Primary cutaneous perivascular epithelioid cell tumors: two cases and a review of the literature

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Abstract

Perivascular epithelioid cell tumors, also known as PEComas, are mesenchymal neoplasms which uncommonly originate within the skin, with only 23 cases documented within the literature. These rare neoplasms classically display epithelioid cells composed of granular or clear cytoplasm arranged in sheets, nests, or cords. Their immunoreactivity for melanocytic and smooth muscle markers makes these tumors distinct and unique. We herein present two cases of primary cutaneous PEComas that clinically mimic other common cutaneous neoplasms and illustrate the necessity for clinical-pathologic correlation. A literature review is also presented to compare the different clinical and histological presentations of cutaneous PEComas.

Keywords: epithelioid cell, mesenchymal neoplasm, PEComa, perivascular epithelioid cell tumor

Introduction

Perivascular epithelioid cell tumors, also referred to as PEComas, are a group of rare neoplasms of mesenchymal lineage consisting of characteristic neoplastic cells with no known normal counterpart, which show myomelanocytic differentiation [1]. These tumors often arise in the viscera, commonly of gastrointestinal, genitourinary, or uterine origin; cutaneous PEComas are exceedingly rare [2]. Primary 4cutaneous PEComas are usually discovered on the extremities, most commonly on the lower leg [2]. PEComas have a distinct histopathologic picture composed of epithelioid cells with a clear or granular cytoplasm that tend to be oriented in sheets, nests, or cords [3]. Their immunoreactivity for both melanocytic and smooth muscle markers helps further characterize this family of neoplasms [1]. We present two patients with primary cutaneous PEComas that clinically resembled other common cutaneous neoplasms and illustrate the necessity for clinical-pathologic correlation.

Case Synopsis

Case 1

A 77-year-old woman with a clinical history of extensively sun-damaged skin and squamous cell carcinoma presented to our clinic for her routine skin examination. Upon thorough skin examination, a 0.6cm smooth pink nodule was found on her upper right back (**Figure 1A**). Clinically, the lesion looked suspicious for a basal cell carcinoma and the patient reported no associated symptoms. A shave biopsy was performed. Histopathological examination demonstrated sheets of large, epithelioid cells with vacuolated cytoplasm in a perivascular distribution with unusual hypercellularity in the superficial dermis (**Figure 2**). The immunophenotype of HMB-45+, MiTF+, S100-, SOX-10-, and p40- together

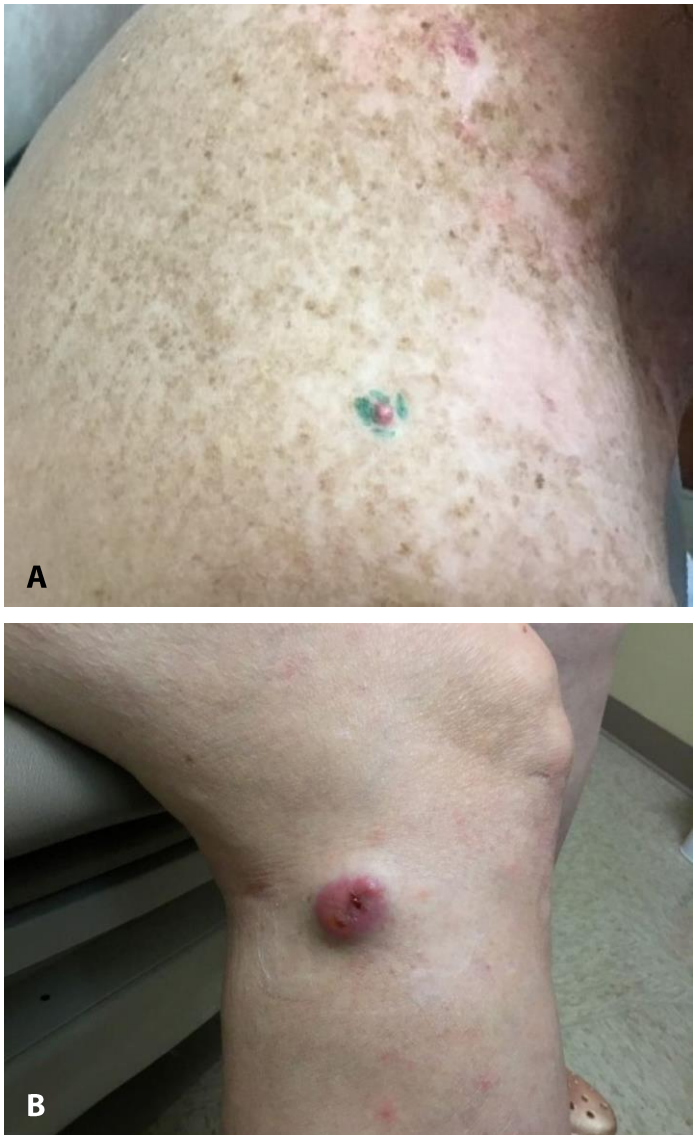

Figure 1. ***A)*** *Smooth pink 0.6cm nodule on right upper back;* ***B)*** *3cm violaceous nodule located on the right lateral lower leg.*

supported the diagnosis of a PEComa. The lesion was narrowly excised with no evidence of recurrence or metastasis to date.

Case 2

A 60-year-old woman with a clinical history of rosacea presented for an enlarging, tender, indurated violaceous smooth three 3cm nodule on the right lateral lower leg (**Figure 1B**). The patient reported the lesion gradually growing for the past year. A punch biopsy was performed with the clinical differential diagnosis including cutaneous lymphoma, cyst, dermatofibrosarcoma protuberans, and other atypical dermal proliferations. Histopathologic examination demonstrated sheets of epithelioid cells with large, clear and some granular cytoplasm from the superficial-to-mid-to-deep dermis with areas of spindled cells intermingled (**Figure 3**). Immunohistochemical

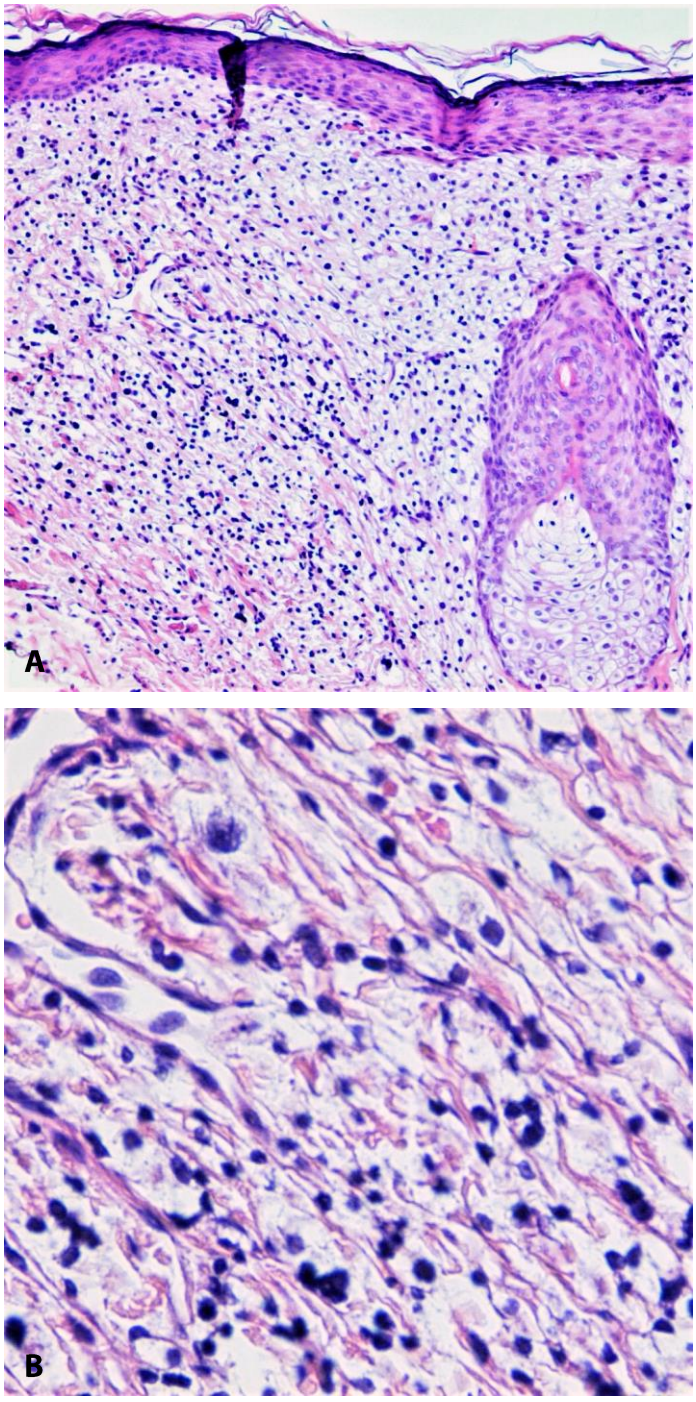

Figure 2. *H&E staining for case 1.* ***A)*** *100×, and* ***B)*** *400× magnifications showing hypercellular dermal collection of epithelioid cells with clear, granular cytoplasm, and evident mitoses.*

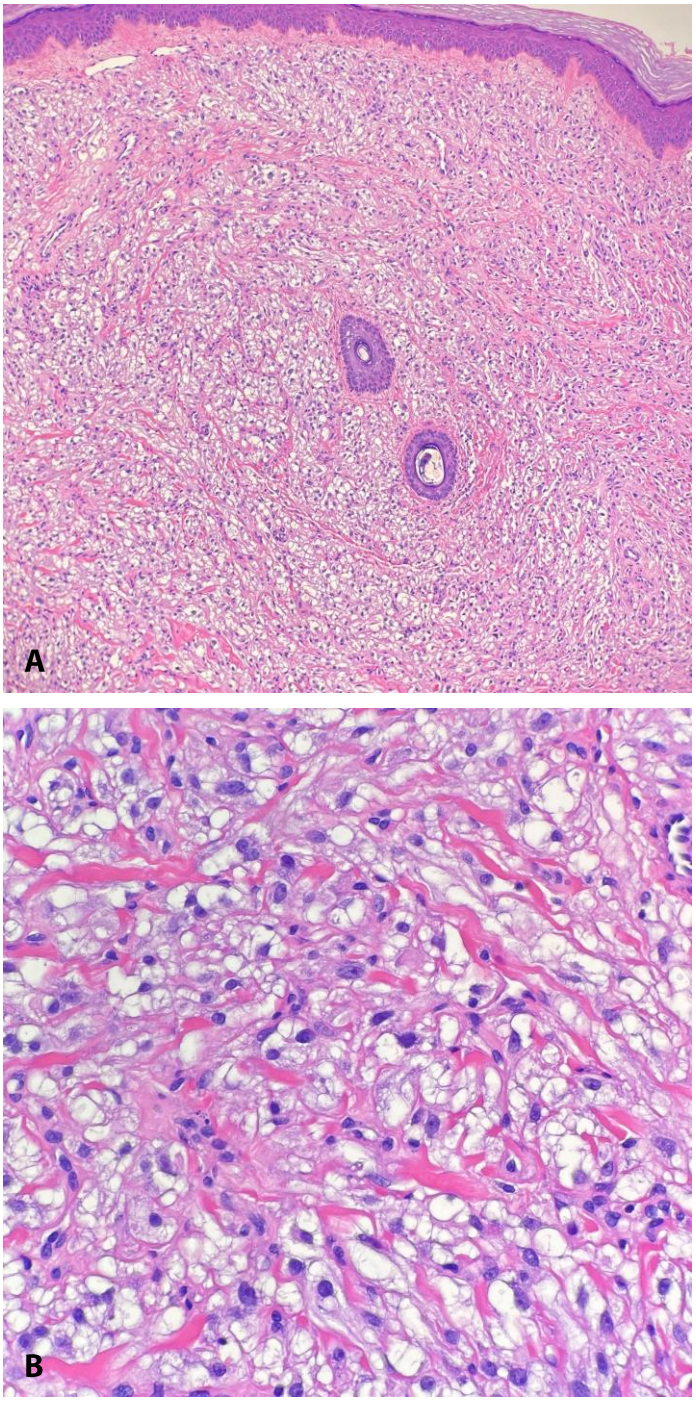

Figure 3. *H&E staining for case 2.* ***A)*** *100× magnification revealing a cellular proliferation of cells in the dermis.,* ***B)*** *200× magnification showing the dermal proliferation is comprised by many clear cells.* ***C)*** *400×, and* ***D)*** *600× magnifications showing the clear epithelioid cells have unremarkable nuclei.*

stains demonstrated the cells to be HMB-45+, CD10+, NKI-C3+, vimentin+, CD68+, melan-A-, SMA-, desmin-, SOX-10-, pancytokeratin AE1/3-, RCC antigen-, CK7-, and S100 (weakly immunoreactive), (**Figure 4**). Periodic acid-Schiff with diastase was negative. Ki67 proliferation index was less than 5% of tumor cells. These findings were consistent with the diagnosis of a cutaneous PEComa.

Case Discussion

PEComas consist of a group of related mesenchymal neoplasms that are all believed to share a special cell known as the perivascular epithelioid cell. These neoplasms include angiomyolipoma, lymphangiomyomatosis, clear cell "sugar" tumor of the lung, and additional rare lesions with morphological and immunophenotypic similarities [4].

PEComas commonly affect females of middle age with predilection for the viscera and are commonly of gastrointestinal, uterine, retroperitoneal, and abdominopelvic origin. However, only a small subset arises within the skin [4]. Primary cutaneous PEComas are uncommon making up only 8% of all PEComas with only 23 cases reported in the literature [2]. Clinically, cutaneous PEComas arise as a solitary, asymptomatic, skin-colored, slow-growing nodule or plaque often arising on the lower legs [1,2].

In Stuart et al.'s five cases of cutaneous PEComa, their clinical impression included cyst, lipoma, dermatofibroma, dermatofibrosarcoma protuberans, and non-melanocytic and melanocytic skin cancer [1]. Four out of five cases were located on the thigh and the remaining case was located on the distal leg, similar to one of our current patients. Our case further supports the previously presented evidence that PEComas commonly affect the lower extremity.

Histologically, PEComas are typically oriented around blood vessels with possible infiltration of the smooth muscle layer of small-to-medium sized vessels. According to Liegl et al., the histological hallmark of cutaneous PEComa are nests or strands of epithelioid cells with pale-clear or granular cytoplasm separated by capillaries [6]. The nuclei are typically not of malignant nature, but occasional cytologic atypia is possible [1]. Mitotic activity is minimal with less than one mitosis per 10 high power fields (HPFs), [1]. PEComas may also have spindled cells, often intermingled with epithelioid cells,

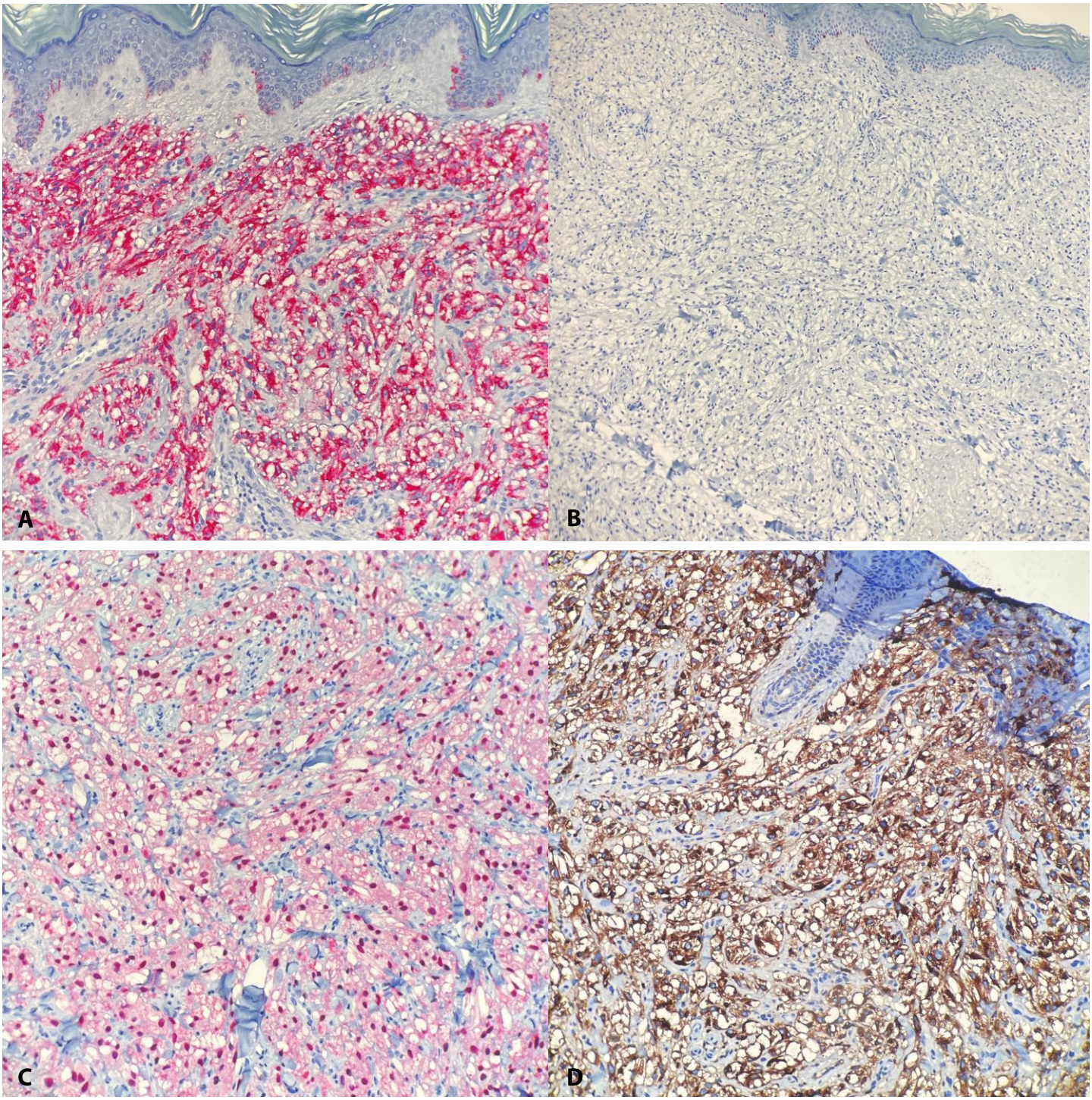

Figure 4. ***A)*** *HMB-45-positive staining, 200×.* ***B)*** *SOX-10 negative staining, 100×.* ***C)*** *MiTF1-positive staining, 200×.* ***D)*** *NKI-C3-positive staining, 200×.*

frequently appearing in the deeper layers of the tumor [3]. Other histological features which may be present include multinucleated giant cells and vacuolated tumor cells.

PEComas are known to immunostain for melanocytic markers, such as HMB-45 and/or melan-A, and smooth muscle markers, such as actin and/or desmin [4]. Among these stains, HMB-45 is the most sensitive marker [1]. Primary cutaneous PEComas less frequently express smooth muscle markers compared to their deep soft tissue and visceral counterparts [1]. Therefore, the absence of myogenic

expression does not exclude the diagnosis of cutaneous PEComa. Llamas-Velasco et al. made an astute observation that spindle cell-predominant PEComas will often have strong actin expression with only focal HMB-45 positivity, whereas lesions composed of clear cells, which are mainly of the cutaneous type, typically have strong HMB-45 expression and weak or negative expression of actin [3]. Despite their epithelioid features, PEComas do not stain for epithelial markers [3]. Negativity for S100 protein and SOX-10 helps distinguish PEComas from melanocytic lesions and from clear cell sarcomas [1]. These rare tumors express NKI/C3 (100%), MITF (100%), HMB-45 (94% of cases), SMA (42%), melan-A (35%), and desmin (30%), [1,7]. Additionally, they typically express strong diffuse CD10 which may pose a challenge when differentiating it from metastatic renal cell carcinoma (RCC). However, RCC can be distinguished by positivity for EMA, PAX-8, and RCC, whereas markers for melanocytic lesions are negative [1].

Chromosomal alterations in the "tuberous sclerosis complex" (TSC) with a loss of function in the *TSC1* and *TSC2* gene, have been evident in visceral PEComa [1]. When such chromosomal abnormality is present, this results in constitutive activation of the mTORC1 pathway and formation of a PEComa in the viscera [3]. However, such dysregulation is not demonstrated in cutaneous PEComas, indicating that the cutaneous variant may have a separate histogenetic root.

Primary cutaneous PEComas are considered benign and the overall prognosis is good with no reported deaths. However, there have only been two reports of "malignant" primary cutaneous PEComas [8,9]. Both cases involved the head and neck which is an unusual location for a cutaneous PEComa to arise indicating that the head and neck may be associated with a malignant variant [3]. Both lesions were excised completely with no evidence of recurrence or metastasis. Clinical or immunohistochemical features that indicate a poor prognosis are still not established due to the rarity of these tumors. Folpe et al. created a classification system which focused on "high risk" features found in a PEComa lesion, which included size >5cm, pattern of infiltrative growth, nuclear grade and increased cellularity, mitotic rate, necrosis, and vascular involvement [10]. If there were greater than two "high risk" features then the lesion would be considered malignant [10]. One of our cases did present with high cellularity, prompting concern for the designation of uncertain malignant potential. Nevertheless, surgical excision for removal of the tumor is recommended for primary cutaneous PEComas on account of the lack of prognostic data and potential for malignancy. Both our patients underwent local excision and have had no report of recurrence or metastasis.

Conclusion

Our cases highlight a rare cutaneous neoplasm that may mimic common benign or malignant growths, emphasizing the importance of a clinical-pathologic correlation of all sampled lesions. Our first case was unique in the fact the lesion presented on the upper back instead of the typical distal extremity location. This growth clinically resembled a small basal cell carcinoma, rather than a larger neoplasm or cyst, which was the major entity in the differential diagnosis in the five cases reported by Stuart et al. [1]. Our second case was clinically concerning for cutaneous lymphoma versus cyst, which followed the trend outlined by Stuart et al. with presentation on the lower extremity. Histologically, both of our cases highlighted HMB-45 positivity in cutaneous PEComas; this marker is more often positive when compared to muscle marker stains. As cutaneous PEComas can masquerade as common benign cutaneous lesions, they should be included in the differential diagnosis of lesions that are of unclear etiology and warrant biopsy for clinicopathologic evaluation.

Potential conflicts of interest

The authors declare no conflicts of interest.

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