Albert Einstein College of Medicine, Bronx, New York. Dr. Maki is from the Departments of Pediatrics and Hematology/Oncology, Mount Sinai Hospital, New York. Dr. Noroff is in private practice, both Jersey City and Short Hills, New Jersey.

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Correspondence: Julia Wu, MD, 1150 Saint Nicholas Ave, Russ Berrie Room 318, New York, NY 10032 (julia.wu@med.einstein.yu.edu).

there is a strong association of AML and LAM with tuberous sclerosis complex, there have been few reported cases showing such a link with other PEComa subtypes.

The tumors are best defined by their histologic and immunophenotypic features. Perivascular epithelioid cells are characterized by their arrangement in nests or sheets of epithelioid (occasionally spindled) cells with clear to granular eosinophilic cytoplasm and a focal association with the vascular lumen. Immunohistochemically, PEComas express both melanocytic markers such as HMB-45, melan-A, tyrosinase, and microphthalmia-associated transcription factor, and myogenic markers such as smooth muscle actin, pan muscle actin, muscle myosin, and calponin. Desmin or S-100 protein expression, which is found in approximately 30% of PEComas, neither excludes PEComa nor implies a smooth muscle or melanocytic malignancy.[3]

In addition to the classical locations of AML, LAM, and clear cell "sugar" tumor of the lung, cases of PEComa remain exceedingly rare in sites other than the abdominal and thoracic cavities. Fewer than 30 cases of cutaneous PEComa have been reported in the English-language literature according to a PubMed search of articles indexed for MEDLINE using the search terms *cutaneous* and *PEComa*, but they represent primary PEComas of the skin rather than cutaneous metastases. Malignant PEComa, similar to a high-grade sarcoma, can be an aggressive disease leading to multiple metastases and ultimately death. An association between tumor size of more than 5 cm, infiltrative growth pattern, high nuclear grade, necrosis, high mitotic activity, and subsequent aggressive clinical behavior was observed.[4] As with patients with AML and LAM, PEComas can respond to sirolimus, an inhibitor of mammalian target of rapamycin downstream of tuberous sclerosis complex 2, which is inactivated in this family of tumors.[5-8] However, case reports indicate lack of activity of such agents in PEComa or AML, indicating the need for a better molecular understanding of these tumors.[9,10]

Given our patient's history of a large primary intra-abdominal PEComa and concomitant pulmonary, adrenal, and paraspinal metastases, the current tumor most likely represents metastatic PEComa to the skin. The diagnosis was supported with an immunophenotypic pattern that was similar to the fine-needle aspiration of the adrenal gland conducted 2 years prior. Importantly, the nodule was not distinctive in its appearance and could be easily dismissed as a benign lesion.

This case should alert dermatologists to consider PEComas in the differential diagnosis of benign and malignant neoplasms presenting in cutaneous or subcutaneous sites. Given their uniform expression of melanocytic markers, it is not surprising that PEComa may be confused with melanoma and clear cell sarcoma of soft tissue. Dermatologists and dermatopathologists should be aware of the diagnosis of PEComa in case they encounter a cutaneous tumor that is HMB-45 positive but is S-100 negative, which would be an exceedingly unusual combination for melanoma.

Julia Wu, MD
Robert G. Maki, MD, PhD
Joan P. Noroff, MD
David N. Silvers, MD

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