Primary cutaneous perivascular epithelioid cell tumor: A clinicopathological and molecular reappraisal

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Background: Perivascular epithelioid cell tumor (PEComa) is a rare neoplasm of uncertain histogenesis with a mixed myomelanocytic immunophenotype, rarely arising in the skin (primary cutaneous PEComa [pcPEComa]).

Objective: We analyzed the clinicopathological features of 8 pcPEComas, assayed for DNA copy number changes and for initiating mutations common in melanocytic neoplasms.

Methods: pcPEComas were evaluated using immunohistochemistry, comparative genomic hybridization, and DNA sequencing.

Results: pcPEComas were erythematous nodules, mostly in the lower extremities of women (5/8), composed of large pale-staining epithelioid cells. The patient's age range was 26 to 67 (mean 46) years. The percentages of tumors staining positively were as follows: micro-ophthalmia-associated transcription factor, NKI/C3, bcl-1, E-cadherin, and cathepsin K (100%); HMB-45, 4E-binding protein 1, and CD68 (88%); smooth muscle actin and muscle-specific actin (40%); S100 (38%); calponin (20%); desmin (13%); and melan-A, SOX10, and keratin (0%). No chromosomal copy number changes or initiating mutations were identified.

Limitations: Small sample size is a limitation.

Conclusions: pcPEComas have a different molecular signature than extracutaneous tumors and are unrelated to tuberous sclerosis. However, the common expression of 4E-binding protein 1 points to a role of the mTOR pathway in their pathogenesis. Because pcPEComas are diagnostically challenging, we propose that micro-ophthalmia-associated transcription factor, NKIC3, smooth muscle actin, desmin, bcl-1, cathepsin K, and 4E-binding protein 1 can be used when evaluating a possible pcPEComa. (J Am Acad Dermatol 2014;71:1127-36.)

Key words: array-based comparative genomic hybridization; cutaneous clear cell myomelanocytic tumor; initiating mutations; mTOR pathway; perivascular epithelioid cell tumor.

Many cutaneous mesenchymal tumors show, as can melanocytic neoplasms, clear cell morphology, including adipocytic, xanthomatous, myoepithelial, and fibrohistiocytic proliferations.[1] Among these is an exceedingly rare dermal neoplasm, composed of a perivascular and diffuse proliferation of large and pale epithelioid cells, with a mixed myomelanocytic immunophenotype. This neoplasm, originally designated "cutaneous clear cell myomelanocytic tumor," was subsequently included in the family of perivascular epithelioid cell tumors (PEComas) that usually affect internal organs, and now are commonly termed "cutaneous perivascular epithelioid cell tumors" (primary cutaneous PEComas [pcPEComas]).[2] The precise lineage of

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this enigmatic tumor remains elusive because the proposed perivascular epithelioid cell of origin awaits proper identification and previous immunohistochemical staining results are inconsistent. Furthermore, the relationship between extracutaneous PEComas and pcPEComas is uncertain.[3] In this study we describe a substantial series of these tumors, to further characterize their clinicopathological and immunohistochemical features. Finally, via array-based comparative genomic hybridization (aCGH) and DNA sequencing, we assayed for initiating mutations commonly observed in melanocytic neoplasms and DNA copy number changes as often seen in melanoma.

CAPSULE SUMMARY

- Cutaneous perivascular epithelioid cell tumors are tumors with a mixed myomelanocytic immunophenotype.
- Cutaneous perivascular epithelioid cell tumors lack gross chromosomal aberrations and initiating mutations common to melanocytic tumors whereas 4E-binding protein 1 expression plausibly relates them to the mTOR pathway.
- An immunohistochemical panel including micro-ophthalmia-associated transcription factor, NKIC3, smooth muscle actin, desmin, bcl-1, cathepsin K, and 4E-binding protein 1 is recommended for their evaluation.

METHODS

Eight pcPEComas were identified in the author's (P. E. L.) consultation files. Clinical information was obtained through contributing clinicians. In each case, formalin-fixed paraffin-embedded tissue sections had been stained with hematoxylin-eosin. We included only lesions centered in the dermis that fulfilled the presently accepted criteria for PEComa.[3] A broad panel of immunohistochemical stains was performed on formalin-fixed paraffin-embedded tissue. Antibodies, clones, dilutions, and sources are outlined in Table I. Appropriate controls were used in parallel.

Array-based comparative genomic hybridization

DNA was extracted from formalin-fixed paraffin-embedded tissue as described previously.[4,5] aCGH was carried out with 500 to 1000 ng of genomic DNA on Agilent Human 4x180k oligomicroarrays (G4449A, Agilent Technologies, Santa Clara, CA). aCGH methodology details and data analysis were as described in a recent publication.[6]

DNA sequencing

Polymerase chain reaction assays using primers specific for BRAF exon 15; NRAS exons 1 and 2; KIT exons 11, 13, 17, and 18; GNAQ exon 5; and GNA11 exon 5 were used to amplify DNA as described previously.[7] Polymerase chain reaction products were purified using ExoSAP-IT (USB Corp, Cleveland, OH) and sequenced directly using a 3500 DNA Analyzer (Applied Biosystems, Foster City, CA). The sequences were analyzed using Mutation Surveyor software (Softgenetics, State College, PA).

The Committee on Human Research from the University of California San Francisco granted approval for this study originally titled "Histologic, immunohistochemical, and genetic study on cutaneous neoplasms" under the study number 11-05569. This covers archival paraffin blocks.

RESULTS

Clinical features

Clinical findings are summarized in Table II. pcPEComas occurred in 5 women and 3 men. The mean age of patients at the time of presentation was 46 years. pcPEComas predominated in the lower extremities (5/8). Most were described as indurated nodules (Fig 1). In no case was the correct diagnosis inferred clinically; the most common impression being dermatofibroma (3/8). None of the patients had history of tuberous sclerosis complex (TSC). Follow-up data were available for 6 of 8 patients and ranged between 24 and 171 (mean 66.5) months. No local recurrences or metastases developed in these cases.

Histopathologic and immunohistochemical features

The histologic size of pcPEComas ranged from 4 to 20 mm. Neoplasms spared the epidermis and occupied the entire dermis except for a thin layer of uninvolved papillary dermis (grenz zone) (5/8), or occurred exclusively in the reticular dermis (3/8). A diffuse, highly cellular and sheetlike growth pattern was observed in 4 cases, the rest displayed less cellularity and lesional cells arranged as thin aggregates, strands and singly in an interstitial array with perivascular and periadnexal accentuation (Fig 2). The interface between the tumors and the surrounding tissues was well circumscribed. In all cases, lateral borders were irregular and cells were interposed between thickened collagen bundles (Fig 3). A similar configuration was observed in the deep margin in 2 cases where lesional cells did not