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ABSTRACT

Cutaneous *P*erivascular *E*pithelioid *C*ell tumors (PEComas) are a family of mesenchymal tumors with shared microscopic and immunohistochemical properties: they exhibit BOTH smooth muscle cell and melanocytic differentiation. Non-neoplastic counterpart of *PEComa cells* are unknown, as well as the relationship between extracutaneous PEComas and primary cutaneous PEComas. We will review the clinical setting, histopathologic features, chromosomal abnormalities, differential diagnosis and treatment options for cutaneous PEComas.

KEY WORDS: PEComa, skin, cutaneous Perivascular Epithelioid Cell tumors, clear cell myomelanocytic tumor.

CORE TIP

We provide a comprehensive review of a rare neoplasm, cutaneous PEComa.

**Audio Core Tip**

Cutaneous *P*erivascular *E*pithelioid *C*ell tumors (PEComas) are a family of mesenchymal tumors with shared microscopic and immunohistochemical properties: they exhibit BOTH smooth muscle cell and melanocytic differentiation. Non-neoplastic counterpart of *PEComa cells* are unknown, as well as the relationship between extracutaneous PEComas and primary cutaneous PEComas. We will review the clinical setting, histopathologic features, chromosomal abnormalities, differential diagnosis and treatment options for cutaneous PEComas.

COVER LETTER

We have reviewed current literature about cutaneous PEComas, and our group has published several series and case reports on this ~~u~~infrequent neoplasms. This neoplasms should be known by dermatopathologists. We have added a clinical picture as proposed for the reviewers. We have also added an additional reference, because a relevant article appeared after we have finished writting this manuscript.

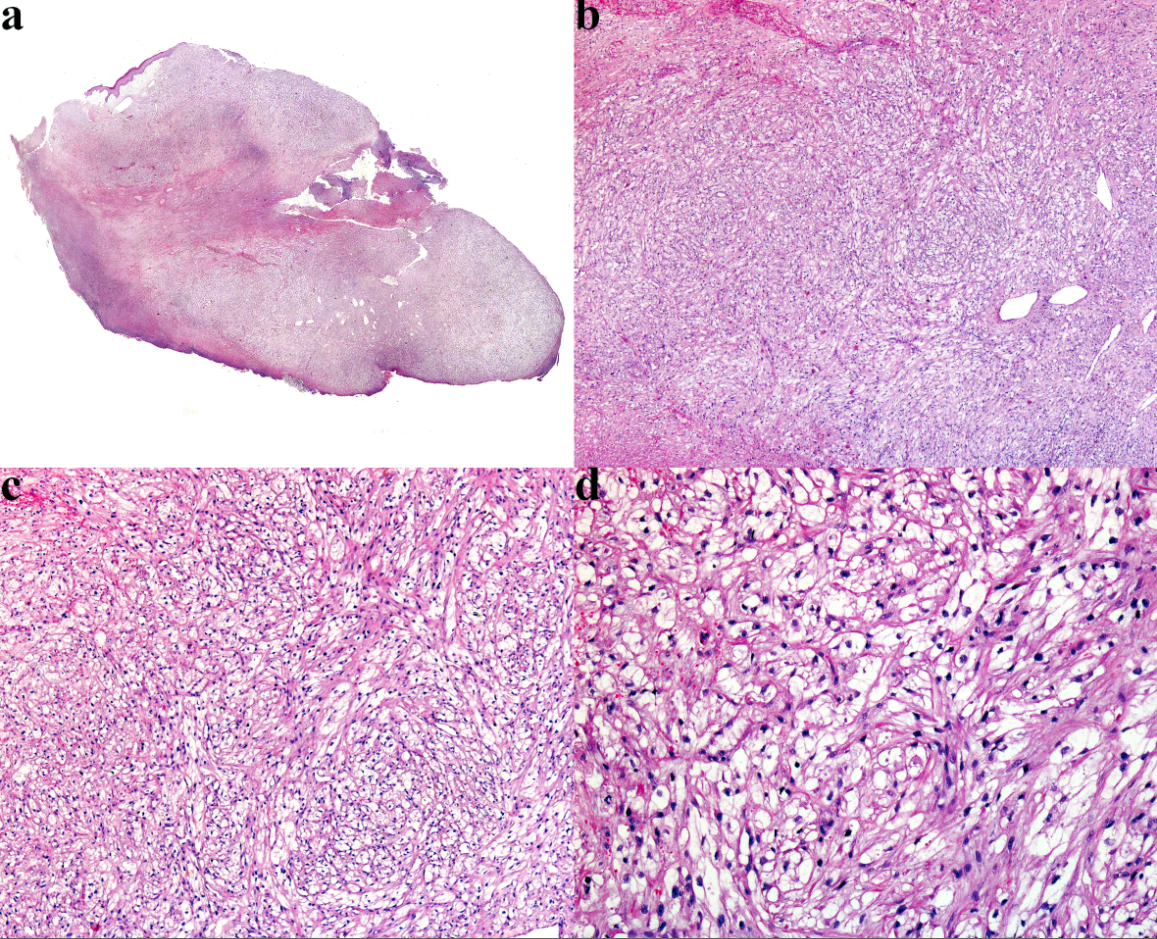
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**FIGURE 1**



**Figure 1.** Pinky plaque with well-defined edges and a centrally located crust.

**FIGURE 2**



**Figure 2:** 2a) Low power image of cutaneous PEComa. 2b) Medium power image showing the lobular arrangement of a neoplasm composed by clear cells. 2c) Perivascular arrangement of neoplastic cells may be easily observed. 2d) Detail of the cells with an ovoid homogeneous nuclei and a clear cytoplasm.

**INTRODUCTION**

Cutaneous *P*erivascular *E*pithelioid *C*ell tumors (PEComas) are a family of mesenchymal tumors with shared microscopic and immunohistochemical properties (they exhibit BOTH smooth muscle cell and melanocytic differentiation). [1]

This term, *PEComa*, introduced by Zamboni *and colleagues* [2], includes a group of tumors with distinctive perivascular epithelioid cells such as *angyomiolipomas*, *lymphangiomyomatosis*, *clear cell sugar tumor of the lung* and the so-called *PEComa*, that have been described in various organs and tissues, including the skin. [3-12] In any case, PEComas are exceedingly rare; . Moreover, tumors fitting the definition of PEComa have been reported under different names, including “*clear cell myomelanocytic tumor*”, “*abdominopelvic sarcoma of perivascular epithelioid cells*” and “*primary extrapulmonary sugar tumor*”. [13] PEComas

First “legitimate” *cutaneous PEComa* was reported by Crowson *and colleagues* as an abstract. After that, several other reports appeared, as well as the first series of *cutaneous PEComas*. [9]

The most characteristic histopathologic ~~more defining~~ feature of these neoplasms is that they are composed of ~~are made up of~~ epithelioid cells with a clear or granular cytoplasm that tend to be arranged in perivascular fashion~~ly~~. [1]

Normal counterpart of PEComa cell ~~are~~ is unknown, but there are several hypotheses including: (1) a differentiation line close to undifferentiated cells of the neural crest, (2) a myoblastic origin along with a molecular alteration that led to a melanogenesis activation or, (3) as a third option, a pericytic cell~~s’~~ origin. Furthermore, the relationship between *extracutaneous PEComas* and *primary cutaneous PEComas* remains ~~is~~ uncertain. [23]

**CLINICAL FEATURES**

PEComas, as stated previously, are rare tumors, preferably located in subcutaneous soft tissues in the female genital tract or in the thorax (Figure 1). *Cutaneous PEComas* account for just 8% of cases, located mostly on the lower leg and, less commonly, on the forearm or the back. They usually behave in a benign fashion [8], although malignant examples have also been reported. [7] They typically appear in middle-aged adult females. [24] In our review of literature, we have found described 34 “legitimate” *primary cutaneous PEComas*. [23] Some of these neoplasms may be associated with *tuberous sclerosis complex* [4] but cutaneous lesions are mostly solitary lesions with no other associated anomalies~~pathologies~~. [24]

**HISTOPATHOLOGIC CHARACTERISTICS**

Cutaneous PEComas present usually as a well-demarcated dermal lesion that can extends to subcutis, composed of ~~nested or trabeculary-arranged~~ epithelioid cells with a large, clear or slightly granular cytoplasm and a centrally located nuclei arranged in nested or trabecular pattern (Fig 1). [13] These cells are usually arranged around the vessels, which in cutaneous PEComas are present as a rich network ~~capillaries~~ that may ~~can~~ range from thin capillaries to hyalinized arterioles. [7] Up to 15% of the PEComas present cords of neoplastic cells in a desmoplastic stroma. [25] PEComa cells can also become vacuolated. There have been descriptions of PEComas with presence of multinucleated giant cells and with some degree of nuclear pleomorphism, which have been named as *symplastic PEComas*. [4] Although *pure spindle cell* ~~pure~~ variants may be found, usually spindle cells are intermingled with the epithelioid cells and usually appear~~s~~ in the deeper areas ~~parts~~ of the neoplasm. Some PEComas may present with slightly pleomorphic multinucleated giant cells with few or no mitotic figures. The more characteristic feature of perivascular epithelioid cells in PEComas is their immunophenotype that exhibit both smooth muscle cell and melanocytic markers. PEComas express melanocytic markers such as HBM45 (Human melanoma black 45), that is the most sensitive, expressed in 100% of reported PEComas [8]; Melan A (72%); and MiTF in most cases (%???????). They also express smooth muscle markers such as desmin (typically in a greater degree in cutaneous PEComas when compared with their visceral counterparts [24]); and smooth muscle actin (SMA), that may be the most sensitive marker within this group [4]. ~~Caldesmon and calponin are usually negative. Thus, cutaneous PEComas may be positive with HMB45, melan-A, MITF-1, NKI/C3 and tyrosinase as well as with SMA, desmin, myosin and calponin~~. [26-28] It is important to underline that up to 30% of visceral PEComas stain positive with S100 protein. [4]

Pusiol and colleagues have recently published a case of a HMB-45 negative tumor that they have named PEComa. In ~~but in~~ our opinion, microphotographs accompanying this paper are of insuficient quality ~~are not enough to review the diagnosis~~ and ~~as~~ the authors only describe positivity for ~~reported positive~~ CD68 and NKI-C3 in neoplastic cells, with no information about immunohistochemical results for muscular markers, such as smooth muscle actin and desmin. Therefore, the diagnosis of PEComa for this case is doubtful. ~~cells without giving any information about smooth muscle actin but only on desmin positivity, we think that this peculiar staining pattern should be reproduced in later studies to assure its validity.~~ [29]

PEComas are ~~exclusively~~ characteristically negative for epithelial markers despite their morphologic epithelioid features. Both types of cells, epitheloid and fusiform ones, may express CD1a and cyclin D1.[30] Ultraestructural studies showed that PEComa cells contain a large cytoplasm with microfilament bundles showing electron-dense condensations, numerous mitochondria and membrane-bound dense granules that match premelanosomas. [12, 26, 27]

PEComas’ duality lets cells modulate their morphology and immunophenotype. Cases composed mainly of spindled cells usually show a strong expression of actin, but only focal expression of HMB45, whereas cases composed of clear cells usually show strong expression of HMB45 whereas actin is ~~are~~ negative or only focally positive.

Finally, only a few malignant cutaneous PEComas have been reported [7, 31]; one of them a scalp lesion that lately metastasized to a regional lymph node. [7]

Criteria for diagnosis of malignant PEComa have been proposed by Folpe and coworkers.~~but their visceral counterparts may be diagnosis attending Folpe´s criteria~~**[4]. See table 1.**

**Table 1: Malignant PEComa’s criteria ~~based on Folpe article~~[4].**

|  |  |
| --- | --- |
| ***Features*** | ***Definition*** |
| Tumor size greater than 5 cm.  Infiltrative growth pattern.  High nuclear grade.  Necrosis.  Mitotic activity > 1/50 high power field.  Aggressive clinical behavior. | ***Benign*** *(none criteria).*  ***Malignant*** *(2 or more features).*  ***Uncertain*** *malignant potential (1).* |

**CHROMOSOMAL ABNORMALITIES**

Recently, recurrent chromosomal alterations have been demonstrated in visceral PEComas. They are related to the genetic alterations of “*tuberous sclerosis complex*” (due to losses of TSC1 (9q34), TSC2 (16p13.3)), which seem to have a role in the regulation of the Rheb/mTOR/p70S6K pathway [12]. TSC1 is a tumor suppressor gene encoding for hamartin, which creates a complex with TSC2 protein (tuberin) thus with an important role in the mTORC1 pathway.

In the skin, chromosomal losses may be found [5], as well as alterations on chromosome 16 p (TSC2); this has been previously reported in angiomyolipomas [5] and also in visceral PEComas, but to date has not been found in the cutaneous lesions, thus lacking evidence of a link between *cutaneous PEComas* and *tuberous sclerosis complex*. [32] In visceral PEComas these alterations produce a constitutive activation of the mTORC1 pathway. [33] Some soft tissue PEComas in patients without tuberous sclerosis complex are immunohistochemically positive for TFE3, [34, 35] but these findings have not yet been detected in cutaneous PEComas, a feature that suggests that the histogenesis of cutaneous PEComas might be different from the visceral ones. [36]

Finally, a recent study of Charli-Joseph and *colleagues* using array-based comparative genomic hybridization and a complete immunohistochemical study in 8 cases of primary cutaneous PEComas did not find any chromosomal imbalances or initiating mutations~~in those cases~~. [23] After their ample immunohistochemical study they have proposed a panel including MITF, NKIC3, SMA, desmin, bcl-1, cathepsin K and 4EB-protein 1 (4EBP1) as the ideal immunohistochemical panel ~~one~~ for the evaluation of these neoplasms ~~evaluation~~. [23] The more interesting immunohistochemical marker within this panel is 4EBP1 as it is a downstream target in the mTOR pathway, [37] suggesting, WHEN POSITIVE, an activation of the pathway independently of the mutational status of TSC1/TSC2. [23]

**DIFFERENTIAL DIAGNOSIS**

*Clear cell myomelanocytic tumor* is now included within the PEComa group [9, 38], as the previously described as *clear cell dermatofibroma* [39] although it was considered a different neoplasm for a while. [10, 40]

Cutaneous PEComa should be differentiated from *xanthomatous lesions*, *granular cell tumors*,*myoepithelioma*, *cutaneous meningioma*,*epithelioid sarcoma*,*melanocytic neoplasms with balloon cell change*, *clear cell sarcoma*, *metastatic clear cell carcinomas* (particularly renal cell carcinoma), *dermal clear cell tumor* and from *gastrointestinal stromal tumor*.

*Xanthomas* may be a manifestation of hyperlipidemia; they are histopathologically characterized by a dermal collection of foamy histiocytes and thus they are positive for CD68, CD163 and, in some cases, for adipophilin. [41]

*Granular cell tumors cells* are characterized by a prominent cytoplasm replete with eosinophilic, PAS positive, diastase-resistant granules immunohistochemically characterized for the expression of S-100 protein, PGP9.5, NKIC3, CD68, nerve growth factor receptor 75 and SOX10, which ~~that~~ differs from the immunophenotype usually found in cutaneous PEComas, although both neoplasms share ~~are~~ MITF-1 positivity~~;~~ the rare *congenital granular cell tumors* show also  ~~their stroma is usually~~ richly vascularized stroma. [42, 43] In any case, to make the diagnosis even trickier, granular cell tumors may present clear-cell areas, usually as a focal finding, ~~in a focal way~~ but sometimes occupying most of the tumor [44].

*Myoepitheliomas* are composed of polygonal shaped cells positive for EMA, calponin, AE1/AE3, ~~and~~ smooth muscle actin and desmin, ~~but also positive for~~ and S100 protein; but negative for HMB-45, melan-A, tyrosinase and MITF. [45]

*Primary extracraneal meningioma* often presents islands of clear cells and the distinction from cutaneous PEComa is usually straightforward, ~~easy~~ but as this tumor is typically EMA positive, with a variable positivity for S-100 protein and HMB45 negative, immunohistochemistry may be a useful tool ~~help~~ in doubtful cases. [46, 47]

*Epithelioid sarcoma* is a malignant neoplasm ~~tumor~~ characterized by polygonal cells with an eosinophilic cytoplasm positive for high and low weight cytokeratins, EMA and vimentin; and negative for S-100 and HMB45. [48] Characteristically, the nuclei of neoplastic cells of epithelioid sarcoma show loss of expression on INI-1.

*Melanocytic neoplasms with balloon cells* usually present junctional ~~juntural~~ nests and express S100 protein along with other melanocytic markers. Balloon cells are usually a focal finding, although some tumors may appear ~~are~~ entirely composed of them. [49] Even when SMA may be positive in desmoplastic melanoma, [50, 51] the absence of S-100 protein staining and the positivity for SMA favor the diagnosis of PEComa. Recently, a case of pigmented PEComa with presence of focal melanin pigmentation and strong positivity for HMB-45 has been published and may represent a mimicker of melanoma. [52]

Neoplastic cells of *c~~C~~lear cell sarcoma* often show ~~has~~ an eosinophilic (rather than clear) cytoplasm and, in challenging cases, the detection of t (12;22)(q13;q12), with the resultant EWSR1-ATF1 fusion product, is diagnostic. Some peculiar cases of clear cell sarcoma-like tumor of the gastrointestinal tract presents EWSR1-CREB1 instead of the more commonly found EWSR1-ATF1, thus fluorescence in situ hybridization for EWSR1 gene rearrangement may be also useful. [33]

*Metastatic clear cell carcinomas* express cytokeratins and PEComa is negative for them.

*Clear cell dermal mesenchymal tumor* is usually located on the legs of adults, and histopathologically shows dermal sheets of oval to polygonal cells with abundant clear to slightly granular PAS-negative cytoplasm that is also positive for NKIC3, CD68 and vimentin, whereas melanocytic and muscular markers ~~stainings~~ are consistently negative. [53] Some authors consider that this tumor is possibly associated with PEComas, but ~~is~~ still remains considerated as a different entity based on the negativity for melanocytic markers. [54]Finally, Tomasini and colleagues published a peculiar neoplasm under the name of eruptive dermal clear cell desmoplastic mesenchymal tumor with perivascular myoid differentiation. This neoplasm showed~~, a neoplasm characterized by~~ multiple perivascular spindled to oval cells, intermingled with clear and granular cells as well as prominent desmoplasia, and a high degree of capillary vessels with hemangiopericytoma-like features; [55] this tumor was positive for h-caldesmon, smooth muscle actin, CD13, CD68 and NKI~~/~~C3. [55]

Visceral PEComas do not express CD34 or c-kit, which is in contrast with ~~contrary to~~ *GIST*.

Recently a case of *cutaneous metastasis from ~~of~~ an adrenal PEComa* has~~ve~~ been reported showing the same characteristics than a primary cutaneous PEComa, thus making necessary clinicopathologic correlation for a correct diagnosis as the patient presented with widespread metastatic disease. [56]

**TREATMENT**

As most PEComas are benign tumors, surgical removal is curative. [1] A recent review on PEComas located on head and neck suggests that they may be more aggressive, as one of the two malignant cutaneous PEComas and one ~~another~~ soft tissue malignant PEComa [57] were in this loca~~liza~~tion. Besides surgery, drugs inhibiting the activation of mTOR, such as rapamycin, may be useful. [58-62] As patients with tuberous sclerosis have abnormalities in the TSC2 gene and that activates mTOR leading tumorogenesis, this explain why treatment with rapamycin seems to be useful in the treatment of renal angiomyolipomas and skin lesions of ~~in~~ this syndrome, and may be also useful in a subset of PEComas with mTOR activation. Symplastic PEComas portend an unknown biological behaviour. [63]

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