PEComas: the past, the present and the future

Guido Martignoni · Maurizio Pea · Daniela Reghellin · Giuseppe Zamboni · Franco Bonetti

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Abstract The perivascular epithelioid cell (PEC) is a cell type constantly present in a group of tumors called PEComas. PEC expresses myogenic and melanocytic markers, such as HMB45 and actin. Recently, recurrent chromosomal alterations have been demonstrated in PEC. At present, PEComa is a widely accepted entity. In the past 10 years, the use of this term has allowed to report and describe numerous cases permitting to start highlighting the biology of this group of lesions. PEComas are related to the genetic alterations of tuberous sclerosis complex (TSC), an autosomal dominant genetic disease due to losses of TSC1 (9q34) or TSC2 (16p13.3) genes which seem to have a role in the regulation of the Rheb/mTOR/p70S6K pathway. There are some open questions about PEComas regarding its histogenesis, the definition of epithelioid angiomyolipoma and the identification of the histological criteria of malignancy. An innovative therapeutic trial using rapamycin is under way for tumors occurring in TSC such as renal angiomyolipoma and lymphangioleiomyomatosis. Its success could provide the rationale for the use of the same drug in other lesions composed of PECs, especially in the malignant ones.

Keywords PEComa · PEC · Angiomyolipoma · Lymphangioleiomyomatosis · Sugar tumor · TSC · mTOR · Rapamycin

What is the perivascular epithelioid cell?

The perivascular epithelioid cell (PEC) (Fig. 1) is a cell type constantly present in a group of tumors including angiomyolipoma (AML), clear-cell “sugar” tumor (CCST) of the lung and extrapulmonary sites, lymphangioleiomyomatosis, clear-cell myomelanocytic tumor of the falciform ligament/ligamentum teres and rare clear-cell tumors of other anatomical sites.

It has morphologic, immunohistochemical, ultrastructural and genetic distinctive features such as an epithelioid appearance with a clear to granular cytoplasm, a round to oval, centrally located nucleus and an inconspicuous nucleolus. PEC has mild to any atypia and a typical perivascular location [13]. At present, PEC has not a known normal counterpart.

Immunohistochemically, PEC expresses myogenic and melanocytic markers, such as HMB45, HMSA-1, MelanA/Mart1, microphthalmia transcription factor (Mitf), actin and, less commonly, desmin [13, 55, 126]. Its immunoreactivity for vimentin is usually inconspicuous.

At ultrastructural analysis, PEC contains microfilament bundles with electron-dense condensation, numerous mitochondria and membrane-bound dense granules [11, 118].

It is thought that PEC can modulate its morphology and immunophenotype: given all the characteristics described above (Fig. 2), PEC can show muscular features with a spindle shape and a stronger positivity for actin than for HMB45 or it can have an epithelioid feature with a strong positivity for HMB45 and a mild, if any, reaction for actin (Fig. 3). PEC can also become vacuolized acquiring the feature of an adipocyte. Progesterone receptor positivity has been described in PEC with spindle morphology; this suggests a possible role of progesterone in this morphologic modulation [13, 107].
Recently, recurrent chromosomal alterations have been demonstrated in PEC [87].

**What is a PEComa?**

The World Health Organization defines PEComa as “a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells” [37].

At present, this neoplasm is a widely accepted entity. However, some authors cast doubts on the existence of PEComa as a distinctive tumor, particularly as regards the uterine ones that they view as leiomyosarcoma with aberrant expression of HMB45 [102–104]. Although we understand their perplexity, we would like to underline some points. First, it has been demonstrated that there are different gene expression profiles among uterine smooth muscle tumors, demonstrating their heterogeneity [105, 106, 119]. Second, we think that it is difficult to explain, in uterine smooth muscle neoplasms, both HMB45 and Mitf positivity as an aberrant expression or antibody cross-reactivity involving both antigens [81]. Third, we think that the absence of a recognized normal counterpart for PEC is not a sufficient reason to reject the concept of PEComa; in fact, there are other well-accepted soft-tissue neoplasms, such as alveolar soft-part sarcoma and epithelioid sarcoma, that still have not a known normal counterpart.

Some authors have questioned about the use of the term “PEComa”. They consider it ambiguous because it is not clear whether this term should be restricted to purely epithelioid tumors as CCST or whether the term should be more broadly applied to include AML and lymphangioleiomyomatosis [80, 111].

We believe that AML, CCST and pulmonary lymphangioleiomyomatosis are composed of PECs in different stages of modulation, and these lesions, together with clear-cell myomelanocytic tumor of the falciform ligament/ligamentum teres, belong to the same family of tumors, the PEComas.

Nevertheless, we think that it is better to continue to name some of them (i.e. AML and pulmonary lymphangioleiomyomatosis) also with their established names which identify their clinical and morphological aspects and are well known by clinicians and pathologists [15].

Moreover, in the past 10 years, the use of the term PEComa has permitted to report and describe numerous cases with the morphological and immunohistochemical features of this tumor permitting to start to understand the biology of this group of lesions.
PEC and tuberous sclerosis

PEComas are related to the tuberous sclerosis complex (TSC) or, better, to the genetic alterations of TSC, an autosomal dominant genetic disease due to losses of TSC1 (9q34) or TSC2 (16p13.3) genes [112, 116] and characterized by mental retardation, seizures and cellular proliferations (AMLs, subependymal giant cell tumors, cutaneous angiofibromas, cardiac rhabdomyomas, lymphangioleiomyomatosis, pulmonary multifocal micronodular hyperplasia). Similar alterations of the TSC genes have been demonstrated in a significant number of PEComas, both occurring within the TSC and in sporadic cases.

In recent years, great advances have been made in our knowledge of TSC and related lesions. In particular, TSC genes seem to have an important role in the regulation of the Rheb/mTOR/p70S6K pathway [62]. Kenerson et al. [59] have recently demonstrated increased levels of phospho-p70S6K, a marker of mTOR activity, in sporadic AMLs. The associated reduced phospho-AKT expression is consistent with the disruption of TSC1/2 function.

Similar findings were obtained analysing extrarenal PEComas.

PEComa: the past

PEC was first described in 1943 by Apitz [5] as an “abnormal myoblast” in renal AML, as reported by Masson [77] in his famous book.

The idea of a possible link between AML and other two lesions, CCST and lymphangioleiomyomatosis, came from the fact that the same epithelioid cell was observed in them. Moreover, this cell was HMB45-positive in all three lesions [9, 93, 94].

Later, ultrastructural examination revealed the presence of premelanosomes both in CCSTs of the lung and in epithelioid clear-cell component of renal and hepatic AMLs [9, 42, 43, 93, 94, 118].

In addition, the possibility of a relationship between AML and lymphangioleiomyomatosis was suggested by the fact that both occur in TSC [10].

We proposed that CCST should be also included in this syndrome [10], and the first description of this tumor in a patient with TSC confirmed this idea [35].

In 1996, we described the first case of pancreatic CCST and suggested the name PEComa for neoplasms composed of a pure proliferation of PECs [125].

Moreover, the fact that the same clear epithelioid cell composing pulmonary “sugar” tumor was present in AML and was the only component of some small renal microhamartoma (Fig. 4) suggested to us the idea of the existence of a monotypic epithelioid AML of the kidney. We looked for them, and we found them [96].

PEComa: the present

PEComas have been described in different organs and are considered ubiquitous tumors.

Kidney

PEComas of the kidney include classic AML, microscopic AML (so-called microhamartoma), intraglomerular lesions, cystic AML, epithelioid AML, oncocytoma-like AML and lymphangiomyomatosis of the renal sinus.

Classic angiomylipoma is the most common mesenchymal tumor of the kidney. Being composed of a variable mixture of adipose tissue and spindle and epithelioid smooth muscle cells mixed together with abnormal thick-walled blood vessels, AML is the prototype of the capacity of PEC to modulate its morphology [29, 76].

For a long time, AML has been considered a hamartoma rather than a true neoplasm, but, at present, its clonal nature has been demonstrated [19, 57, 101]. In patients with TSC, renal AMLs are found in both sexes, in the third and fourth decades of life, with a female predominance; they are usually asymptomatic, bilateral, small and multifocal. Sporadic AMLs occur in older patients, in the fourth to sixth decades of life, with a female predominance; they are single, unilateral and larger than those associated with TSC [76]. Classic AML contains more than one cell type; if a particular cell type predominates, AML is consequently named (lipoma-like AML or leiomyoma-like AML) [6].
Classic AML has a benign outcome. Multifocality and regional lymph node involvement can occur, and this is considered to represent a multifocal growth pattern rather than a metastasis [1, 110]. Three cases of sarcoma developing in sporadic AML have been reported. Similar cases have not been described in TSC patients [22, 32, 73].

Both inherited and sporadic AML frequently demonstrates loss of heterozigosity of chromosome 16p (containing the TSC2 locus). The TSC1 gene occasionally shows loss of heterozigosity [17, 50].

Microscopic angiomyolipomas (so-called microhamartomas) They are small nodules often present in a kidney with an AML. They are not homogeneous in appearance and display all the heterogeneous morphologic aspects of AML; microscopic AMLs do not contain thick-walled blood vessels [13, 20].

Intraglomerular lesions with similar features of AML have been reported in patients with and without tuberous sclerosis and in the TSC2/PKD1 contiguous gene syndrome, a disease with a deletion disrupting both TSC2 and PKD1 (autosomal dominant polycystic disease gene) [74].

Cystic angiomyolipoma is a recently described variant of AML [25, 33]. It is a solid-cystic lesion that, microscopically, is composed of epithelial cysts lined by cuboidal to hobnail cells, positive for cytokeratin; a compact subepithelial “cambium-like” layer of stromal cells positive for HMB45, Melan-A, CD10, estrogen and progesterone receptors and a solid extracystic component with the morphology of a muscle-predominant (Fig. 5) AML, which is positive for HMB45, estrogen and progesterone receptors, smooth muscle actin and desmin and which is associated with irregular blood vessels. Some authors think that the subepithelial “cambium-like” layer is a manifestation of a Mullerian differentiation of NEC. If the epithelial cysts represent entrapped renal tubular epithelium [33] or are also related to PEC is unknown.

Only 1 of the 16 cases described to date had a history of TSC [33].

Epithelioid angiomyolipoma is another recently described variant of AML. It is composed of purely epithelioid cells with melanogenesis markers immunoreactivity arranged in sheets. Both adipocytes and abnormal blood vessels are not present. The cytoplasm of the neoplastic cells varies from faintly eosinophilic to clear. Tumor cells can display considerable nuclear atypia, and necrosis can be present. This tumor can recur locally and metastasise causing death. On the basis of histology alone, it is not possible to predict malignant behaviour in these neoplasms, and further data are needed to better define it. However, at the present time, all epithelioid AMLs should be closely followed clinically. Epithelioid AMLs has been described in patient with or without evidence of TSC and in the TSC2/PKD1 contiguous gene syndrome.

Loss of heterozigosity of TSC2 have been reported in some cases of sporadic epithelioid AML [28, 72, 74, 84, 96].

Oncocytoma-like angiomyolipomas are tumors composed of a homogeneous population of HMB45-positive polygonal cells with strongly eosinophilic cytoplasm. They have been described in patients with and without TSC. Recognition of this variant is important because oncocytomas in the same kidney with AMLs have been reported repeatedly and in patients with TSC oncocytomas seem to occur more frequently than in general population [75].

Lymphangiomyomatosis of the renal sinus is a plaque-like mass in the wall of the renal pelvis. All three cases reported to date also had renal AMLs, but in only one of them careful postmortem examination of the lungs revealed pulmonary lymphangiomyomatosis [74, 78].

Bladder and prostate

In 2003, Pan et al. [85, 86] have reported two PEComas of the genitourinary tract in patients without TSC. Both tumors were composed of a variable percentage of epithelioid and spindle cells with clear to granular cytoplasm arranged in nests separated by a vascular stroma. Neoplastic cells were positive for HMB45 but not for epithelial markers, vimentin and S100 protein. The prostatic tumor (Fig. 6) showed a low mitotic activity, coagulative necrosis and a malignant behaviour, whereas the neoplasm
of the bladder (Fig. 7), lacking these histologic findings, behaved in a benign fashion. Another case of primary PEComa of the bladder has recently been described; also in this case, the patient is well and alive at 48 months after surgery [90].

Finally, Weinreb et al. [120] have recently described a case of PEComa of the urachal cyst composed of pleomorphic cells and containing necrosis and a high mitotic activity. In this case, they also found a peculiar aspect that they named “pecosis”: remote from the tumor, there were isolated capillaries surrounded by a single layer of clear cells.

**Uterus**

The first case of PEC tumor of the uterus was reported by Pea et al. [95]: it was a polypoid neoplasm involving the endometrium, which showed morphological features overlapping those of the CCST of the lung (Fig. 8).

Vang and Kempson [115] described eight cases of uterine PEC tumor (“PEComa”). They distinguished a morphologic spectrum of neoplasms varying from tumors with a tongue-like growth pattern composed of sheets of HMB45-positive clear epithelioid cells, which they called group A, to circumscribed tumors composed of hyalinized stroma and neoplastic cells focally positive for HMB45 and extensively immunoreactive for actin and desmin, which they refer to as group B. In two of these eight cases, pelvic lymph nodes contained lymphangiomyomatosis.

Lesions considered to be uterine involvement of lymphangioleiomyomatosis are usually asymptomatic, and some of them correspond to an incidental finding in patients with TSC.

PEComas of the uterus have usually shown benign behaviour, but 13 tumors, 2 of them associated with TSC, were aggressive [16]. In two of six uterine PEComas described by Folpe et al. [39], patients have metastases and one of six patients died of PEComa.

Fadare et al. [31] described a case of uterine PEComa in a patient with TSC in which there was intra-abdominal “PEComatosis”: surgeon found small foci of epithelioid cells in the lamina propria of the small intestine, myometrium and ovarian hilum.

**Ovary, vulva and vagina**

A tumor with a strong and diffuse HMB45 expression morphologically corresponding to an epithelioid angiomylipoma has been reported in the ovary [4].

Tazelaar et al. [111] reported a case described as primary extrapulmonary clear-cell “sugar” tumor of the vulva.
Finally, cases of vaginal PEComa have also been described [39, 83].

Lung

PEComas of the lung include lymphangioleiomyomatosis and clear-cell “sugar” tumor.

_Lymphangioleiomyomatosis_ (LAM) (Fig. 9) is a rare and progressive disease that affects the lungs of women, usually in premenopausal age; occasionally, it can be extrapulmonary (as described above). It consists of a nodular, often widespread and bilateral interstitial proliferation of HMB45, actin and desmin-positive smooth muscle cells which can vary from small spindle-shaped cells to large epithelioid cells, usually arranged around thin-walled, branching vascular channels; this proliferation is associated with dilated lymphatics and cystic changes [9, 11, 18, 113].

LAM is usually sporadic; patients with TSC are frequently afflicted.

In many cases of LAM, there is a slow progression to pulmonary failure, and the only therapy is lung transplantation. In no-transplanted patient, there is a median survival of 8–10 years [113].

_CCST_ (Fig. 10) was originally described in the lung [68]. It is a rare and benign neoplasm composed of a uniform population of round-to-polygonal epithelioid cells, with a clear or eosinophilic cytoplasm and well-defined cell borders. Tumor cells are surrounded by prominent and thin-walled vascular channels. CCST has a nested or alveolar appearance. We have also observed adipocytic cells in a few cases of CCST [12]. Tumor cells are positive for HMB45 (Fig. 11) [12, 41, 93].

Pulmonary CCST is rarely associated with TSC [35]; in the vast majority of cases, it is a sporadic lesion.

Pancreas

PEComa of the pancreas was reported for the first time in 1996 by Zamboni et al. [125]. It was actually the first time that the very term PEC was introduced (Fig. 12).

The paper reported a tumor with overlapping features of the “benign clear-cell sugar tumor of the lung”. This finding was in our opinion consistent with the hypothesis that similar tumors could possibly arise in many if not all locations.
Thus the term PEComa was introduced to include all similar lesions arising outside the lung. At the time, we believed this to be a unique case. However, in the following years we have observed other two cases of PEComa of the pancreas with overlapping morphological, phenotypical and clinical features. Thus, while still a very rare disease of the pancreas, PEComa is not an extraordinary finding in this location.

The clinical aspects of PEComa of the pancreas are interesting because they are discovered incidentally during echography of the abdomen and then investigated usually with cytology. The observation of clear epithelioid cells can understandably lead to the wrong diagnosis of clear-cell carcinoma of the pancreas and thus lead to duodenocephalectomy.

A primary angiomyolipoma of the pancreas has also been described. It was a cephalopancreatic nodule in a non-TSC woman [51].

Liver

Apart from kidney and liver, classic or even epithelioid angiomyolipoma can occur in different visceral and somatic sites as gastrointestinal tract, pelvis [14, 34, 47], nasal cavity [7], soft tissues [49] retroperitoneum [63], bone [53] and orbit [54].

Clear-cell “sugar” tumor has been described in a variety of extrapulmonary sites, apart from uterus and pancreas: skin [26], soft tissues [40], breast [45], skull base [66], gastrointestinal tract [8, 111], inter-atrial cardiac septum [111] and oral mucosa [61].

Clear-cell myomelanocytic tumour of the falciform ligament/ligamentum teres (CCMMT) is a PEComa showing predominantly spindled cell morphology.

It has been first described in 2000 by Folpe et al. [36] who presented seven cases of PEComa arising in the abdomen. All patients but one were women ranging from 3 to 21 years of age. These neoplasms were composed of spindle cells arranged in fascicles and nests, positive for HMB45 and, in three cases, also for Melan-A, microophthalmia transcription factor (Mif) and actin. Also in these cases, premelanosomes were ultrastructurally detected. At follow-up, in one patient presumed lung metastasis developed.

CCMMT has also been described in thigh [38] and in the skin [79].

PEComa: the future

PEComas are a group of ubiquitous neoplasms sharing morphological, immunohistochemical, ultrastructural and genetic distinctive features.

There are some open questions about PEComas: the histogenesis and the normal/physiological counterpart of
| Reference                          | Diagnosis        | Site                           | Sex/age | Outcome            | Comments                                                                 |
|-----------------------------------|------------------|--------------------------------|---------|--------------------|--------------------------------------------------------------------------|
| Sale and Kulander [100]           | CCST             | Lung                           | n.a./n.a.| AWD at 10 years    | Hepatic metastases at 10 years                                         |
| Ferry et al. [32]                 | Epithelioid AML  | Kidney                         | F/49    | DOD at 5.5 months  |                                                                          |
| Al-Saleem et al. [3]              | Epithelioid AML  | Kidney                         | F/21    | DOD at 3 months    |                                                                          |
| Pea et al. [96]                   | Epithelioid AML  | Kidney                         | F/24    | DOD at 1 year      | Pelvic and hepatic metastases                                          |
| Pea et al. [96]                   | Epithelioid AML  | Kidney                         | M/29    | DOD at 18 months   | Pulmonary and hepatic metastases                                       |
| Christiano et al. [21]            | Epithelioid AML  | Kidney                         | M/42    | AWD at 15 months   |                                                                          |
| L’Hostis et al. [67]              | Epithelioid AML  | Kidney                         | F/71    | DOD at 2 years     |                                                                          |
| Folpe et al. [36]                 | PEComa           | Ligamentum teres falciform ligament | M/29 | DOC at 1 year     | Radiographically suspected lung metastasis at 3 months                  |
| Martignoni et al. [73]            | Epithelioid AML  | Kidney                         | F/50    | AWD at 10 years    | Local recurrence at 7 years; pulmonary, pelvic and abdominal metastases at 10 years |
| Bonetti et al. [14]               | PEComa           | Uterus                         | F/41    | ANED at 6 months   | Ovarian mass at presentation                                            |
| Bonetti et al. [14]               | PEComa           | Uterus                         | F/19    | AWD at 18 months   | Aggressive local recurrence at 1 month; lung and bone metastases at 11 months |
| Bonetti et al. [14]               | PEComa           | Terminal ileum and cecum       | F/28    | DOD at 28 months   | Hepatic metastasis                                                      |
| Cibas et al. [22]                 | Epithelioid AML  | Kidney                         | F/49    | AWD at 6 months    |                                                                          |
| Saito et al. [99]                 | CCST             | Kidney                         | F/23    | DOD at 1 year      | Retroperitoneal recurrence at 3 months                                  |
| Yamamoto et al. [122]             | Epithelioid AML  | Kidney                         | M/47    | DOD                | DOD with spinal, lung and lymph node metastases (autopsy case)          |
| Dimmler et al. [27]               | PEComa           | Uterus                         | F/61    | AWD at 7 years     | Lung metastases                                                        |
| Greene et al. [46]                | PEComa           | Uterus and pelvic side wall    | F/79    | DOD at several months | Pelvic and mesenteric recurrence at 2 years                             |
| Lau et al. [63]                   | Epithelioid AML  | Retroperitoneum                | M/29    | ANED at 18 years   | Liver metastases at 9 years; thymus and lung metastases at 17 years     |
| Leclerc et al. [64]               | Epithelioid AML  | Kidney                         | F/36    | ANED               | Lymph node metastases                                                  |
| Lin et al. [69]                   | Epithelioid AML  | Kidney                         | n.a./58 | AWD                | Liver and lymph node metastases                                        |
| Ong et al. [82]                   | Epithelioid AML  | Kidney                         | F/74    | AWD                | Adrenal metastases                                                     |
| Pan et al. [85]                   | PEComa           | Prostate                       | M/46    | DOD at 4 years     | Submitted to adjuvant chemotherapy; lung metastases at 3 years          |
| Reference | Diagnosis Type | Site | Sex/Age | Outcome | Comments |
|-----------|----------------|------|---------|---------|----------|
| Takahashi et al. [109] | Epithelioid AML | Kidney | F/40 | DOD at 18 months | Submitted to adjuvant chemotherapy; pulmonary metastases |
| Takahashi et al. [109] | Epithelioid AML | Kidney | M/44 | DOD at 60 months | Splenic and retroperitoneal metastases at 3 years; hepatic metastases at 60 months |
| Yanai et al. [123] | PEComa | Jejunum | F/32 | AWD at 25 months | Pelvic wall recurrence/local metastases at 13 months; ovarian metastases at 25 months |
| Durai et al. [24] | Epithelioid AML | Urach | F/n.a. | AWD | Lymph node metastases |
| Harris et al. [49] | PEComa | Soft tissue near knee | M/87 | AWD at 40 months | Inguinal lymph node and lung metastases at 13 months |
| Lehman [66] | PEComa | Skull base | F/49 | DOD at 3 months | Parspinal and lung metastasis at 6 weeks |
| Bosincu et al. [16] | PEComa | Uterus | M/87 | DOD at 1 year | Pelvic recurrence at 6 months |
| Evert et al. [30] | PEComa | Rectovaginal space | F/56 | AWD | Pulmonary metastases at presentation |
| Folpe et al. [39] | PEComa | Neck | F/77 | ANED at 6 months | Re-excision and submitted to adjuvant radiotherapy |
| Folpe et al. [39] | PEComa | Forearm | M/71 | ANED at 10 months | Re-excision and submitted to adjuvant radiotherapy |
| Folpe et al. [39] | PEComa | Broad ligament | F/16 | ANED at 18 months | Re-excised |
| Folpe et al. [39] | PEComa | Falciiform ligament | F/15 | ANED at 35 months | Re-excised |
| Folpe et al. [39] | PEComa | Uterus | F/56 | AWD at 11 years | Submitted to adjuvant radio and chemotherapy; lung and bone metastases |
| Folpe et al. [39] | PEComa | Pelvic soft tissue | F/72 | AWD at 15 months | Local recurrence |
| Folpe et al. [39] | PEComa | Omentum | M/40 | AWD at 24 months | Extensive intra-abdominal recurrence/local metastases |
| Folpe et al. [39] | PEComa | Uterus | F/59 | AWD at 30 months | Submitted to adjuvant chemotherapy; liver and lung metastases at 30 months |
| Folpe et al. [39] | PEComa | Mesentery | F/46 | DOD at 27 months | Submitted to adjuvant chemotherapy; extensive intra-abdominal recurrence and liver metastases at 22 months |
| Folpe et al. [39] | PEComa | Uterus | F/36 | DOD at 39 months | Submitted to adjuvant chemotherapy; lung metastases at 12 months and liver metastases at 36 months |
| Svec and Velenska [108] | Epithelioid AML | Kidney | F/47 | ANED at 5 months | Recurrence at 3 months |
| Yu et al. [124] | Epithelioid AML | Kidney | F/12 | DOD at 9 months | Lymph node metastases; submitted to adjuvant chemotherapy |
| Agaimy and Wünsch 2006 [2] | PEComa | Ileum | F/63 | AWD at 14 months | Abdomino-pelvic recurrence |
| Kim et al. [60] | CCMT | Broad ligament | F/12 | AWD at 1 year | Iliac fossa recurrence |
| Mai and Belanger [70] | PEComa | Thigh | M/56 | DOD at 1 year | Pulmonary and brain metastases |
| Mai and Belanger [70] | PEComa | Thigh | F/60 | DOD at 1 year | Pulmonary metastases |
PEC, the definition of epithelioid AML and the identification of the histological criteria of malignancy.

The histogenesis and the normal/physiological counterpart of PEC are unknown, but some hypotheses have been proposed. One hypothesis is that PEC derives from undifferentiated cells of the neural crest that can express dual smooth muscle and melanocytic phenotype; a second hypothesis is that PEC has a myoblastic, smooth muscle origin with a molecular alteration that brings to expression of melanogenesis and melanocytic markers [107]; a third hypothesis is that PEC has a pericytic origin. As regards PEComa’s histogenesis, the involvement of TSC pathway in these neoplasms can suggest some possibilities: it has been previously proposed that B-raf activity in cells lacking TSC2 may play a role in cell differentiation [56]. Moreover, TSC pathway regulates negatively Wnt/beta-catenin pathway [71] and beta-catenin regulates transcription of genes involved in cell proliferation and differentiation. Nevertheless, more cases should be analysed to better understand PEC origin and PEComa’s histogenesis.

The second issue regarding PEComas is which cases should be classified as epithelioid AML particularly in the kidney and liver, where AML occurs with higher frequency. We defined epithelioid AML as a neoplasm composed of purely epithelioid cells with melanogenesis markers immunoreactivity arranged in sheets, without adipocytes and abnormal blood vessels.

However, in otherwise classic AML, areas of epithelioid cells can be observed, raising the question how much they should be represented to call a tumor “epithelioid angio-myolipoma”. The collection of such cases and a consensus meeting could be useful tools to answer to this problem.

Malignant PEComa can be a very aggressive disease leading to multiple metastases and death as expected with a high-grade sarcoma [3, 14, 16, 32, 39, 52, 66, 67, 70, 85, 96, 97].
A few malignant PEComas metastasised after several years (7–9 years) [27, 73, 89, 100] (Table 1).

Recently, Folpe et al. [39] reported 26 cases of PEComas of soft tissue and gynaecologic origin proposing criteria for the classification of these tumors as “benign”, “of uncertain malignant potential” and “malignant”. In this study, they observed a significant association between tumor size >5cm, infiltrative growth pattern, high nuclear grade, necrosis and mitotic activity >1/50 HPF and subsequent aggressive clinical behaviour of PEComas.

We think that this approach is the best available at the moment. While more cases with long follow-up are needed to verify the effectiveness of this prognostic classification, we believe that all cases of PEComa should be classified according to the criteria proposed by Folpe et al.

Another future challenge regarding PEComas is their management.

Surgery seems to be the only approach for aggressive cases, as chemio- and radiotherapy has not shown significant results. However, this derives from anecdotal cases as no therapeutic trial has so far been implemented. There are obvious difficulties to perform a therapeutic trial mainly due to the rarity of the disease. An international cooperative study is needed to address this problem.

A very different problem is posed by lymphangioleiomomatosis. In fact, lymphangioleiomomatosis is composed of a population of cells with no atypia. Mitotic activity is virtually absent or extremely low. In spite of this, the disease usually progresses inexorably towards lung-function impairment. Recently, Kenerson et al. [59] demonstrated TSC1/2 inactivation and m-TOR hyperactivation in non-TSC AMLs and in extrarenal PEComas using immunohistochemistry and Western blot analysis. In particular, m-TOR hyperactivation can be studied in such lesions using immunohistochemical detection of p70S6K. As we have previously mentioned, p70S6K is a protein kinase activated by m-TOR. Immunohistochemical reaction for p70S6K can stain both p70S6K, which gives a cytoplasmic signal (Fig. 14), and a second isoform of kinase, p85S6K, which is also activated by m-TOR and which gives a nuclear signal.

Rapamycin is a specific inhibitor of m-TOR [23] which is approved by the US Food and Drug Administration for immunosuppression therapy after renal transplant [117], and it has recently been approved also for therapy of renal cell carcinomas and acute myeloid leukemia [88, 97]. Preclinical studies in animal models of TSC have shown significant in vivo response to rapamycin [58, 65].

As regards LAM, an innovative therapeutic trial is under way. Rapamycin seems to block signaling through the Akt cell growth and survival pathway (for up-to-date information, see http://www.thelamfoundation.org).

A similar trial has already shown a positive effect on renal AML, and we can hope to see the same effect on LAM.

If this will be the case, this could provide the rationale for the use of the same drug in other lesions composed of PECs.

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