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MINIREVIEWS

Cutaneous perivascular epithelioid cell tumors: A review on an infrequent neoplasm

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Abstract

"Perivascular epithelioid cutaneous" cell tumors (PEComa) 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's cells are unknown, as well as the relationship between extracutaneous PEComa and primary cutaneous ones. We will review the clinical setting, histopathologic features, chromosomal abnormalities, differential diagnosis and treatment options for cutaneous PEComa.

Key words: Perivascular epithelioid cell tumor; Skin; Cutaneous perivascular epithelioid cell tumors; Clear cell myomelanocytic tumor

Core tip: We provide a comprehensive review of a rare neoplasm, cutaneous perivascular epithelioid cell tumor.

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INTRODUCTION

"Perivascular epithelioid cutaneous" cell tumors (PEComa) are a family of mesenchymal tumors with shared microscopic and immunohistochemical properties (they exhibit both smooth muscle cell and melanocytic

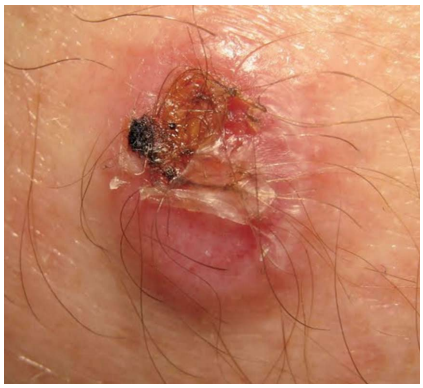

Figure 1 Pinky plaque with well-defined edges and a centrally located crust.

differentiation)[1].

This term, PEComa, introduced by Zamboni *et al*[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[3-13]. In any case, PEComa are exceedingly rare; have been described in the pancreas[2], pelvic cavity[14], uterus[15], prostate[16], urinary bladder[17], digestive tract[18], vulva[18], heart[18], trachea[19], lymph node[7], breast[20], bone[21] and soft tissues[22]. 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].

"PEComa"

First "legitimate" cutaneous PEComa was reported by Mentzel *et al*[9] as an abstract. After that, several other reports appeared, as well as the first series of cutaneous PEComa[9].

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

Normal counterpart of PEComa's cells 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 origin. Furthermore, the relationship between extracutaneous PEComa and primary cutaneous ones remains uncertain[23].

CLINICAL FEATURES

PEComa, as stated previously, are rare tumors, preferably located in subcutaneous soft tissues in the female genital tract or in the thorax (Figure 1). Cutaneous ones 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 PEComa[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[24].

HISTOPATHOLOGIC CHARACTERISTICS

Cutaneous PEComa presents usually as a well-demarcated dermal lesion that can extend to subcutis, composed of epithelioid cells with a large, clear or slightly granular cytoplasm and centrally located nuclei arranged in nested or trabecular pattern (Figure 2)[13]. These cells are usually arranged around the vessels, which in cutaneous PEComa are present as a rich network that may range from thin capillaries to hyalinized arterioles[7]. Up to 15% of PEComa present cords of neoplastic cells in a desmoplastic stroma[25]. PEComa's cells can also become vacuolated. There have been descriptions of PEComa with presence of multinucleated giant cells and with some degree of nuclear pleomorphism, which have been named as symplastic PEComa[4]. Although pure spindle cell variants may be found, usually spindle cells are intermingled with the epithelioid cells and usually appear in the deeper areas of the neoplasm. Some PEComa may present with slightly pleomorphic multinucleated giant cells with few or no mitotic figures. The more characteristic feature of perivascular epithelioid cells in PEComa is their immunophenotype, which exhibits both smooth muscle cell and melanocytic markers. PEComa express melanocytic markers such as: (1) HBM45 [human melanoma black 45, the most sensitive (expressed in 100% of reported PEComa[8])]; (2) Melan A (72%); and (3) MiTF in most cases. They also express smooth muscle markers such as desmin (typically in a greater degree in cutaneous PEComa when compared with their visceral counterparts[24]); and smooth muscle actin (SMA), that may be the most sensitive marker within this group[4,26-28]. It is important to underline that up to 30% of visceral PEComa stain positive with S100 protein[4].

Pusiol *et al*[29] have recently published a case of a HMB-45 negative tumor that they have named PEComa. In our opinion: (1) microphotographs accompanying this paper are of insufficient quality; and (2) the authors only describe positivity for CD68 and NKI-C3 in neoplastic cells, with no information about immunohistochemical results for muscular markers, such as SMA and desmin; therefore, the diagnosis of PEComa for this case is doubtful[29].

PEComa are characteristically negative for epithelial markers despite their morphologic epithelioid features. Both types of cells, epithelioid and fusiform ones, may express CD1a and cyclin D1[30]. Ultrastructural studies showed that PEComa's cells contain a large cytoplasm with microfilament bundles showing electron-dense con-

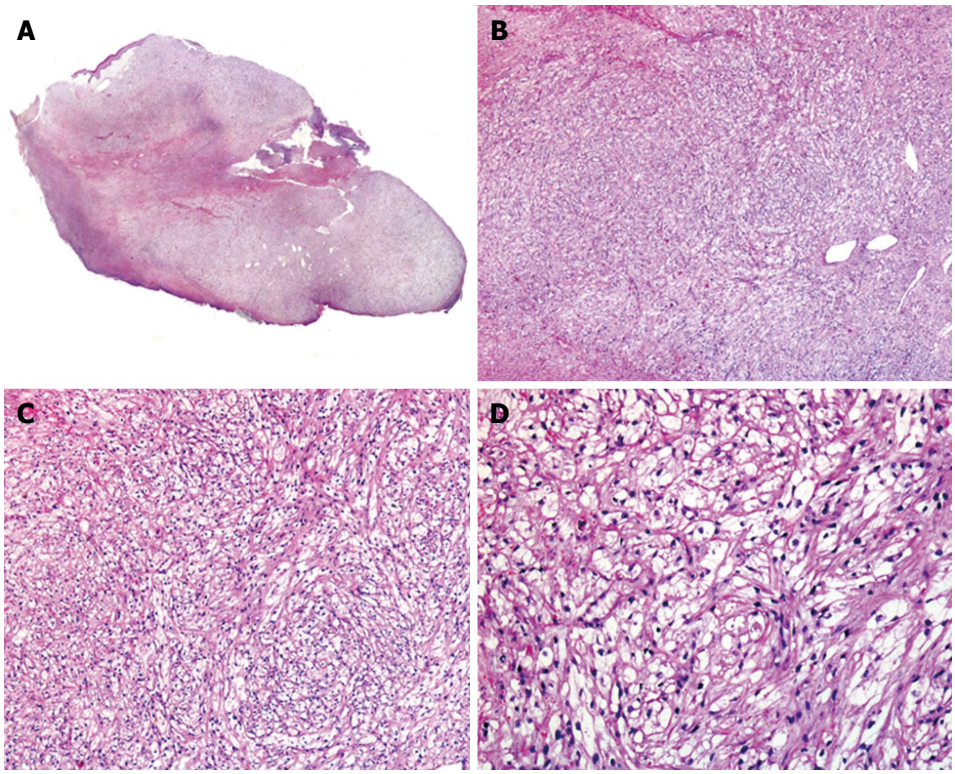

Figure 2 Histopathology of cutaneous perivascular epithelioid cell tumor. A: Low power image of cutaneous perivascular epithelioid cell tumor; B and C: Medium power image showing the lobular arrangement of a neoplasm composed by clear cells; D: Detail of the cells with an ovoid homogeneous nuclei and a clear cytoplasm.

Table 1 Malignant perivascular epithelioid cell tumor's criteria[4]

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

densations, numerous mitochondria and membrane-bound dense granules that match premelanosomas[12,26,27].

PEComa's 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 and actin is negative or only focally positive.

Finally, only a few malignant cutaneous PEComa 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 *et al*[4] (Table 1).

CHROMOSOMAL ABNORMALITIES

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

Finally, a recent study of Charli-Joseph *et al*[23] using array-based comparative genomic hybridization and a complete immunohistochemical study in 8 cases of primary cutaneous PEComa did not find any chromosomal imbalances or initiating mutations. 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 for the evaluation of these

neoplasms[23]. The most 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 differs from the immunophenotype usually found in cutaneous PEComa; although both neoplasms share MITF-1 positivity the rare congenital granular cell tumors show also 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, but sometimes occupying most of the tumor[44].

Myoepitheliomas are composed of polygonal shaped cells positive for EMA, calponin, AE1/AE3, SMA and desmin, 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, 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 in doubtful cases[46,47].

Epithelioid sarcoma is a malignant neoplasm 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 nests and express S100 protein along with other melanocytic markers. Balloon cells are usually a focal finding, although some tumors may appear 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 clear cell sarcoma often show 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 are consistently negative[53]. Some authors consider that this tumor is possibly associated with PEComa, but still remains considerated as a different entity based on the negativity for melanocytic markers[54]. Finally, Tomasini *et al*[55] published a peculiar neoplasm under the name of eruptive dermal clear cell desmoplastic mesenchymal tumor with perivascular myoid differentiation. This neoplasm showed 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, SMA, CD13, CD68 and NKIC3[55].

Visceral PEComa do not express CD34 or c-kit, which is in contrast with GIST. Recently a case of cutaneous metastasis from an adrenal PEComa has 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 PEComa are benign tumors, surgical removal is curative[1].

A recent review on PEComa located on head and neck suggests that they may be more aggressive, as one of the two malignant cutaneous PEComa and one soft tissue malignant PEComa[57] were in this location.

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 this syndrome, and may be also useful in a subset of PEComa with mTOR activation.

Symplastic PEComas portend an unknown biological

behaviour[63].

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