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Cutaneous perivascular epithelioid cell tumor (PEComa): case report and world literature review of clinical and molecular characteristics

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Abstract

Perivascular epithelioid cell tumor (PEComa) expresses melanocytic and smooth muscle markers. A man with a primary malignant cutaneous (distal left forearm) PEComa is reported. Immunohistochemistry demonstrated MiTF, HMB-45, caldesmon, desmin, and smooth muscle actin, as well as BCL1, CD10, and CD68. Next generation sequencing showed four pathogenic genomic aberrations involving *BIRC3*, *FANCC*, *TP53*, and *TSC1* genes. His work-up was negative for metastatic disease; a wide local excision was performed. Including the reported patient, cutaneous PEComa has been described in 65 individuals: primary benign (N=58), primary malignant (N=5), and metastatic malignant (N=2). Cutaneous PEComa typically presented as a painless, slowly growing nodule of <2 centimeters on the lower extremity of a woman in her fifth decade. The neoplasms consisted of epithelioid cells, spindle cells, or both. The most reliable markers were MiTF (100%), HMB45 (94%), and NKIC3 (94%) for melanocytes and smooth muscle actin (43%) and desmin (40%) for smooth muscle. There has been no reported recurrence of a primary cutaneous benign or malignant PEComa after complete excision. Genomic alterations in malignant PEComas frequently involve *TSC1* and *TSC2* genes (mTOR activators), as well as *TFE3* fusions. In November 2021, the FDA approved nab-sirolimus (mTOR inhibitor) for PEComas.

Keywords: aberration, cell, epithelioid, generation, genomic, next, PEComa, perivascular, sequencing, tumor

Introduction

Perivascular epithelioid cell tumor (PEComa) is a tumor with cells that immunohistochemically exhibit both melanocytic and smooth muscle differentiation. Most PEComa are systemic (also referred to as visceral or internal) since they originate from internal visceral organs or soft tissue. In contrast, primary cutaneous PEComa is an uncommon—usually benign—neoplasm. However, albeit rare, primary malignant cutaneous PEComa or metastatic malignant cutaneous PEComa of the skin have been observed [1,2].

A man with a primary malignant cutaneous PEComa is described. Evaluation did not demonstrate any systemic involvement and his management consisted of a wide local excision of the tumor site. Next generation sequencing of the tumor was performed and several actionable genomic aberrations were detected.

The features of systemic PEComas are summarized [3-6]. Also, a comprehensive review of the world literature—including the tumor from the patient in this report—has been performed; the salient characteristics of the 65 cutaneous PEComas

Figure 1. *Clinical presentation of a primary malignant cutaneous perivascular epithelioid cell tumor (PEComa). A 10×10×5-millimeter flesh-colored, exophytic nodule that had appeared on the extensor surface of a 43-year-old man's left distal. There was a collarette of epithelium surrounding the ulcerated nodule.*

reported are presented [7-31]. In addition, the gene abnormalities detected on next generation sequencing of the primary malignant cutaneous PEComa of the reported patient are discussed with regard to potential therapeutic interventions if his tumor was to recur or develop metastatic disease. It is also discussed in the context of the literature on the molecular drivers of this disease [1-69].

Case Synopsis

A healthy 43-year-old man presented for evaluation of an enlarging lesion on his distal left forearm. There had been no trauma to the site. The growth had been present for five months; it began as a small, raised area and continued to grow for three months to its current size. The nodule would occasionally bleed.

His family history was significant for cutaneous squamous cell carcinoma. In addition, his mother, father, and grandfather had melanoma and his sister had breast cancer. He had a history of hypertension, hyperlipidemia, and hypothyroidism. He had previously worked as a welder for several years; however, more recently, he had been promoted to management.

Cutaneous examination revealed a painless, flesh-colored exophytic scaly nodule that was located on

the extensor surface of his distal left forearm, just proximal to the wrist. The tumor measured 10×10×5 millimeter and had central ulceration. There was a collarette of epithelium surrounding the nodule (**Figure 1**). There were no palpable axillary lymph nodes. The clinical impression was a keratoacanthoma.

An excisional biopsy, using the shave technique, was performed. Microscopic examination of hematoxylin and eosin-stained sections of the tissue specimen showed a dermal nodular proliferation with an epithelial collarette and surface ulceration. The epithelioid cell component of the tumor showed epithelioid cells with clear to lightly eosinophilic cytoplasm with variably enlarged vesicular nuclei exhibiting open chromatin and prominent nucleoli. Some of these clear cells were irregularly enlarged with extensive foamy cytoplasm. In addition, pleomorphic tumor giant cells were present. Scattered mitoses, three per ten high power fields, were also seen. Toward the periphery, the cells were
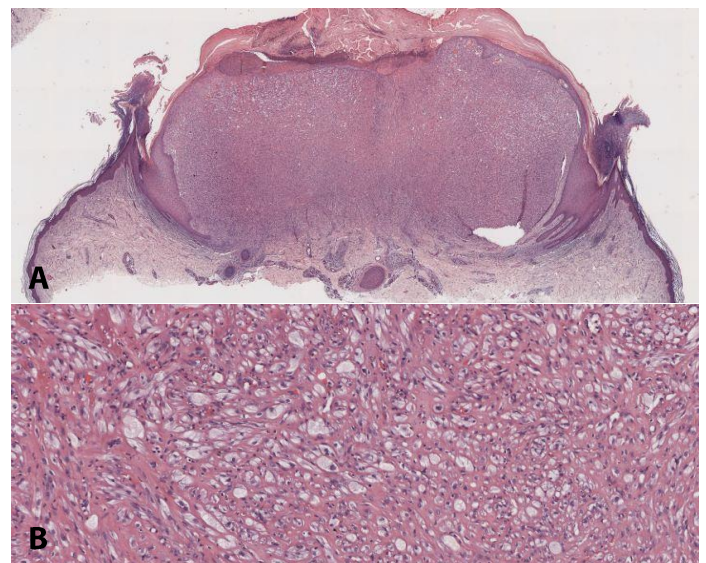
Figure 2. *Microscopic examination of hematoxylin and eosin-stained sections of a primary malignant cutaneous perivascular epithelioid cell tumor (PEComa). Lower **A)** and higher **B)** magnification views show a collarette of epithelium extending from the epidermis into the dermis and surrounding a dermal tumor; numerous capillaries are also seen. There is ulceration and crust overlying the epithelium. The tumor cells are predominantly epithelioid with clear cytoplasm; some of the cells have foamy cytoplasm. Multinucleated tumor cells, high-grade nuclear atypia, and three mitoses per ten high-power fields are present. At the periphery of the tumor, the neoplasm contains spindle tumor cells. H&E, **A)** 2×; **B)** 20×.*

less epithelioid, more spindled, with brightly eosinophilic and variable vesicular cytoplasm and ovoid-to-elongated nuclei. Numerous intervening capillaries were also noted (**Figure 2**).

Immunohistochemical stains showed that the clear tumor cells were positive for B-cell leukemia 1 (BCL1), caldesmon (**Figure 3A**), cluster of differentiation (CD)10, and microphthalmia transcription factor (MiTF), (**Figure 3B**). There was variable patchy positivity for CD68, desmin, and smooth muscle actin (SMA). Human melanoma black-45 (HMB-45) showed very weak, almost negative, staining (**Figure 3C**). The tumor cells were negative for activin receptor-like kinase-1 (ALK-1), CD31, CD34, CD45, epithelial membrane antigen (EMA), melanoma antigen recognized by T-cell 1 (MART1, also known
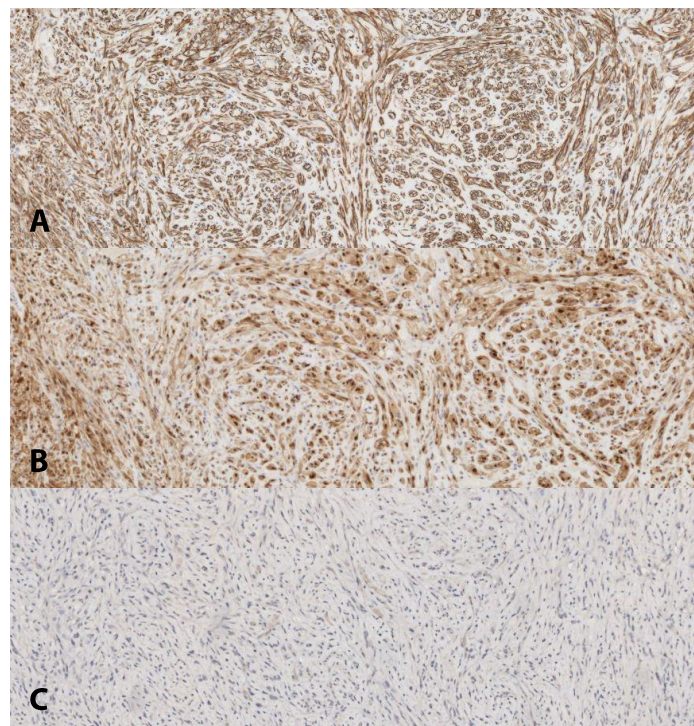
Figure 3. *A) Microscopic examination of caldesmon-stained sections of a primary malignant cutaneous perivascular epithelioid cell tumor (PEComa), 20×. The tumor cells show strong and diffuse staining with the smooth muscle marker caldesmon. B) Microscopic examination of microphthalmia transcription factor (MiTF)-stained sections of a primary malignant cutaneous PEComa, 20×. The tumor cells show strong and diffuse expression of the melanocytic marker MiTF. C) Microscopic examination of human melanoma black-45 (MHB45)-stained sections of a primary malignant cutaneous PEComa, 20×. The tumor cells show very weak, almost negative, diffuse staining with the melanocytic marker HMB45.*

as Melan A), pancytokeratin (Cam5.2/AE1/AE3), tumor protein 63 (P63), and neurone-specific enolase and Sangtec 100 (S100). Ki67 showed a gradient of increased positive staining of nuclei approaching ten percent focally in the periphery of the tumor. However, overall, the Ki67 staining of the entire tumor was less than one percent.

Correlation of the findings observed on hematoxylin and eosin-stained sections and the presence of immunohistochemical co-expression of melanocytic and muscle markers established a diagnosis of a cutaneous PEComa. The presence of two high-risk, worrisome, features (including the increased mitotic activity and the scattered nuclear pleomorphism) classified the tumor as malignant. The PEComa did not have any of the other high-risk features associated with malignancy for this tumor: infiltrative growth pattern, necrosis, tumor size greater than five centimeters, or vascular invasion.

He was referred to a medical oncologist for systemic evaluation. His work-up included computerized tomography and positron emission tomography with computerized tomography scans of the thorax, abdomen, and pelvis. All the scans were negative for metastases; hence, his finalized diagnosis was a primary malignant cutaneous PEComa.

Molecular profiling of both his blood and the tumor tissue specimen was performed. Genomic analysis of his blood and the tumor revealed a germline mutation and four actionable aberrations, respectively. Specifically, analysis of his blood showed that he had a *Fanconi anemia complementation group C* (*FANCC*) germline mutation. The tissue next generation sequencing showed four pathogenic genomic aberrations: *baculoviral IAP repeat containing three* (*BIRC3*) splice site 1622-27_1631del37, *FANCC* R185*, *tumor protein 53* (*TP53*) R248W, and *tuberous sclerosis complex 1* (*TSC1*) T4151.

He was also referred to a surgeon who performed a wide local excision of the tumor site. Follow-up evaluation, four weeks after his initial visit, showed complete healing of the surgical site; a complete skin examination did not show any similar lesions or precancerous skin lesions or cutaneous

Table 1. *Historical perspective of perivascular epithelioid cell tumor (PEComas) research highlights.*

Author (publication year)	Comments	Ref
Bonetti et al. 1992	After similarities in morphology, immunohistochemistry, and ultrastructure between angiomyolipoma of the kidney, clear cell ("sugar") tumor, and lymphangiomyomatosis of the lung were noted, the descriptive term PEC was suggested to identify the "novel" cell type present in the three tumors.	[32]
Zamboni et al. 1996	A clear cell "sugar" tumor of the pancreas in a 60-year-old woman was described; the investigators proposed that the term PEComa for neoplasm composed of perivascular epithelioid cells.	[33]
Crowson et al. 2003	First abstract—presented at a meeting of the United States and Canadian Academy of Pathology in Washington, DC from March 22-28, 2003--describing the first cutaneous PEComa which presented as a 0.8 centimeter tan nodule that had been present for six months on the scalp of a 58-year-old man; the tumor was biopsied and reported as a cutaneous clear cell myomelanocytic tumor-perivascular epithelioid cell tumor.	[26]
de Saint Aubain Somerhausen et al. 2005	First case report describing a clear cell 'sugar' tumor (PEComa) of the skin which appeared on the thigh of a 60-year-old woman.	[19]
Mentzel et al. 2005	First series of seven women with cutaneous PEComa located on the lower (six cases) or upper (one case) extremity.	[13]
Folpe et al 2005	A provisional classification of PEComas--based on a study of 26 cases and literature review of perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin--as either benign, uncertain malignant potential, or malignant. The evaluation did not include any skin-derived tumors.	[3]
Akumalla et al. 2020	Genomic landscape of 31 malignant PEComa showed alterations in TSC2 (ten cases), TSC1 (three cases), TFE3 (five cases, all fusions) and FLCN (two cases). The PEComa specimen was from the skin for one of the patients.	[31]
Cohen et al. 2022	World literature review of cutaneous PEComa and case report of a 43-year-old man with a malignant cutaneous PEComa with results of next generation sequencing of the tumor showing four actionable genomic aberrations: BIRC3 splice site 1622-27_1631del37, FANCC R185*, TP53 R248W, and TSC1 T4151.	CR

BIRC3, baculoviral IAP repeat containing 3; CR, current report; FANCC, Fanconi anemia complementation group C; FLCN, folliculin; PEC, perivascular epithelioid cell; PEComa, perivascular epithelioid cell tumor Ref, references; TFE3, transcription factor binding to immunoglobulin heavy contrast Mu (IGHM) enhancer 3; TP53, tumor protein 53; TSC, tuberous sclerosis complex.

malignancies. Subsequently, there has been no recurrence or metastasis of the tumor after six months of follow-up. He will continue to be followed by both the dermatologist (every three months for the first year followed by every six months for the next four years and then yearly) and medical oncologist (every six months).

Case Discussion
History
Perivascular epithelioid cell tumor is a rare neoplasm. It is composed of perivascular epithelioid cells. The perivascular epithelioid cell was initially described by Bonetti et al. in 1992 (**Table 1**), [3,13,19,26,31-33].

The distinctive perivascular epithelioid cell has been observed in several neoplasms. Indeed, it was only four years later that Zamboni et al. introduced the acronym PEComa [33]. In addition to PEComa tumors, this group of neoplasms also includes angiomyolipomas, lymphangiomas, and clear cell sugar tumors [1-3].

Systemic PEComa
Epidemiology
Systemic PEComa has been observed in patients ranging from three to 97 years old. The tumor occurs more frequently in women than men. Indeed, the incidence of PEComa in women compared to men ranges from 4:1 to 7:1 [6,34].

Tumor origin
Systemic PEComa have been observed in several visceral organs and soft tissue. The organs of involvement in patients with systemic PEComa have included adrenal gland, biliary tract, bone, breast, cervix, colon, common bile duct, digestive tract, eye, eye socket, gall bladder, greater omentum, groin, heart, kidney, liver, lung, lymph node, nasal cavity, nasopharynx, ovary, pancreas, pelvic cavity, pericardium, prostate, rectum, retroperitoneum, rib, skull base, thigh bone, throat, trachea, upper airway, urinary bladder, uterus, vagina, and vulva [1,4,34-36]; genitourinary organs tend to be a common site of origin [3,34]. In addition, cutaneous PEComa have been reported (**Tables 2-4**), [7-31]. Both benign and malignant variants of the tumor have been observed [4,34].

Pathology
Hematoxylin and eosin staining
Systemic PEComa are composed of an admixture of blood vessels and tumors cells that are epithelioid, spindle, or a mixture of both. The tumor cells are arranged as bands, nests or whirls. The cytoplasm of the epithelioid cells ranges from being clear to granular. Nuclei and often prominent nucleoli are present. In benign lesions, atypia and mitoses are uncommon [3,6].

Immunohistochemical studies
A retrospective immunohistochemical study of 26 systemic PEComa derived from genitourinary organs and soft tissue published in 2005 demonstrated that each tumor had at least one melanocytic marker. The most sensitive marker was HMB45 (92%), followed by

Table 3. *Characteristics of cutaneous perivascular epithelioid cell tumor (PEComas) in men.*

C	A	Site	Size (cm)	Pathology	Cl	Treatment	F-up (mo)	Ref
1	15	Calf	2.0	Epi	Be	Lumpectomy	NS	[23]
2	34	Lower leg	1.6	Epi,MG	Be	Ex	NS	[24]
3	41	Leg	1.5	ECC/ES	Be	NS	NS	[11] C4
4	41	Leg	1.2	Epi	Be	NS	NS	[11] C10
5	42	Leg	0.6	ECC/ES	Be	NS	NS	[11] C3
6	43	Forearm	1.0	MES,M,MG,NP	Ma	ExB,Ex	NR,4	CR
7	44	Leg	1.3	Epi,MG	Be	IEx	NR,108	[10] C8
8	44	Cheek	1.0	MES,M,NP	Ma	ExB,Ex,XRT	NR,24	[25]
9	45	Abdomen	1.0	Epi	Be	Ex	NR,41	[12] C6
10	46	NS	1.7	ECC/ES	Be	NS	NS	[11] C2
11	53	Nose	0.3	Epi	Be	IEx,Ex	NS	[20] C2
12	55	Buttock	2.5	CCMMT	Be	NS	NS	[11] C12
13	58	Scalp	0.8	CCMMT	Be	NS	NS	[26]
14	59	Lower leg	1.0	Epi	Be	Ex	NR,171	[12] C3
15	60	Thigh	NS	Sp	Be	Ex	NR,64	[12] C1
16	60	Foot	3.0	Epi	Be	Ex	NR,12	[27]
17[a]	67	Forehead	0.3	Epi,M,NP	Ma	Bx	NS	[28]
18	71	Thigh	1.5	Epi	Be	IEx,Ex	NS	[20] C3
19	72	Distal leg	1.2	Epi	Be	IEx,MMS	NR,15	[15] C4
20	73	Thigh	1.2	CCMMT	Be	NS	NS	[11] C14
21	76	Scalp	1.6	Epi,M,NP	Ma	Ex	NS[b]	[29]
22	78	Forearm	0.7	Epi	Be	IEx	NS	[10] C1

A, age at diagnosis (years); Be, benign; C, case; cm, centimeters; CCMMT, clear cell myomelanocytic tumor; Cl, classification; ECC/ES, mixed epithelioid and clear cell or mixed epithelioid and spindle cell; Epi, epithelioid cell; Ex, excision (with tumor-free margins); ExB, excisional biopsy (with tumor-free margins); F-up, follow-up; IEx, incomplete excision (with positive margins for tumor); M, mitoses (greater than one per 50 high power fields) present; Ma, malignant; MES, mixed epithelioid cell and spindle cell; MG, multinucleated giant tumor cells; MMS, Mohs micrographic surgery; mo, months; NP, nuclear pleomorphism; NR, no recurrence or metastases; NS, not state; PEComa, perivascular epithelioid cell tumor; Ref, references; Sp, spindle cell; XRT, radiotherapy.
[a] The patient presented with a malignant right adrenal gland PEComa with metastases to not only both adrenal glands, but also his lung and soft tissue. Two years later, he developed a PEComa metastasis to his skin presenting as a forehead nodule.
[b] The patient presented with metastatic melanoma of unknown primary (versus a PEComa metastasis after retrospective assessment). Four years later a scalp nodule that had been present for years began to enlarge; malignant PEComa was diagnosed after excision of the scalp nodule one year later.

Table 4. *Characteristics of cutaneous perivascular epithelioid cell tumor (PEComas) in patients whose gender was not stated.*

C	A	Site	Size (cm)	Pathology	Cl	Treatment	F-up (mo)	Ref
1	44	LowerLeg	1.0	Epi	Be	Ex	NS	[30]
2ᵃ	NS	NS	NS	NS	Ma	NS	NS	[31]

A, age at diagnosis (years); Be, benign; C, case; cm, centimeters; Cl, classification; Epi, epithelioid cell; Ex, excision (with tumor-free margins); F-up, follow-up; Ma, malignant; mo, months; NS, not state; PEComa, perivascular epithelioid cell tumor; Ref, references
ᵃ Investigators report the results, in aggregate, of the comprehensive genomic profiling of 31 primary malignant PEComas; one of the tumors originated from the skin.

Mart1/Melan A (72%) and MiTF (50%); only 33% of the tumors expressed S100. The tumors also demonstrated expression of smooth muscle markers: SMA (80%) and desmin (36%). Vimentin (86%), transcription factor binding to immunoglobulin heavy contrast Mu (IGHM) enhancer three (TFE3, 29%), and pan-cytokeratin (13%) expression were also observed [3].

When the investigators reviewed the previously published 61 PEComas, they observed similar results. Positive staining for melanocytic markers was observed with HMB45 (100%), Mart1/Melan A (41%), and S100 (11%). Smooth muscle expression was demonstrated by smooth muscle actin or pan-muscle actin (59%) and desmin (31%). None of the tumors expressed cytokeratin [3].

A more recent study of 26 PEComa (including 24 renal, one liver, and one retroperitoneal) showed similar immunohistochemical expression of the tumors. Nearly all the tumor cells expressed both Mart1/Melan A (100%) and HMB45 (96%). Although only 27% of the tumors had nests of cells that expressed S100, 54% of the tumors showed single or small clusters of S100 positive staining cells within the fatty tissue. Similarly, smooth muscle markers (smooth muscle actin and calponin) were also expressed by the tumor cells of all 26 tumors. None of the tumors expressed TFE3 [6].

Pathogenesis
The derivation of the PEComa cell remains to be established; indeed, a normal counterpart of the cell has not been identified. Several hypotheses for the origin of the PEComa cell have been postulated. Undifferentiated cells of the neural crest may be the source of the cells, enabling expression by these cells of both melanocytic and smooth muscle markers.

Indeed, positive expression of the tumor cells for S100, CD56, and CD99 supports this possible origin of the PEComa cells [6]. Alternatively, the melanogenesis activation may have resulted from a myoblastic cell origin in combination with a subsequent molecular mutation of the cell that allows it to express melanocytic markers [4]. Third, the cells may have been derived from a cell of pericytic origin [1]. In addition, a possible differentiation of the tumor cells toward adipose tissue was suggested by the investigators of one study which demonstrated single or small clusters of S100-positive staining tumor cells within the fatty tissue [6].

Some of the patients with systemic PEComa have demonstrated mutations in the *tuberous sclerosis complex* (*TSC*)—either loss of *TSC1* (which is a tumor suppressor gene encoding for hamartin and located at chromosome 9q34) or *TSC2* (*tuberin* and located at chromosome 16p13.3). Most of these patients do not have clinical stigmata or other features of tuberous sclerosis. Other patients with systemic PEComa have *TFE3* gene alterations. Indeed, in a study of patients with uterine PEComas the investigators were able to demonstrate a correlation between diffuse HMB45 melanocytic marker expression and *TSC/TFE3* fusions [5]. However, the presence of mutations in *TSC* or *TFE3* genes are generally mutually exclusive in PEComa [37-41].

Malignancy criteria
The criteria for malignancy classification of PEComa was derived predominantly from pathologic features observed in non-cutaneous tumors by Folpe et al. in 2005. They identified six high-risk features: high nuclear grade and cellularity, infiltrative growth pattern, mitotic rate greater than one per 50 high power fields, necrosis, tumor size greater than five

centimeters, and vascular invasion. Based on these features, three risk categories were defined: benign (in which the tumor contains less than two high-risk features and size less than five centimeters), malignant (in which the tumor has two or more high-risk factors), and uncertain malignant potential (in which the tumor size is greater than or equal to five centimeters or the tumor cells demonstrate nuclear pleomorphism/multinucleated giant cell only [3,34]. Other investigators have confirmed their support of this classification. Particularly, Hornick and Fletcher commented that, in their experience, the PEComas with the potential to behave in a malignant fashion were those demonstrating marked pleomorphism and nuclear atypia [42].

The reports of malignant PEComa have increased since the diagnostic criteria for malignancy was defined. Folpe et al. identified 17 PEComa with aggressive behavior from the total group of 87 tumors (20%) in 2005 [3]. In 2012, Bleeker et al. identified 234 PEComas reported in the English literature; sufficient information to evaluate malignancy risk status was only available in 93 of the tumors—87 of the PEComas were determined to be malignant [34]. A review on the diagnosis and treatment of malignant PEComa tumors in 2020 commented that fewer than 100 malignant PEComas have been described in the literature [36].

Treatment
Small PEComas, without worrisome histologic features, are usually benign [3]. Therefore, surgical removal of these benign PEComas is typically curative [1]. Indeed, even tumors with worrisome histologic features—yet not fulfilling the diagnostic criteria to be classified as malignant—often behave in a benign manner after excision [35].

The management of malignant PEComa initially involves radical surgical resection since the tumors are generally resistant not only to chemotherapy but also to radiotherapy [34,36]. In addition, many of the malignant tumors have mutations in the *TSC1/TSC2* genes, thereby resulting in excessive activity of the mammalian target of rapamycin complex 1 (*mTORC1*). Also, a subset of malignant PEComas have *TFE3* gene fusion/translocation which causes increased activation of the mammalian target of

rapamycin (mTOR) signaling pathway [36,43]. Thus, molecularly-targeted therapy with mTOR pathway inhibitors, such as sirolimus (also known as rapamycin), have been used in the treatment of malignant PEComa [1,36,43]. With the expanding access to, and use of next generation sequencing, personalized therapies directed at the specific genomic aberrations in each patient's tumor will be available for treatment consideration [1,31,34,36,43].

Cutaneous PEComa
History
Several years following the discovery of systemic PEComa, the cutaneous variant of this tumor was eventually described (**Table 1**), [3,13,19,26,31-33]. The first case was described in an abstract in 2003 as a cutaneous clear cell myomelanocytic tumor-perivascular epithelioid cell tumor [26]; subsequently, a report was published that referred to the tumor as a clear cell "sugar" tumor (PEComa) of the skin [19]. Earlier that same year, in 2005, it was presented as cutaneous clear cell myomelanocytic tumour (CCMMT) in a case series of seven women [13]. Thereafter, in 2007 and 2008, it was finally presented as a PEComa of the skin and primary cutaneous PEComa, respectively [9,10].

Incidence
In a comprehensive literature review performed in 2005, 61 previously reported PEComa were identified. The authors added 26 additional tumors from a retrospective study of their pathology files. Only seven of the 87 tumors (eight percent) were primary cutaneous PEComa [3]. A follow up study in 2012 by one of the previous authors identified 234 cases of PEComa reported in the English literature; 22 (nine percent) of the tumors originated in the skin [34].

To the best of our knowledge, cutaneous PEComa has been reported in 65 patients including 41 women, 22 men, and two individuals whose gender was not described (Tables 2, 3, and 4), [7-31]. Several patients—some of whom have been included in prior studies by earlier researchers—were not included in this report since we and other investigators were not able to determine if the PEComa involved both the dermis and subcutaneous [44-46]. In addition, other papers

Table 5. *Diagnosis age of woman and men with cutaneous perivascular epithelioid cell tumor (PEComas)*[*].

Age range (years) at diagnosis	Women number (percent)	Men number (percent)	Total number (percent)
Less than 20	4 (6.3%)	1 (1.6%)	5 (7.9%)
20 to 29	2 (3.2%)	0 (0.0%)	2 (3.2%)
30 to 39	8 (12.7 %)	1 (1.6%)	9 (14.3%)
40 to 49	11 (17.5%)	8 (12.7%)	19 (30.2%)
50 to 59	6 (9.6%)	4 (6.3%)	10 (15.9%)
60 to 69	9 (14.3%)	3 (4.7%)	12 (19.0%)
70 to 79	0 (0.0%)	5 (7.9%)	5 (7.9%)
80 or older	1 (1.6%)	0 (0.0%)	1 (1.6%)
Total	41 (65.2)	22 (34.8)	63 (100.0%)

PEComa, perivascular epithelioid cell tumor; %, percent
[*]In addition to 63 patients included in the table, two additional patients whose gender was not provided, also had a primary cutaneous PEComa. The first patient was a 44-year-old individual with a one-centimeter benign tumor on the lower leg; the PEComa was excised, and pathology demonstrated a tumor consisting of epithelioid cells [30]. The second patient had a primary malignant cutaneous PEComa which was evaluated using next generation sequencing in a study that also included 30 systemic PEComa; the genomic results of the study were reported in aggregate and no additional specific details of this patient were provided [31].

describing cutaneous PEComas presented tumors that only affected the soft tissue without dermal involvement [8,37,47-51].

Epidemiology
Primary cutaneous PEComa has been described in 97% of the patients (63 of the 65 individuals). The patients—for whom gender was provided—include 40 women and 21 men. Hence, in comparison to the marked prevalence of PEComa of visceral organs and soft tissue in women, the prevalence of women to men (a 2:1 ratio) in patients with primary cutaneous PEComa is much lower (Tables 2, 3), [7-29]. The remaining two of the 65 patients (three percent) with cutaneous involvement of PEComa were individuals who developed metastatic PEComa (originating in the uterus of a 62-year-old woman or the adrenal glands in a 67-year-old man) to the skin, [21,28].

Cutaneous PEComa patients ranged in age at diagnosis from 1.7 years to 81 years (median, 47 years), (**Table 5**), [7-31]. The women ranged in age at diagnosis from 1.7 years to 81 years (median, 46 years); the most frequent decade for diagnosis was between ages 40 to 49 years: 11 of the 41 women (27%). The men ranged in age at diagnosis from 15 years to 78 years (median, 54 years); similar to the women, the most frequent decade for diagnosis was between ages 40 to 49 year: eight of the 22 men (36%).

Nearly 80% (50 of 63 patients) of the individuals with cutaneous PEComa were diagnosed between the ages of 30 years to 69 years. The most frequent decade of diagnosis was between 40 to 49 years: 19 of 63 patients (30%). Diagnosis of cutaneous PEComa was less common either under the age of 30 years (seven of 63 patients, 11%) or over the age of 79 years (six of 63 patients, 9.5%), (**Table 5**), [7-31].

Clinical characteristics
Location
The most common location of a cutaneous PEComa was the patient's extremity; approximately three-quarters of the tumors (47 of 64 PEComa) developed on either the leg or arm (**Table 6**), [7-31]. Indeed, nearly two-thirds of the tumors (40 of 64 PEComa) occurred on the lower extremity. Cutaneous PEComas were also observed, in order of decreasing frequency, on the head and neck (nine of 64 tumors, 14%), the upper extremity (seven of 64 tumors, 11%), the torso (five of 64 tumors, eight percent), and the buttock (three of 64 tumors, five percent).

Size
The size of the cutaneous PEComas ranged from 0.3 to 5.9 centimeters (median, 1.2 centimeters), (**Table 7**), [7-31]. In women, the tumors ranged in size 0.3 to 5.9 centimeters (median, 1.3 centimeters). In men, the tumors ranged in size 0.3 to 3.0 centimeters (median, 1.2 centimeters). The tumor was 1.0

Table 6. *Location of cutaneous perivascular epithelioid cell tumor (PEComas).*

Location	Women[a] number (percent)	Men[b] number (percent)	Gender NS[c] number (percent)	Total[d] number (percent)
Lower extremity[e]	27 (42.3%)	12 (18.7%)	1 (1.6%)	40 (62.6%)
Head and neck[f]	4 (6.2%)	5 (7.9%)	0 (0.0%)	9 (14.1%)
Upper extremity[g]	5 (7.9%)	2 (3.0%)	0 (0.0%)	7 (10.9%)
Torso[h]	4 (6.2%)	1 (1.6%)	0 (0.0%)	5 (7.8%)
Buttock	2 (3.0%)	1 (1.6%)	0 (0.0%)	3 (4.6%)
Total[a,b,c,d]	42 (65.6%)	21 (32.8%)	1 (1.6%)	64 (100.0%)

NS, not stated; PEComa, perivascular epithelioid cell tumor; %, percent.
[a] There were 41 women with cutaneous PEComa; there was one location for 40 women, two locations for one patient, and no locations stated for two patients. Therefore, there was a total of 42 locations.
[b] There were 22 men with cutaneous PEComa; there was one location for 21 men, and no locations for one man. Therefore, there was a total of 21 locations.
[c] There were two patients with cutaneous PEComa for whom gender was not stated; there was one location for one patient, and no locations stated for one patient. Therefore, there was a total of one location.
[d] There were 65 patients with cutaneous PEComa; there was one location for 62 patients, two locations for one patient, and no locations stated for two patients. Therefore, there was a total of 64 locations.
[e] Lower extremity includes thigh (13 tumors), distal or lower leg (11 tumors), legs (not otherwise specified), (nine tumors), calf (three tumors), foot (two tumors), popliteal fossa (one tumor, and shin (one tumor).
[f] Head and neck includes cheek (three tumors), scalp (two tumors), forehead (one tumor), lip (one tumor), neck (one tumor), and nose (one tumor).
[g] Upper extremity includes arm (two tumors), wrist (two tumors), and forearm (one tumor).
[h] Torso includes back (two tumors), abdomen (one tumor), lower spine (one tumor), and shoulder (one tumor).

centimeters in one patient for whom gender was not provided.

Nearly half of the cutaneous PEComas ranged in size from 1.0 to 1.9 centimeters. Indeed, nearly 75% of the tumors were less than 2.0 centimeters and 95% of the tumors were smaller than 4.0 centimeters. Only 3.6% of the cutaneous PEComas were larger than 5.0 centimeters (**Table 7**), [7-31].

Both largest tumors (measuring 5.9 and 5.0 centimeters) were fibroma-like cutaneous PEComas;

the third fibroma-like cutaneous PEComa was 1.3 centimeters. None of these lesions had any high-risk pathology features. Also, they did not recur or metastasize [7,8].

The size of the metastatic cutaneous PEComa was reported in one of the two patients, 0.3 centimeters [13]. Including the patient in the paper, the size of the primary cutaneous malignant PEComa was reported for four of the five individuals [16,25,29]. In these individuals, the size ranged from 1.0 to 3.5 centimeter (median, 1.3 centimeters).

Table 7. *Size of cutaneous perivascular epithelioid cell tumor (PEComas).*

Size (centimeters)	Women[a] number (percent)	Men[b] number (percent)	Gender NS[c] number (percent)	Total[d] number (percent)
0.1 to 0.4	2 (3.6%)	2 (3.6%)	0 (0.0%)	4 (7.2%)
0.5 to 0.9	7 (12.3%)	3 (5.5%)	0 (0.0%)	10 (17.8%)
1.0 to 1.4	9 (16.1%)	8 (14.3%)	1.0 (1.7%)	18 (32.1%)
1.5 to 2.0	4 (7.2%)	5 (8.9%)	0 (0.0%)	9 (16.1%)
2.0 to 2.9	6 (10.7%)	2 (3.6%)	0 (0.0%)	8 (14.3%)
3.0 to 3.9	3 (5.5%)	1 (1.7%)	0 (0.0%)	4 (7.2%)
4.0 to 4.9	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
5.0 to 5.9	2 (3.6%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
Total[a,b,c,d]	34 (60.7%)	21 (37.6%)	1 (1.7%)	56 (100.0%)

NS, not stated; PEComa, perivascular epithelioid cell tumor; %, percent.
[a] There were 41 women with cutaneous PEComa; however, the size was only reported for 34 of the women.
[b] There were 22 men with cutaneous PEComa; however, the size was only reported for 21 of the men.
[c] There were two patients with cutaneous PEComa for whom gender was not stated; however, the size was only reported for one of the patients.
[d] There were 65 patients with cutaneous PEComa; however, the size was only reported for 56 of the patients.

Table 8. *Clinical differential diagnosis of cutaneous perivascular epithelioid cell tumor (PEComas).*

Diagnosis	References
Amelanotic melanoma	[15]
Cyst	[9,15,24,25]
Dermatofibroma	[11,12,15,30]
Dermatofibrosarcoma protuberans	[15]
Lipoma	[15]
Keratoacanthoma (type of squamous cell carcinoma)	Current report
Non-melanoma skin cancer	[15]
Sarcoma	[15]
Soft tissue fibroma	[8]

Morphology
The morphologic presentation of a cutaneous PEComa is rather generic. It usually presents as an asymptomatic, slowly enlarging, nodule. The typically painless tumor is often flesh-colored [22]; however, the color can vary: brown [20], grey-brown [30], pink [15,17,20], red [19,23], violaceous [15], or yellow-brown [15].

Clinical differential diagnosis
The clinical differential diagnosis of the cutaneous PEComa was provided by some of the researchers (**Table 8**), [8,9,11,12,15,24,25,30]. The most common considerations were either a cyst (which was either not otherwise specified or suggestive of an epidermoid inclusion cyst) or a dermatofibroma. The tumor on the distal forearm extensor surface of the man in this report clinically mimicked a keratoacanthoma type of squamous cell carcinoma; a collarette of epithelium surrounding the tumor nodule which had an invaginated central area caused by the crust-covered ulceration.

Pathology
The description of the pathologic findings of cutaneous PEComa varied and reflected the prevailing nomenclature that corresponded to the year when the paper was published. Earlier reports referred to the tumor and its cells as either a clear-cell myomelanocytic tumor or a clear-cell sugar tumor; review of these reports shows that the tumor cells were epithelioid in morphology [13,19,26]. Subsequently, reports of cutaneous PEComas referred to the tumor cells as either epithelioid (with cytoplasm which was either clear, or occasionally granular, or both), spindle, or a mixture of both cell types. Similar to systemic PEComas, cutaneous PEComas consisted of an admixture of tumor cells and blood vessels.

Hematoxylin and eosin staining
At low magnification, several of the tumors have silhouette of a fibrous dermatofibroma. Hyperplasia of the overlying epithelium, similar to that observed in a dermatofibroma, was noted in one tumor [11]. In addition, at the periphery of the tumor, the nests of tumor cells had an infiltrative growth pattern that dissected the adjacent collagen bundles [10,12,24].

Ninety-two percent (59 of 64 tumors) of the cutaneous PEComa consisted of tumor cells that are either only epithelioid cells (45 of 64 tumors, 70%) or a mixed cell population of epithelioid and spindle cells (nine of 64 tumors, 14%); some of the patients had tumors that were reported in a category of either mixed epithelioid and clear or mixed epithelioid and spindle (five of 64, eight percent). Only eight percent (five of 64 tumors) consisted of spindle cells alone [7,8,11,12]. These included the three tuberous sclerosis patients with fibroma-like cutaneous PEComa [7,8] and two other individuals with tumors on their thigh, a 23-year-old woman with a two-centimeter tumor [11] and a 60-year-old man [12].

Periodic acid-Schiff staining
The cytoplasm of the epithelioid cells of cutaneous PEComas almost always demonstrated positive staining with periodic acid-Schiff stain. However, when periodic acid-schiff and diastase was used, there was no staining of the cell cytoplasm. These observations confirm that the cytoplasm of the epithelioid cells contains glycogen [9,15,17]. Yet, the stains for glycogen (alcian blue with periodic acid-Schiff and periodic acid-Schiff post-diastase digestion) were negative for one tumor [26].

Cytologic atypia
Cutaneous PEComas can have nuclear pleomorphism or mitoses or both. Nuclear pleomorphism was observed—including the current report—in eight tumors [9,13,16,25,28,29]; five of these individuals, including the reported patient, had primary or metastatic malignant PEComa [16,25,28,29]. Greater than one mitosis per 50 high

power fields was noted in seven tumors, including the reported patient [13,14,16,25,28,29]; five of these individuals, including the reported patient, also had primary or metastatic malignant PEComa [16,25,28,29]. Three patients whose tumors had nuclear atypia [9,13] and two patients whose tumors had increased mitoses [13,14] had benign primary cutaneous PEComas.

Multinucleated giant tumor cells

Multinucleated giant tumor cells is a pathologic feature of PEComas that alone, or with high-grade nuclear atypia, has been suggested by Folpe et al. to prompt classification of the tumor to be of uncertain malignant potential. Tumor size greater than five centimeters is an independent criterion of a PEComa of uncertain malignant potential [3]. Including the patient in this report, seven primary cutaneous PEComa had giant tumor cells [10,15,20,24]. Except for the reported patient, the multinucleated giant cells present in the other cutaneous PEComas were benign in appearance and not associated with a malignant neoplasm.

One primary cutaneous PEComa had unusual features including not only multinucleated tumor giant cells but also focal rhabdoid cytoplasmic inclusions. The 1.2 centimeter tumor on the buttock of a 53-year-old woman had been present for 12 months; although the investigators considered the PEComa to be benign, a sentinel lymph node biopsy was performed, and the neoplasm was re-excised with a wide margin. There was no evidence of recurrence or metastases during 37 months of follow-up [10].

Other pathologic features

Similar to the malignant tumor of the patient in this report, a benign primary cutaneous PEComa was also observed to be surrounded by a peripheral collarette of epithelium; the 3-centimeter tumor consisted of epithelioid cells and was located on the foot of a 60-year-old man [27]. In some of the patients, the tumor cells were restricted to the dermis [10,11,17,23]. However, for several patients, the tumor cells were not only in dermis but also found to be extending into the underlying subcutaneous fat [10,11,13,20,24].

Pathologic differential diagnosis

The pathologic differential diagnosis of cutaneous PEComas is extensive (**Table 9**), [1,3,10,15,17,19-22,24,29,30,36,41,52-56,69]; several papers have reviewed and summarized the immunohistochemical differentiation of these tumor [1,3,10,20,36,56]. The neoplasms that can pathologically masquerade as a cutaneous PEComa include both benign and malignant tumors of melanocyte and smooth muscle origin. The tumors have cells that are epithelioid with either clear or

Table 9. *Pathologic differential diagnosis of cutaneous perivascular epithelioid cell tumor (PEComas).*

Diagnosis	References
Agminated clear cell tumor	[52]
Clear cell tumor with melanocytic differentiation and *ACTIN-MITF* translocation	[69]
Dermal clear cell mesenchymal neoplasm	[10,20,22,24,53]
Eruptive dermal clear cell desmoplastic mesenchymal tumor with perivascular myoid differentiation	[41]
Fibrous papule, clear cell variant	[52,54,55]
Gastrointestinal stromal tumor	[3,36]
Granular cell tumor	[1,19]
Granular cell tumor, clear cell variant	[20]
Hepatocellular carcinoma, metastatic	[30]
Leiomyoma, granular cell	[19]
Leiomyosarcoma, granular cell	[19,30,36]
Leiomyosarcoma, uterine	[56]
Melanoma	[3,10,15,19,21,24,29,36,56]
Melanoma, balloon cell	[1,10,20,22,30]
Meningioma, primary extracranial	[1]
Metastatic clear cell carcinomas	[1,4,20]
Myoepithelioma	[1]
Neurothekeoma, cellular variant	[52]
Nevus, balloon cell	[1,10,20,22,30]
Paraganglioma-like dermal melanocytic tumor	[20]
Rhabdomyosarcoma, pleomorphic	[56]
Renal cell carcinoma, metastatic	[20,22,24,36,56]
Sarcoma, alveolar soft part	[36,56]
Sarcoma, clear cell	[1,3,10,17,19,22,36]
Sarcoma, epithelioid	[1,56]
Sarcoma, endometrial stromal	[56]
Sebaceous carcinoma	[20,22]
Xanthoma	[1]
Xanthoma, clear cell variant	[20,22]

granular cytoplasm. In addition, cutaneous metastases of visceral malignancies characterized by tumor cells with clear cytoplasm, such as renal cell carcinoma, mimic cutaneous PEComa.

The pathology changes on hematoxylin and eosin-stained tissue section of melanoma, especially balloon cell or clear cell melanoma, can mimic those of PEComa. In addition, both melanoma and PEComa express melanocytic markers when the tissue sections are evaluated immunohistochemically. Indeed, the diagnosis of benign primary cutaneous PEComa [10], primary malignant cutaneous PEComa [29], and metastatic malignant PEComa [21] were delayed since the initial evaluation of the patients' tumors was diagnosed as malignant melanoma instead of PEComa.

In addition to melanocytic neoplasms, clear cell sarcoma may be the most likely diagnosis to be confused with cutaneous PEComa based on histopathology. Clear cell sarcoma is composed of polygonal-to-fusiform cells that grow in nests or fascicles. Similar to cutaneous PEComa, clear cell sarcoma expresses HMB45 and MART1. However, in contrast to PEComa, it also typically demonstrates positive staining for both S100 and Sry-related HMg-box gene 10 (SOX-10). Also, in contrast to PEComa, clear cell sarcoma is negative for smooth muscle markers. In addition, documentation of EWS-ATF1 gene fusion can definitively establish the diagnosis of clear cell sarcoma since it is not found in PEComa [10,15,16].

Immunohistochemistry studies
Immunohistochemistry studies were essential in establishing the diagnosis of cutaneous PEComa; similar to systemic PEComa, a cutaneous PEComa was characterized by co-expression of melanocytic markers and smooth muscle markers. Cutaneous PEComa also universally showed positive staining for CD10, BCL1, E-cadhedrin, and cathepsin; they almost always stained positive for 4E-binding protein (4EPB1) and the tumor cells frequently demonstrated expression of CD68. In contrast, cutaneous PEComa universally showed negative staining for cytokeratins and almost always did not stain for TFE3.

Melanocytic markers
The most reliable melanocytic marker in cutaneous PEComa was MiTF; 100% (33 of 33) of the PEComas tested with this antibody demonstrated positive tumor cell staining (**Table 10**), [7-30]. Also, HMB45 and melanoma-associated antigen (NKIC3, also known as CD63) were both equally reliable to demonstrated melanocyte expression; 94% positive staining of the tumor cells was observed (51 of 54 tumors and 17 of 18 tumors, respectively). One-third (33%, 16 of 48) of the tumors exhibited expression of MART1 (also referred to as Melan A). Only 11% (six of 53) of tumors stained with S100 showed positivity and none of the tumors tested with either Sry-related HMg-box gene 10 (SOX10, zero of 19), or preferentially expressed antigen in melanoma (PRAME, zero of one) demonstrated melanocytic expression. Hence, similar to our patient's tumor, at least 21 additional PEComas demonstrated positive staining for HMB45 and negative staining not only for S100 but also MART1 [7,13,15,16,19-21,22,24,28,30].

In addition, similar to our patient whose PEComa had strongly positive staining with MiTF and very weak HMB45 staining, a PEComa from a patient of Ghazali et al. demonstrated positive staining with both MiTF and MART1 but did not show staining to HMB45 [14]. Other investigators have observed PEComas in which less than five percent of the tumor cells demonstrated HMB45 staining [3,10,13]. Therefore, when the possibility of PEComa is entertained and HMB45 staining is weak or absent, positive staining for MiTF can be useful to support a PEComa diagnosis [10,14].

Smooth muscle markers
The most reliable smooth muscle markers in cutaneous PEComa were SMA and desmin; 43% (22 of 51) and 40% (19 or 48) of the PEComas tested with these antibodies demonstrated positive tumor cell staining, respectively (**Table 11**), [7-30]. Other smooth muscle antibodies were less successful in demonstrating tumor cell expression for smooth muscle: positive tumor cell staining was observed with 14% (three of 22 tumors) with caldesmon, 14% (three of 22 tumors) with calponin, and 13% (two of

Table 10. *Immunohistochemical staining patterns of melanocytic markers in cutaneous perivascular epithelioid cell tumor (PEComas)[a]*.

First author, year of publication	MiTF	HMB45	NKIC3	MART1	S100	SOX10	Ref
Crowson, 2003	NS	1/1	NS	1/1	1/1	NS	[26]
Mentzel, 2005	7/7	7/7	6/6	1/7	0/7	0/2[b]	[13]
dSAS, 2005	NS	1/1	NS	0/1	0/1	NS	[19]
Tan, 2007	NS	2/2	NS	2/2	0/2	NS	[9]
Liegl, 2008	5/5	10/10	NS	5/7	1/10	NS	[10]
Calder, 2008	NS	1/1	NS	1/1	0/1	NS	[29]
Chaplin, 2010	1/1	1/1	NS	NS	0/1	NS	[17]
Ghazali, 2010	1/1	0/1	NS	1/1	0/1	NS	[14]
Pusiol, 2012	1/1	0/1	0/1	0/1	0/1	NS	[27]
Trotot-Voilliot, 2013	NS	1/1	NS	0/1	1/1	NS	[18]
Llamas-Velasco, 2013	NS[c]	NS[c]	NS[c]	NS[c]	NS[c]	0/3	[11]
Greveling, 2013	1/1	1/1	NS	1/1	0/1	NS	[25]
Zhang, 2014	NS	1/1	NS	1/1	0/1	NS	[23]
Wu, 2014	NS	1/1	NS	0/1	0/1	NS	[28]
Ieremia, 2014	1/1	1/1	NS	0/1	0/1	NS	[24]
Charli-Joseph, 2014	8/8	7/8	8/8	0/7	3/8	0/7	[12]
Kneitz, 2015	1/1	1/1	1/1	0/1	0/1	NS	[30]
Fernandez-Flores, 2016	3/3	3/3	NS	0/3	0/3	0/2	[20]
Parra-Medina, 2017	NS	1/1	NS	0/1	0/1	NS	[21]
Stuart, 2017	1/1	5/5	1/1	2/5	0/4	0/3	[15]
Larque, 2018	NS	2/2	NS	1/1	0/1	NS	[8]
Odono, 2020	NS	1/1	NS	0/1	0/1	0/1	[7]
Ueberschaar, 2020	1/1	1/1	NS	0/1	0/1	NS	[22]
Cole, 2021	1/1	1/1	1/1	0/1	0/1	0/1	[16]
Cohen, 2022	1/1	1/1	NS	0/1	0/1	NS	CR
Total	33/33	51/54	17/18	16/48	6/53	0/19	
Percent positive cases	100	94	94	33	11	0	

CR, current report; dSAS, de Saint Aubain Somerhausen; HMB-45, human melanoma black-45; MART1, melanoma antigen recognized by T-cells one (also referred to as Melan A); MiTF, microophthalmia transcription factor; NKIC3, melanoma-associated antigen (also known as CD63); NS, not stated; PEComa, perivascular epithelioid cell tumor; S100, neurone-specific enolase and Sangtec 100; SOX10, Sry-related HMg-box gene 10.
[a] An additional melanocytic marker--preferentially expressed antigen in melanoma (PRAME)--was not expressed in one patient (0/1), [16].
[b] These are two of the 17 cases that were reported in a subsequent publication by some of the authors [11].
[c] The tumor cells from all seven of the patients expressed at least one melanocytic marker.

15 tumors) with muscle-specific actin (MSA). Smooth muscle myosin heavy chain (SMMHC) showed positive staining for one of two tested tumors [20] and no staining was observed for one tumor tested with myogenin (Myog), [7]. A skeletal muscle antibody (MyoD1) did not show positive staining in the three tumors tested [7,9,14].

CD10 staining
CD10 is a marker expressed by 100% of metastatic renal cell carcinoma metastases and 89% to 100% of primary renal cell carcinomas [20]. CD10 expression has also been observed in other malignant tumors such as the clear-cell variant of atypical fibroxanthoma. In addition, benign tumors such as dermatofibromas and xanthomatous clear lesions such as xanthelasma, xanthogranuloma, and xanthoma can demonstrate CD10 expression [22]. Expression of CD10 has been observed in systemic PEComa from oral mucosa [57].

Similar to metastatic renal cell carcinoma, cutaneous PEComa often consists of epithelioid cells with clear cytoplasm. To date, positive staining for CD10 has been demonstrated in 100% (ten of ten) of PEComas that have been tested (**Table 12**), [15,16,20,22,25]. Hence, CD10 expression cannot be used to differentiate PEComa from metastatic renal cell carcinoma to skin.

The first observation of positive CD10 expression was a 44-year-old man with primary cutaneous malignant PEComa on his left cheek in 2013 [25]. Two

Table 11. *Immunohistochemical staining patterns of smooth muscle markers in cutaneous perivascular epithelioid cell tumor (PEComas)[a].*

First author, publication year	SMA	Desmin	Caldesmon	Calporin	MSA	Ref
Crowson, 2003	1/1	1/1	NS	NS	0/1	[26]
Mentzel, 2005	1/7	1/6	NS	2/4	0/6	[13]
dSAS, 2005	0/1	1/1	NS	NS	NS	[19]
Tan, 2007	1/2	0/2	NS	NS	NS	[9]
Liegl, 2008	1/10	5/10	0/10	0/10	NS	[10]
Calder, 2008	1/1	NS	NS	NS	NS	[29]
Chaplin, 2010	0/1	NS	NS	NS	0/1	[17]
Ghazali, 2010	1/1	1/1	1/1	NS	NS	[14]
Pusiol, 2012	NS	1/1	NS	NS	NS	[27]
Trotot-Voilliot, 2013	0/1	0/1	NS	NS	NS	[18]
Llamas-Velasco, 2013	NS[b]	NS[b]	0/7	NS[b]	NS[b]	[11]
Greveling, 2013	1/1	0/1	0/1	NS	NS	[25]
Zhang, 2014	0/1	1/1	NS	0/1	0/1	[23]
Wu, 2014	1/1	1/1	NS	NS	NS	[28]
Ieremia, 2014	0/1	0/1	0/1	0/1	NS	[24]
Charli-Joseph, 2014	7/8	1/8	NS	1/5	2/5	[12]
Kneitz, 2015	0/1	0/1	NS	NS	NS	[30]
Fernandez-Flores, 2016	1/3	0/2	NS	0/1	NS	[20]
Parra-Medina, 2017	1/1	1/1	NS	NS	NS	[21]
Stuart, 2017	1/4	1/4	NS	NS	0/1	[15]
Larque, 2018	1/1	1/1	NS	NS	NS	[8]
Odono, 2020	0/1	1/1	NS	NS	NS	[7]
Ueberschaar, 2020	1/1	1/1	NS	NS	NS	[22]
Cole, 2021	1/1[c]	0/1	1/1	NS	NS	[16]
Cohen, 2022	1/1	1/1	1/1	NS	NS	CR
Total	22/51	19/48	3/22	3/22	2/15	
Percent positive cases	43	40	14	14	13	

CR, current report; dSAS, de Saint Aubain Somerhausen; MSA, muscle specific actin; NS, not stated; PEComa, perivascular epithelioid cell tumor; SMA, smooth muscle actin.
[a] Additional smooth muscle markers were also evaluated in a small number of patients. Smooth muscle myosin heavy chain (SMMHC) was expressed in one patient of two patients that were tested (1/2), [20]. Myogenin (Myog) was not expressed in one patient (0/1), [7] and MyoD1 (a skeletal muscle marker) was not expressed in three patients (0/3), [7,9,14].
[b] The tumor cells from all seven of the patients expressed at least one smooth muscle marker.
[c] SMA expression of the tumor cells was negative from the biopsy specimen; however, SMA expression of the tumor cells was positive from the subsequent excision specimen.

additional patients with primary cutaneous metastatic PEComa also had tumors that expressed CD10; they included the 43-year-old man presented in this report with a tumor on his left forearm and the 42-year-old woman with a right shoulder PEComa reported in 2021 [16]. Seven other patients with cutaneous PEComa, whose tumors were tested, also showed positive staining for CD10: three patients of Fernandez-Flores et al. in 2016 [20], three patients of Stuart et al. one year later in 2017, and one patient of Ueberschaar et al. in 2020 [22].

CD68 staining
CD68 is expressed by macrophages. However, nearly two-thirds (65%, 24 of 37) patients had cutaneous PEComa whose tumor cells stained for CD68 (**Table 12**), [9,10,12,13,15,16,20,23-25,27]. CD34 and CD31 are expressed by vascular cells. Although none of the four patients' cutaneous PEComa tumor cells stained with CD31, the blood vessels in two of the patients were commented to express this marker [23,30]. It was unexpected that two of the six (33%) of patients showed positive staining PEComa tumor cells with CD34 [14,15].

Table 12. *Immunohistochemical staining patterns of miscellaneous markers in cutaneous perivascular epithelioid cell tumor (PEComas).*

First author, year of publication	CD10	CD31	CD34	CD68	TFE3	EMA	Ref
Crowson, 2003	NS	1/1	1/1	NS	NS	NS	[26]
Mentzel, 2005	NS	NS	NS	5/7	0/7[a]	NS	[13]
dSAS, 2005	NS	NS	NS	NS	NS	NS	[19]
Tan, 2007	NS	NS	0/1	2/2	NS	0/2	[9]
Liegel, 2008	NS	NS	NS	2/10	NS	0/10	[10]
Calder, 2008	NS	NS	NS	NS	NS	0/1	[29]
Chaplin 2010	NS	NS	NS	NS	NS	NS	[17]
Ghazali, 2010	NS	NS	0/1	NS	NS	0/1	[14]
Pusiol, 2012	NS	NS	NS	0/1	NS	NS	[27]
Trotot-Voilliot, 2013	NS	NS	NS	NS	NS	NS	[18]
Llamas-Velasco, 2013	NS	NS	NS	NS	0/10	NS	[11]
Greveling, 2013	1/1	NS	NS	1/1	NS	NS	[25]
Zhang, 2014	NS	0/1	NS	0/1	NS	0/1	[23]
Wu, 2014	NS	NS	NS	NS	NS	NS	[28]
Ieremia, 2014	NS	NS	NS	0/1	NS	NS	[24]
Charli-Joseph, 2014	NS	NS	NS	7/8	NS	NS	[12]
Kneitz, 2015	NS	0/1	NS	NS	NS	0/1	[30]
Fernandez-Flores, 2016	3/3	NS	NS	2/2	NS	0/2	[20]
Parra-Medina, 2017	NS	NS	NS	NS	NS	NS	[21]
Stuart, 2017	3/3	0/1	1/2	3/3	0/2	0/2	[15]
Larque, 2018	NS	NS	NS	NS	0/1	NS	[8]
Odeno, 2020	NS	NS	NS	NS	1/1[b]	0/1	[7]
Ueberschaar, 2020	1/1	NS	NS	NS	NS	0/1	[22]
Cole, 2021	1/1	NS	0/1	1/1	0/1	NS	[16]
Cohen, 2022	1/1	0/1	0/1	1/1	NS	0/1	CR
Total	10/10	1/5	3/7	24/37	1/22	0/23	
Percent positive cases	100	20	43	65	5	0	

CD, cluster of differentiation; CR, current report; dSAS, de Saint Aubain Somerhausen; EMA, epithelial membrane antigen; PEComa, perivascular epithelioid cell tumor; Ref, reference; TFE3, transcription factor binding to immunoglobulin heavy contrast Mu (IGHM) enhancer 3
[a] These are seven of 17 cases that were reported in a subsequent publication by some of the authors [11].
[b] The investigators mention that the positive staining was patchy and faint.

Cytokeratin staining
The cutaneous PEComas were evaluated with various cytokeratin stains: pan cytokeratin (35 tumors), AE1/AE3 (12 tumors), CAM5.2 (seven tumors), MNF116 (four tumors), CK7 (three tumors), CK20 (two tumors), and CK903 (one tumor). None of the cutaneous PEComa tumor cells demonstrated expression of cytokeratin (**Table 13**), [7-30]. Also, none of the 23 tumors that were evaluated expressed EMA (**Table 12**), [7-30].

TFE3 gene locus rearrangement
A subset of systemic PEComas have rearrangement of *TFE3* gene locus [3,6,56]. Characteristics of these tumors include diffuse positive TFE3 and HMB45 expression, weak positive expression of SMA, no or focal expression of MiTF or MART1, no expression to TSC1 or TSC2, and no response to mTOR inhibitors [6]. Except for a single patient with fibroma-like PEComa (who had tuberous sclerosis and genetically proven to be heterozygous for a pathogenic TSC2 mutation), [7], all the 21 additional patients with cutaneous PEComa who were evaluated for TFE3 expression using immunohistochemical staining showed negative results (**Table 12**), [5,8,11,13,16].

Other immunohistochemical study results
Immunohistochemical studies using several other antibodies have also been performed on cutaneous PEComas from a limited number of patients. Uniformly positive staining was noted to the following antibodies: cathepsin (eight tumors), [12], CD57 (one tumor), [20], CD63 (one tumor), [9], CD99 (one tumor), [7], BCL1 (nine tumors, including

Table 13. *Immunohistochemical staining patterns of cytokine markers in cutaneous perivascular epithelioid cell tumor (PEComas).*

First author, year of publication	PanCK	AE1/AE3	CAM5.2	MNF116	CK 7	CK 20	CK 903	Ref
Crowson, 2003	NS	0/1	NS	NS	NS	NS	NS	[26]
Mentzel, 2005	0/7	NS	NS	NS	NS	NS	NS	[13]
dSAS, 2005	NS	0/1	NS	NS	NS	NS	NS	[19]
Tan, 2007	0/1	0/1	NS	0/1	NS	NS	NS	[9]
Liegel, 2008	0/10	0/2	0/3	NS	NS	NS	NS	[10]
Calder, 2008	NS	0/1	NS	NS	NS	NS	0/1	[29]
Chaplin, 2010	0/1	NS	NS	NS	NS	NS	NS	[17]
Ghazali, 2010	0/1	NS	NS	NS	NS	NS	NS	[14]
Pusiol, 2012	0/1	NS	0/1	NS	NS	NS	NS	[27]
T-V, 2013	NS	NS	NS	NS	NS	NS	NS	[18]
L-V. 2013	NS	NS	NS	NS	NS	NS	NS	[11]
Greveling, 2013	NS	0/1	NS	0/1	NS	NS	NS	[25]
Zhang, 2014	NS	0/1	NS	NS	NS	NS	NS	[23]
Wu. 2014	NS	NS	NS	NS	NS	NS	NS	[28]
Ieremia, 2014	NS	0/1	NS	0/1	0/1	0/1	NS	[24]
C-J, 2014	0/6	NS	NS	NS	NS	NS	NS	[12]
Kneitz, 2015	0/1	NS	NS	NS	NS	NS	NS	[30]
F-F, 2016	0/2	NS	NS	NS	0/1	NS	NS	[20]
P-M, 2017	NS	0/1	NS	NS	0/1	0/1	NS	[21]
Stuart, 2017	0/3	0/1	0/2	NS	NS	NS	NS	[15]
Larque, 2018	NS	NS	NS	NS	NS	NS	NS	[8]
Odono, 2020	NS	0/1	NS	NS	NS	NS	NS	[7]
Ueberschaar, 2020	0/1	NS	NS	NS	NS	NS	NS	[22]
Cole, 2021	NS	NS	0/1	0/1	NS	NS	NS	[16]
Cohen. 2022	0/1	NS	NS	NS	NS	NS	NS	CR
Total	0/35	0/12	0/7	0/4	0/3	0/2	0/1	
Percent positive cases	0	0	0	0	0	0	0	

AE1/AE3, a pan cytokeratin antibody that detects low and high molecular weight cytokeratins such as cytokeratins 1-8, 10, 14-16 and 19; CAM5.2, a low molecular weight cytokeratin; CK, cytokeratin; CR, current report; dSAS, de Saint Aubain Somerhausen; F-F, Fernandez-Flores; L-V, Llamas-Velasco; NS, not stated; MNF116, cytokeratin, pan antibody; PanCK, pancytokeratin; P-M, Parra-Medina; PEComa, perivascular epithelioid cell tumor; Ref, reference; T-T, Trotot-Voilliot.

current report), [12], E-cadhedrin (eight tumors), [12], factor XIIIA [26], protein gene product (PGP9.5, one tumor), [16], tyrosinase (two tumors), [20,25], and vimentin (three tumors), [15,25]. A mixed response was described to the following antibodies: c-Myc (three of eight tumors), [12], CD31 (one of five tumors), (**Table 12**), CD34 (three of seven tumors), (**Table 12**), CD117 (two of three tumors), [15,20,24], chromogranin-A (one of five tumors), [9,15,21,25], 4EPB1 (seven of eight tumors), [12], lysozyme (one of two tumors), [15,20], integrase interactor one (INI1, staining retained for one of two tumors), [7,16], and p16 (three of six tumors), [12]. Uniformly negative staining was observed to the following antibodies: ALK1 (one tumor, current report), carbonic anhydrase 9 (CAIX, one tumor), [22], calretinin (one tumor), [16], CD1a (two tumors), [15,20], CD21 (one tumor), [15], CD30 (one tumor, current report), CD45 (three tumors, including current report), [15,29], CD56 (ten tumors), [9,12,25], CD163 (two tumors), [20,24], carcinoembryonic antigen (CEA, one tumor), [15], epithelial membrane antigen (23 tumors), (**Table 12**), inhibin (two tumors), [15,16], p63 (five tumors, including current report), [15,16,20], PAX2 (one tumor), [16], PAX8 (four tumors), [15,16,22], placental alkaline phosphatase (PLAP, two tumors), [15,29], PU.1 (one tumor), [16], renal cell carcinoma marker (RCC—also known as proximal nephrogenic renal antigen, PNRA—two tumors), [15,20], synaptophysin (five tumors), [15,20,21,25], thyroid transcription factor (TTF, one tumor), [21], and tryptase (one tumor), [15].

Ki67 staining

Ki67 staining was evaluated for 13 cutaneous PEComas. It was only found to be increased at 30% [12] or 40% [21] in two benign tumors. The man in this report with a malignant PEComa had increased Ki67 staining approaching 10% focally in the periphery of the tumor. However, overall, the Ki67 staining of the entire tumor was less than one percent. Similarly, in the other benign PEComas, the Ki67 staining was virtually zero (one tumor), [14], five percent (one tumor), [15] or less than five percent (seven tumors), and one percent (one tumor), [23].

Pathogenesis

The pathogenesis of primary cutaneous PEComa remains to be definitively determined. Similar to systemic PEComa, the tumor cells may be derived from undifferentiated neural crest cells that can express both melanocytic and smooth muscle markers, myoblastic cells that also express melanocytic markers after a genomically mutating event, or pericytes [1]. However, immunohistochemical studies demonstrating an absence of positivity for TFE3 raise the possibility that the histogenesis of primary cutaneous PEComa may differ from that of systemic PEComa [11].

Indeed, in contrast to systemic PEComa, TFE3 fusions have not been observed in primary cutaneous PEComa [11]. However, immunohistochemical studies of a fibroma-like cutaneous PEComa, from a 20-month-old girl with TSC2 mutation-associated tuberous sclerosis, showed patchy faint staining for TFE3 [7]. The researchers commented not only that weak to moderate TFE3 positivity does not correlate with the presence of TFE translocations, but also that TSC2 alterations and TFE translocations are mutually exclusive genetic alterations in PEComas and their patient had an established TSC2 mutation [7,58].

Documentation of TSC mutations in cutaneous PEComas is also lacking [12,15]. Indeed, with the exception of three patients with fibroma-like cutaneous PEComa, none of the other 60 patients—including the man presented in this report—with primary cutaneous PEComa have tuberous sclerosis [8,48]. Yet, most of the patients with primary cutaneous PEComa have not been evaluated for TSC mutations. When next generation sequencing

studies were performed on the PEComa of the man presented in this report, a genomic aberration of TSC1 T4151 was discovered. The significance of this observation remains to be determined; however, it does provide information regarding potentially therapeutic alternatives directed toward a genomically-actionable aberration in his malignant tumor.

Treatment

The treatment of cutaneous PEComa was described for 53 individuals and involved a biopsy for either diagnosis and treatment or for diagnosis only and was subsequently followed by an excision to establish tumor-free margins and/or to provide a wider margin of tumor-free skin at the site of the PEComa (Tables 2-4), [7-31]. Sixty percent (32 of 53) of the patients only had one surgical procedure—either a biopsy, an incomplete biopsy, an excisional biopsy, or an excision. Thirty-four percent (18 of 53) of the patients had two surgical procedures—an excision following either a biopsy, an incomplete biopsy, or an excisional biopsy. Three patients had more than two treatment intervention: a sentinel lymph node biopsy that was preceded by an incomplete biopsy and excision [10] or adjuvant radiotherapy that was preceded by either an excisional biopsy and excision [25] or a biopsy, incomplete excision, and excision [16].

A biopsy of the lesion was performed in four (8%) of the patients [15,16,20,28]. This was followed by an excision of the tumor in three patients [15,16,20] and additional management was not stated for the fourth patient [28]. An excision, without any additional treatment, was performed in 23 (43%) of the tumors [7,8,10,12,14,18,21-24,27-30].

Ten (19%) of the patients-including the man in this report—with cutaneous PEComa had an excisional biopsy whereby the tumor was removed at the time of the biopsy [9,13,15,19,25]; however, nine of these patients—including the man in this report—had a subsequent excision of the tumor site [9,13,19,25]. An incomplete excision was performed at the time of biopsy for 16 (30%) of the PEComa patients [10,13,15,17,20]; a complete excision of the residual tumor was done for nine of these patients [10,15,20]. However, seven of the 16 patients with an initial

incomplete excision of their benign primary cutaneous PEComa had no further treatment [10,13,15,17].

Two of the primary malignant cutaneous PEComa patients received postoperative adjuvant radiotherapy. The 42-year-old woman with a right shoulder tumor initially had a biopsy followed by an incomplete excision; the residual tumor was subsequently excised, and she completed six weeks of radiation consisting of 60 Gray in 30 fractions to the postoperative area and a one Gray boost in five fractions with computerized tomography simulation [16]. The 44-year-old man with a left cheek tumor initially had an extirpation of the presenting nodule followed by an excision of the tumor site with two-centimeter margins and subsequent radiotherapy [25]. Both patients had no evidence of recurrent or metastatic PEComa at 10 [16] and 24 [25] months, respectively.

One patient has a sentinel lymph node biopsy because the initial diagnosis of her tumor was malignant melanoma. She was a 53-year-old woman who presented with a one-centimeter nodule on her buttock of one-year duration. After an incomplete excision of the tumor, a wide local excision of the residual tumor and biopsy of the draining sentinel lymph node was performed. There has been no evidence of recurrent or metastatic tumor during 37 months of follow-up [10].

Prognosis
Follow-up after the diagnosis of a benign primary cutaneous PEComa was described in 30 patients (**Table 14**), [7-31]; the duration of follow up ranged from one to 171 months (median, 26 months). Eighty seven percent (26 of 30) of the patients were observed for up to six years without recurrence or metastases. Four of the patients were followed more than eight years (from 108 to 171 months) with no evidence or recurrent or metastatic tumor [8,10,12,13].

The seven patients who had an incomplete excision of their benign primary cutaneous PEComa also had an excellent prognosis. Information was not provided for two of the individuals [10]. The five patients with recorded follow-up had no evidence of

Table 14. *Tumor-free follow-up of patients with benign primary cutaneous perivascular epithelioid cell tumor (PEComas).*

Follow-up (months)	Number of patients	Percent of patients
1-12	10	33.4%
13-24	5	16.7%
25-36	5	16.7%
37-48	3	10.0%
49-60	0	0.0%
61-72	3	10.0%
73-84	0	0.0%
85-96	0	0.0%
97-108	2	6.7%
109-120	0	0.0%
121-132	1	3.3%
133-144	0	0.0%
145-156	0	0.0%
157-168	0	0.0%
169-180	1	3.3%
Total	30	100%

PEComa, perivascular epithelioid cell tumor; %, percent.

local recurrence or metastases during a subsequent period ranging from six to 108 months (median, 30 months), [10,13,15,17].

Treatment of the five patients with primary malignant cutaneous PEComa was only provided for four—including the man in this report—of the individuals [16,25,29]; subsequent follow-up—including the reported patient—was only available for three of these patients [16,25]. There was neither recurrence nor metastases in the three patients during a follow-up period ranging from four to 24 months (median, ten months). After the fourth patient's scalp lesion had been diagnosed as a malignant PEComa, the investigators suggested—but could not confirm—that the metastatic melanoma of unknown primary that presented five years earlier in his cervical lymph node may have been a metastasis from the recently diagnosed scalp tumor which had been present as an asymptomatic nodule for several years prior to the detection of the lymph node tumor [29].

The prognosis for patients with metastatic cutaneous PEComa was not favorable [21,28]. The 62-year-old woman with primary malignant PEComa of her uterus initially developed metastases to her neck and lung; subsequently, she presented with an

additional skin metastasis to her cheek and shortly thereafter with malignant PEComa that had spread to her brain and stomach [21]. The 67-year-old man who presented with bilateral malignant PEComa of his adrenal glands with metastases to his lung and soft tissue developed a skin metastasis to his forehead 21 months later. Additional information on his follow-up was not provided [28].

Fibroma-like PEComa
Fibroma-like PEComa is a recently characterized subset of systemic (soft tissue) and cutaneous primary PEComa [7,8,48]. To date, this rare variant has only been described in five patients each of whom has tuberous sclerosis. The first report, including three individuals, was presented by Larque et al. in 2018 [8]; a fourth patient was described by Harvey et al. in 2019 [34] and the fifth patient was published with a review of the earlier patients by Odono et al. in 2020 [7].

Two of the patients had soft tissue fibroma-like PEComa. The first was a 25-year-old woman with 2.8-centimeter PEComa on her chest wall that presented as an incidental finding—as a mildly hyperdense soft tissue mass—on the chest computerized tomographic scan performed as a routine follow-up of her lung nodules [8]. The second was a 44-year-old man with an infrapatellar 6.5-centimeter soft tissue mass on his right knee of ten years' duration that had progressively enlarged and became painful [48]. Both patients' PEComa was excised [8,48]. There was no evidence of recurrence or metastases during 24 months of follow-up for the woman [8].

Three women had primary cutaneous fibroma-like PEComa; at diagnosis, their ages were 20 months, four years, and 51 years [7,8]. The 20-month-old girl had a painless progressively enlarging 1.3-centimeter nodule of seven months' duration near the midline of the left side of her upper lip. It was excised and there was neither recurrence nor metastasis at one month follow-up [7]. The four-year-old girl had a painless progressively enlarging 5.9-centimeter nodule of 24 months' duration on her wrist. It was excised and there has been no evidence of recurrence or metastasis after six months of follow-up [8]. The 51-year-old woman has a painless progressively enlarging five-centimeter nodule of

less than 12 months' duration on her foot; it was excised and there has been neither recurrence nor metastasis during 131 months of follow-up [8].

Malignant cutaneous PEComa
The criteria for malignancy classification of PEComa—developed based upon the features of systemic PEComa—have been used to evaluate cutaneous PEComas [3,34]. Subsequently, including the man in this report, malignant—either primary or metastatic—cutaneous PEComa have been described [16,21,25,28,29,31]. The tumors include five primary cutaneous malignant PEComa (**Table 15**), [16,25,29,31] and two metastatic cutaneous PEComa (**Table 16**), [21,28].

Primary cutaneous malignant PEComa
Primary cutaneous malignant PEComa are rare. They were observed in five of 63 (eight percent) of the patients with primary cutaneous PEComa (**Table 15**), [16,25,29,31]. In addition, if the number of malignant PEComa is less than 100 [36], the incidence of primary cutaneous malignant PEComa is about six percent of malignant PEComa.

The patients with primary cutaneous malignant PEComa included three men and one woman (42-years of age). The gender was not provided for the fifth patient. The men ranged in age from 43 years to 76 years (median, 44 years).

The tumors were located on the cheek, forearm, scalp, or shoulder. They had been present for two months to years (median, 21 months). All the lesions had increased in size during the prior eight weeks to one year (median, six months); other symptoms included either pain or bleeding, each in one patient.

The tumors ranged in size from one centimeter to 3.5 centimeters (median, 1.3 centimeters). The clinical impression was either a cyst, a pilar cyst, or a squamous cell carcinoma (keratoacanthoma-type). All the tumors had both a high mitotic rate and high nuclear atypia and/or cellularity.

Management of the primary cutaneous malignant PEComa included surgical removal of the tumor; in addition, adjuvant radiotherapy was performed for two of the patients. It is assumed, but not stated, that the scalp tumor of the 76-year-old man was

Table 15. *Characteristics of patients with primary malignant cutaneous perivascular epithelioid cell tumor (PEComas).*

C[a]	A R G	Skin site	Les dur	Symptoms	Size (cm)	Clin dx	Malig criteria	Treatment	Follow-up (POT)	Ref
1	42 Ca W	Right shoulder	36	Inc size x 8 months pain	3.5	NS	HMR HNA	Excision XRT	NED (10)	[16]
2	43 Ca M	Left forearm	5	Bleeding Inc size x three months	1.0	SCC	HMR HNA	Excision	NED (6)	CR
3	44 NS M	Left cheek	2	Inc size x 8 weeks	1.0	Cyst	HMR HNA	Excision XRT	NED (24)	[25]
4[b]	76 Ca M	Occipital scalp	yrs	Inc size x one year	1.6	Pilar cyst	HMR HNA	Excision	NED (NS)	[29]

A, age (years); C, case; Clin dx, clinical (prior to biopsy) diagnosis; cm, centimeters; CR, current report; G, gender; HMR, high mitotic rate (greater than 1/50 high power fields); HNA, high nuclear atypia and/or cellularity; Inc, increased; Les dur, lesion duration (either months--indicated by number--or yrs); M, man; Malig crit, malignancy criteria; NED, no evidence of disease (recurrence or metastasis); NS, not stated; PEComa, perivascular epithelioid cell tumor; POT, period of time (months); R, race; Ref, reference; SCC, squamous cell carcinoma; Txment, treatment; W, woman; x, for; XRT, adjuvant radiotherapy; yrs, years.

[a] Case 5 has no specific details provided by the investigators. Comprehensive genomic profiling of malignant PEComa specimens from 31 patients was performed. The specimen site for one of the patients was the skin [31].

[b] The man had a history--five years prior to his evaluation of the scalp nodule that had been present for years--of metastatic melanoma with unknown primary diagnosed after the excision of an enlarged cervical lymph node; the tumor cells were HMB-45 positive, S100 negative and pan-keratin negative. There was no melanoma metastases or recurrence; slides of the tissue specimen were not available for review. One year prior to excision, the painless scalp nodule rapidly enlarged; evaluation of the excised scalp tumor specimen established a diagnosis of malignant PEComa. The investigators hypothesized, but were not able to confirm, that the 'intranodal melanoma' of unknown primary origin was probably a metastatic PEComa from the primary scalp PEComa since the cervical lymph node corresponded to the lymphatic drainage from the scalp and there are no cases of primary PEComa arising in a lymph node.

completely excised during its resection. Additional evaluation—all negative for metastatic disease—included magnetic resonance imaging of the head and computed tomography scans of the chest, abdomen, and pelvis [29].

The tumor on the cheek of the 44-year-old man was initially extirpated. Once the diagnosis of malignant PEComa was established, he was evaluated by a multidisciplinary head and neck oncology team. Computed tomography and positron emission tomography-computed tomography scans of the thorax were both negative for metastasis. Subsequently, the site was re-excised with a two-centimeter margin and postoperative radiotherapy was given [25].

The patient presented in this report had an excision biopsy which narrowly removed the entire left forearm tumor. He was referred to a medical oncologist for systemic evaluation and a surgeon for excision of the tumor site once the diagnosis of primary cutaneous malignant PEComa was established. His computed tomography and positron emission tomography-computed tomography scans of the thorax, abdomen, and pelvis were all negative for metastasis. Genomic analysis of his serum and the tumor revealed a germline mutation and four actionable aberrations, respectively.

The 42-year-old woman initially had a punch biopsy of her shoulder tumor. After the diagnosis of malignant PEComas was determined, she had a systemic work-up which included computed tomography scans of her chest, thorax, and abdomen (which were deemed negative for any definitive metastatic disease). She was then referred to a surgical oncologist for a radical excision with a two-centimeter margin. She was also evaluated by the institution's surgical oncology tumor board that decided she should receive six weeks of adjuvant radiation therapy (consisting of 60 Gray, in 30

Table 16. *Characteristics of patients with metastatic malignant cutaneous perivascular epithelioid cell tumor (PEComas)*.

C	AG	PS	MS	SS	Comments	Ref
1	62 W	Uterus	Brain, lung, skin, stomach	Neck cheek	The specimen from a hysterectomy, for abnormal uterine bleeding, three years prior was diagnosed as a uterine leiomyosarcoma; she received adjuvant radiotherapy. At the two-year follow-up, excision of a posterior neck mass was diagnosed at malignant melanoma; a lung biopsy was diagnosed as metastatic melanoma. One-year prior, a new right cheek pigmented lesion was diagnosed as melanoma. Subsequently, after a retrospective review, the diagnosis for all the tissue specimens was PEComa. Recently, additional metastatic PEComa to the stomach (gastric lymphovascular invasion) and brain were documented.	[21]
2	67 M	Right adrenal gland	Both adrenal glands, lung, skin, soft tissue	Forehead	Right forehead three-millimeter subcutaneous papule of three months duration. Two years prior, diagnosis of metastatic right adrenal gland PEComa and he was treated with sirolimus; therapy stopped because of constitutional symptoms within a few weeks. Biopsy of scalp lesion confirmed diagnosis of PEComa; treatment and follow-up not provided.	[28]

A, age (years); C, case; G, gender; M, man; MS, metastatic site; PEComa, cutaneous perivascular epithelioid cell tumor; PS, primary site; Ref, reference; SS, skin site; W, woman.
*The malignant cutaneous PEComa is metastatic from a visceral internal organ.

fractions, to the postoperative bed and a one Gray boost, in five fractions, with computed tomography simulation), [16].

Follow-up was conducted for all the patients; there was no evidence of recurrence or metastasis. The duration of follow-up ranged from six months to 24 months (median, ten months). The man with the scalp tumor previously had a diagnosis of metastatic melanoma of unknown primary that presented in his cervical lymph node. Although the pathology slides from the lymph node tumor could not be obtained for review, the investigators postulated that the lymph node tumor was a metastasis from his primary cutaneous malignant scalp PEComa [29].

Metastatic cutaneous malignant PEComa
Two of the 65 patients (three percent) with cutaneous PEComa had tumors that metastasized from a systemic PEComa to their skin (**Table 16**), [21,28]. The primary tumor site for the metastatic malignant cutaneous PEComa was the uterus in a 62-year-old woman and the adrenal glands in a 67-year-old man. The malignant uterine PEComa not only spread to the skin (of her neck and subsequently cheek), but also to her brain, lung, and stomach. The

malignant adrenal gland PEComa not only spread to the man's forehead skin, but also the other adrenal gland, lung, and soft tissue.

PEComa genomics
Next generation sequencing
Next generation sequencing is a method that can be used to sequence genes and thereby determine if genomic alterations are present. In cancer patients, next generation sequencing can be performed using either tumor tissue specimens or liquid biopsies (most commonly derived from blood) from which circulating cell-free DNA is assessed. Genomic profiling, classified by targetable genetic aberrations, can be used in the precision medicine management of a specific individual's cancer [59-65].

PEComa genomic landscape
Next generation sequencing has been performed in some of the patients with benign or malignant PEComa [5,31,43,66]. A study of the genomic landscape (405 genes) of advanced/metastatic malignant PEComa (N=31 patients) was recently conducted. The results were reported in aggregate; however, one of the patients had a primary malignant cutaneous PEComa [31]. Overall, 100

genomic aberrations were discerned in the 31 patients, with a mean of 3.2 alterations/patient. The most common molecular alterations were as follows: *TSC2* gene, 32.3% of cases; *TSC1*, 9.6%; TFE3 fusions, 16.1%; and folliculin (*FLCN*), 6.4%. Seventy percent of *TSC2*-aberrant cases and all *TSC1* mutant cases had biallelic inactivation of the locus (**Table 17**), [31].

Actionable genomic alterations
Some of these alterations are actionable. For instance, *TSC1* and *TSC2* alterations both activate the mTor pathway. The AMPECT trial assessed nab-sirolimus (nano-particle albumin-bound sirolimus, an mTOR inhibitor) and demonstrated a response rate of 39% (95% confidence interval: 22–58%), resulting in FDA approval on November 23, 2021. In a subset analysis of patients with *TSC2* mutations, the independently reviewed response rate was an impressive 89% (95% confidence interval: 57–99%), [66]. However, not all patients respond [67].

Primary malignant cutaneous PEComa genomic aberrations
The man presented in this report with a primary malignant cutaneous PEComa had next generation sequencing not only of his blood, but also the tumor

Table 17. *Molecular alterations association with perivascular epithelioid cell tumor (PEComas)*[*].

Altered gene	Percent of PEComa patients with altered gene	Pathway activated	Drugs with impact on target
TSC2	32.3%	mTor	Sirolimus (rapamycin) Everolimus Temsirolimus
TSC1	9.6%	mTor	Sirolimus (rapamycin) Everolimus Temsirolimus
TFE3 fusions	16.1%	Unclear	None known
FLCN	6.4%	Unclear	None known

FLCN, folliculin; PEComa, perivascular epithelioid cell tumor; TFE3, transcription factor binding to immunoglobulin heavy contrast Mu (IGHM) enhancer 3; TSC, tuberous sclerosis complex; %, percent
[*]Most PEComas analyzed for molecular alterations using next generation sequencing were malignant and were not cutaneous [31].

specimen. The analysis of both his blood and his tumor demonstrated a somatic aberration of *FANCC,* a gene involved in Fanconi anemia when germline; the protein product of this gene is implicated in DNA damage repair. In addition to the aberration of *FANCC* R185*, his tumor tissue also harbored three other deleterious gene alterations: *BIRC3* splice site 1622-27_1631del37 (a gene whose protein product inhibits apoptosis by binding to tumor necrosis factor receptor-associated factors), *TP53* R248W (*TP53* being a tumor suppressor gene commonly mutated in cancer), and *TSC1* T4151 (a gene associated with tuberous sclerosis when aberrant in the germline (our patient had no cutaneous features or systemic manifestations of tuberous sclerosis); *TSC1* alterations activate the mTor pathway.

Conclusion
Perivascular epithelioid cell tumor, a rare tumor—with benign and malignant variants—that expresses both melanocytic and smooth muscle markers, most commonly originates from visceral organs and soft tissue. Alterations in the tuberous sclerosis gene complex or *TFE3* gene alterations have been demonstrated in some patients with systemic PEComa. Cutaneous PEComa, including the man in this report, has been described in 65 individuals: 41 women, 22 men and two whose gender were not described. Hence, in contrast to systemic PEComa that has a woman-to-man ratio ranging from 4:1 to 7:1, cutaneous PEComa has a woman-to-man ratio of 2:1. Primary cutaneous PEComa was either benign (58 patients) or malignant (five patients); metastatic malignant cutaneous PEComa occurred in two patients. The patient's age at diagnosis of cutaneous PEComa ranged from 1.7 to 81 years (median, 47 years); indeed, 30% of the patients were between 40 to 49 years old. The cutaneous PEComa, in 74% of patients, was most commonly located on an extremity; the lower extremity was the tumor site in 63% of individuals. Most tumors (96%) were smaller than 5.0 centimeters, and 75% of cutaneous PEComas were less than 2.0 centimeters. Cutaneous PEComa typically appeared as an asymptomatic, painless, slowly growing, flesh-to-brown-to-red nodule. Prior to microscopic examination, the most

suspected clinical diagnoses were either a cyst or a dermatofibroma. Similar to systemic PEComas, cutaneous PEComas were composed of an admixture of tumor cells (that were either epithelioid or spindle or both) and blood vessels. The pathologic differential diagnosis included not only melanocytic and smooth muscle tumors, but also epithelioid cell neoplasms with clear or granular cytoplasm. Immunohistochemical studies were essential in establishing the diagnosis cutaneous PEComa, which express both melanocytic and smooth muscle markers. MiTF (100%), HMB45 (94%) and NKIC3 (94%) were the most reliable melanocytic markers; smooth muscle actin (43%) and desmin (40%) were the most reliable smooth muscle markers. Positive staining was also demonstrated by all tested cutaneous PEComas for CD10, BCL1, E-cadhedrin, and cathepsin. Tumors also stained positive almost always for 4EPB1 and frequently for CD68. Cutaneous PEComas never expressed cytokeratin and only showed patchy faint positive staining for TFE3 in one patient who had tuberous sclerosis (with a proven TSC2 alteration) and a fibroma-like cutaneous PEComa.

In contrast to patients with systemic PEComas, very few cutaneous PEComas have undergone next generation sequencing. Both tuberous sclerosis (due to germline *TSC* mutations) and somatic *TSC* mutations have been demonstrated in individuals who had the rarely observed fibroma-like cutaneous PEComa subtype. The cutaneous PEComa in this report harbored a *TSC1* T4151 somatic mutation. Additional pathogenic genomic aberrations included: *BIRC3* splice site 1622-27_1631del37, FANCC R185*, and *TP53* R248W. Primary malignant cutaneous PEComa are rare; all the tumors were 3.5 centimeters or smaller and the criteria for the classification of these neoplasms as a malignant skin PEComa were based on the high-risk pathology features observed in tumors from patients with malignant systemic PEComas. All the primary malignant cutaneous PEComas progressively increased in size. In addition, other symptoms— either bleeding or pain—were noted in two of these patients' tumors. Metastatic malignant cutaneous

PEComa has been described as originating in the uterus of a woman with additional metastases to her brain, lung, and stomach and in the adrenal gland of a man with additional metastases to his lung, soft tissue, and both adrenal glands. Surgical management, attempting to achieve complete removal of the tumor, was the treatment of choice for cutaneous PEComa. Indeed, to date, there has been no reported recurrence of a primary cutaneous PEComa after complete or partial excision of a benign tumor or completely removing a malignant tumor. Although there is a dearth of sequencing data on cutaneous PEComas, locally advanced and metastatic malignant PEComas that have undergone next generation sequencing show abnormalities in the *TSC1* and *TSC2* genes and in the *FLCN* gene, as well as fusions in the *TFE3* gene. Since *TSC1* and *TSC2* gene alterations activate the mTor pathway, suppressors of this pathway can be used to target these anomalies and, in November 2021, the FDA approved the mTor inhibitor nab-sirolimus for PEComa treatment.

Subsequent to the acceptance of our manuscript, we became aware of the paper by Wong et al. in which two patients with PEComa are described: a 77-year-old woman with a 0.6cm smooth pink nodule on her upper right back (which demonstrated sheets of large, epithelioid cells with vacuolated cytoplasm in a perivascular distribution with unusual hypercellularity in the superficial dermis and an immunophenotype of HMB45+, MiTF+, S100-, SOX10-, and p40-) and a 60-year-old woman with an enlarging, tender, indurated violaceous smooth 3cm nodule on the right lateral lower leg (which demonstrated sheets of epithelial cells with large, clear and some granular cytoplasm from the superficial-to-mid-to-deep dermis with areas of spindled cells intermingled and immmphenotype of HMB45+, CD10+, NKIC3+, vimentin+, CD68+, melan A-, SMA-, destine-, SOX10-, pancytokeratin AE1/3-, RCC antigen-, CK7-, and S100 (weakly immunoreactive); periodic acid-Schiff with diastase was negative and Ki67 proliferation index was less than 5% of tumor cells [70].

Potential conflicts of interest

Dr. Cohen is a consultant for ParaPRO. Dr. Kurzrock receives research funding from Genentech, Merck Serono, Pfizer, Boehringer Ingelheim, TopAlliance, Takeda, Incyte, Debiopharm, Medimmune, Sequenom, Foundation Medicine, Konica Minolta, Grifols, Omniseq, and Guardant, as well as consultant and/or speaker fees and/or advisory board for X-Biotech, Neomed, Pfizer, Actuate Therapeutics, and Roche, has an equity interest in IDbyDNA and CureMatch Inc, serves on the Board of CureMatch and CureMetrix, and is a co-founder of CureMatch.

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Table 2. *Characteristics of cutaneous perivascular epithelioid cell tumor (PEComas) in women.*

C	A	Site	Size (cm)	Pathology	Cl	Treatment	F-up (mo)	Ref
1	1.7[a]	UpperLip	1.3	Sp	Be	Ex	NR,1	[7]
2	4[a]	Wrist	5.9	Sp	Be	Ex	NR,6	[8] C1
3	15	Thigh	NS	Epi,NP	Be	ExB,Ex	NR,12	[9] C1
4	15	Buttock	1.2	Epi,MG	Be	IEx,Ex	NR,36	[10] C5
5	23	Thigh	2.0	Sp	Be	NS	NS	[11] C17
6	26	Leg	NS	Epi	Be	Ex	NS	[12] C7
7	30	LowerLeg	3.0	CCMMT	Be	ExB,Ex	NR,12	[13] C5[b]
8	32	Cheek	2.0	MES,M	Be	Ex	NR,48	[14]
9	32	Leg	1.0	ECC/ES	Be	NS	NS	[11] C9
10	32	Back	NS	Epi	Be	Ex	NR,24	[12] C5
11	34	Shin	2.0	MES	Be	IEx	NS	[10] C2
12	35	Thigh	4.0	Epi	Be	IEx	NR,6	[15] C5
13	37	Arm	0.5	Epi	Be	MEx	NS	[12] C4
14	38	Thigh	NS	MES,NP	Be	ExB,Ex	NS	[9] C2
15	41	LowerLeg	0.5	CCMMT	Be	ExB,Ex	NR,24	[13] C1[b]
16	41	LowerLeg	0.7	CCMMT	Be	IEx	NR,108	[13] C3[b]
17	42	LowerLeg	0.8	CCMMT	Be	IEx	NR,30	[13] C2[b]
18	42	Shoulder	3.5	MES,M,NP	Ma	Bx,IEx,Ex,XRT	NR,10	[16]
19	42	Leg	0.6	CCMMT	Be	NS	NS	[11] C14
20	43	Thigh	0.6	Epi	Be	Bx,Ex	NR,16	[15] C2
21	46	Leg	0.4	ECC/ES	Be	NS	NS	[11] C1
22	47	LowerLeg	NS	Epi	Be	Ex	NR,27	[12] C8
23	48	LowerLeg	1.0	CCMMT,M	Be	ExB,Ex	NR,7	[13] C7[b]
24	48	LowerLeg	1.2	Epi	Be	IEx	NR,12	[17]
25	49	Leg	2.0	Epi	Be	IEx,Ex	NS	[10] C10
26	50	Back	2.0	Epi	Be	MEx	NR,61	[10] C3
27	51[a]	Foot	5.0	Sp	Be	Ex	NR,131	[8] C3
28	52	Lo Spine	1.5	MES	Be	MEx	NE,3	[10] C9
29	53	Buttock	1.0	Epi,MG,RC	Be	IEx,Ex,SLNB	NR,37	[10] C4
30	55	Arm	1.0	Epi	Be	Ex	NR,24	[18]
31	59	Thigh	0.3	Epi,MG	Be	ExB	NS	[15] C3
32	60	Thigh	1.5	CCST	Be	ExB,Ex	-Meta	[19]
33	60	Thigh	1.5	MES	Be	IEx,Ex	NR,36	[10] C6
34	62	Calf	3.0	Epi,MG	Be	Bx,Ex	NS	[20] C1
35	62	Pop Fossa	2.0	CCMMT,NP	Be	ExB,Ex	NS	[13] C4[b]
36[c]	62	Cheek/Nk	NS	Epi	Ma	Ex	Br,Gl	[21]
37	66	Forearm	0.5	CCMMT	Be	MEx	NR,10	[13] C6[b]
38	67	Thigh	1.2	Epi	Be	IEx,Ex	NR,31	[15] C1
39	67	Thigh	NS	Epi	Be	Ex	NR,72	[12] C2
40	67	Wrist	1.0	Epi	Be	Ex	NS	[22]
41	81	Calf	1.5	MES	Be	IEx,Ex	NS	[10] C7

A, age at diagnosis (years); Be, benign; Bx, biopsy; C, case; cm, centimeters; CCMMT, clear cell myomelanocytic tumor; Cl, classification; ECC/ES, mixed epithelioid and clear cell or mixed epithelioid and spindle cell; Epi, epithelioid cell; Ex, excision (with tumor-free margins); ExB, excisional biopsy (with tumor-free margins); F-up, follow-up; IEx, incomplete excision (with positive margins for tumor); Lo, lower; M, mitoses (greater than one per 50 high power fields) present; Ma, malignant; MES, mixed epithelioid cell and spindle cell; MEx, marginal excision (with narrow tumor-free margins); Meta, metastases; MG, multinucleated giant tumor cells; mo, months; Nk, neck; NP, nuclear pleomorphism; NR, no recurrence or metastases; NS, not state; PEComa, perivascular epithelioid cell tumor; Pop, popliteal; RC, rhabdoid cytoplasmic inclusions; Ref, references; SLNB, sentinel lymph node biopsy; Sp, spindle cell; XRT, radiotherapy; -, no

[a]The three female patients have tuberous sclerosus and fibroma-like PEComa [7,8].
[b]Seven of the patients reported by Llamas-Velasco et al. [11], were previously reported by Mentzel et al. [13].
[c]She presented with a malignant uterine PEComa which metastasized to the skin of her neck and her lung two years later; she subsequently developed a cutaneous metastasis to her cheek and shortly thereafter additional visceral metastases to her brain and stomach.