Perivascular Epithelioid Cell Tumor

Henry B. Armah, MD; Anil V. Parwani, MD, PhD

• Perivascular epithelioid cell tumors are mesenchymal neoplasms defined by the presence of histologically and immunohistochemically distinctive perivascular epithelioid cells. The perivascular epithelioid cell has no known normal tissue counterpart and coexpresses myoid and melanocytic markers. This tumor family shows marked female predominance and includes angiomyolipoma, clear cell sugar tumor, lymphangioleiomyomatosis, and a group of rare, morphologically and immunophenotypically similar tumors arising at a variety of visceral and soft tissue sites. This latter subset has been collectively termed perivascular epithelioid cell tumors—not otherwise specified. They are usually composed of epithelioid, but occasionally spindled, cells with clear to granular eosinophilic cytoplasm and focal perivascular accentuation. The mainstay of treatment is wide excision. Although most cases are benign, a subset behaves in a malignant fashion. Since few malignant cases have been reported, firm criteria for malignancy have yet to be established. This review focuses on the perivascular epithelioid cell tumors—not otherwise specified subset. (Arch Pathol Lab Med. 2009;133:648–654)

The World Health Organization defines perivascular epithelioid cell tumors (PEComas) as mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells (PECs).1 In 1991, Pea and colleagues2 first noted this unusual cell in both angiomyolipoma (AML) and clear cell sugar tumor (CCST) of the lung. One year later, Bonetti and colleagues3 proposed a cellular link between AML, CCST, and lymphangioleiomyomatosis (LAM), their association with tuberous sclerosis complex (TSC), and advanced the concept of a family of neoplasms composed of these distinctive cells, which were “immunoreactive with melanocytic markers, and exhibit an epithelioid appearance, a clear-acidophilic cytoplasm, and a perivascular distribution.” In 1996, Zamboni et al4 reported the first case of pancreatic CCST and suggested the name PEComa for these neoplasms composed of a pure proliferation of PECs. There is no known normal cellular counterpart to this PEC, and a precursor lesion for PEComas has not been described.1 Subsequently, the PEComa family of tumors has grown to include AML, CCST, LAM, and a number of rare and unusual visceral, intra-abdominal, soft tissue, and bone tumors, which have been described under a variety of names, including clear cell myometalnocytic tumor of the fallopian ligament/ligamentum teres, abdominopelvic sarcoma of perivascular epithelioid cells, and primary extrapulmonary clear cell sugar tumor, among others. This group of rare, morphologically and immunophenotypically similar tumors arising at a variety of visceral (commonly gastrointestinal, gynecologic, and genitourinary) and soft tissue (commonly retroperitoneal, abdominopelvic, and cutaneous) sites has been collectively termed non-AML, non-LAM, non-CCST PEComas; or PEComas other than AML, LAM, or CCST; or PEComas—not otherwise specified (PEComas-NOS).1 Generally, clear cell myometalnocytic tumor is now not considered a distinct entity, but rather falls within the morphologic spectrum of PEComas-NOS.1

To the best of our knowledge, about 100 PEComas-NOS have been reported in the English language medical literature, of which 38 were uterine PEComas-NOS.5,6,12 These 38 reported cases of uterine PEComas-NOS have usually shown clinically benign behavior, but 13 tumors exhibited locally aggressive behavior, and 4 of these 13 showed distant metastases to liver, lungs, intestines, bone, and lymph nodes up to 7 years after resection of the uterine tumors.5,10,11 Three of these 13 locally aggressive uterine PEComa-NOS were associated with TSC.5,6,9 Although there is a strong association between TSC, AML, LAM, and CCST, this association is much less clear for the rarer PEComas-NOS.1 Since relatively few cases of malignant PEComa have been reported, and the duration of follow-up has been relatively short in the reported cases of PEComa, firm criteria for malignancy have yet to be established. However, a recent original clinicopathologic study of 26 PEComas suggested criteria for malignancy, including a size greater than 8.0 cm, mitotic count of more than 1 per 50 high-power fields and necrosis, and these 3 criteria helped stratify PEComas into benign, uncertain malignant potential, and malignant categories.5 Unfortunately, until more cases of this rare tumor are evaluated in a systematic fashion, firm criteria for malignancy remain uncertain. This review examines the exceedingly rare PEComa-NOS subset of the PEComa family of tumors.

CLINICAL FEATURES OF PEComas-NOS

PEComas-NOS have now been reported in almost every body site, and the growing list of reported sites includes gastrointestinal, gynecologic, genitourinary, extremities, and the skin, as well as single reports in the heart, breast, oral cavity, orbit, and skull base.1,3,12,14 The uterus is the most prevalent reported site of involvement of PEComa-
NOS (accounting for 38 of about 100 reported cases).\textsuperscript{1,5–13} Uterine PEComas-NOS have a mean age at diagnosis of 54 years and patients may present with vaginal bleeding.\textsuperscript{6} The other common sites are the genitourinary tract, gastrointestinal tract, and retroperitoneum, whereas rare sites include somatic soft tissue, skin, and bone.\textsuperscript{1,5–14} Almost all of the reported nonuterine PEComas-NOS have been in women, with a wide age range at diagnosis, and typically present as a painless mass.\textsuperscript{1,5–14} Clear cell myomelanocytic tumor usually occurs in young girls, with a mean age at diagnosis of 11 years, and typically presents as a painful abdominal mass.\textsuperscript{15,16}

**PATHOLOGIC FEATURES OF PEComas-NOS**

**Gross Features**

Grossly, PEComa-NOS is usually tan to gray with variable firm and friable areas. Although it is typically localized and somewhat well circumscribed, no definite capsule is present. Cut surface is generally white-tan to gray-red, with focal areas of hemorrhage and necrosis.

**Microscopic Features**

The PEC is characterized by perivascular location, often with a radial arrangement of cells around the vascular lumen (Figures 1 through 3). Perivascular epithelioid cell tumors—not otherwise specified are usually biphasic tumors with epithelioid and spindle cell components. Typically, PECs in an immediate perivascular location are mostly epithelioid, with spindled cells resembling smooth muscle often away from vessels. Great variation is seen in the relative proportion of epithelioid and spindled cells. Perivascular epithelioid cells can have a variable histologic appearance; they can be epithelioid, elongated and spindle shaped, or vacuolated (adipocyte-like). They have clear to granular, lightly eosinophilic cytoplasm (Figures 2 through 4), rather than the dense eosinophilia of true smooth muscle cells. They typically display small, cen-
trally placed, normochromatic, round to oval nuclei with small nucleoli, slight atypia, and sparse mitotic activity (Figures 2 and 3). However, a significant percentage of reported PEComas display striking nuclear atypia (hyperchromasia and irregularity) and elevated mitotic activity (Figure 4).

The tumor cells are arranged in nested or short fascicular/storiform patterns. However, most cases display a nested pattern and show epithelioid cytomorphology, with spindle cell features being relatively uncommon, and with an approximately equal number of cases composed predominantly of clear cells and cells with granular eosinophilic cytoplasm.\(^1,6,8,12,14,17\) Frequently, a careful search will reveal focal areas where the neoplastic cells are arranged around prominent vascular spaces (Figures 1 through 3), and this is a useful diagnostic clue to prompt immunohistochemical stains to confirm the diagnosis of PEComa.\(^1,6,8,12,14,17\) A small subset of PEComas show abundant stromal hyalinization, and this feature most commonly occurs in uterine, renal, and pararenal/retroperitoneal lesions.\(^8,14\) Uterine PEComas-NOS were subclassified into 2 groups by Vang and Kempson\(^6\) in a recent original clinical-pathologic study. The tumors of one group are morphologically similar to low-grade endometrial stromal sarcomas with diffuse HMB-45 expression and focal expression of smooth muscle markers. The tumors of the other group are morphologically similar to epithelioid smooth muscle tumors and composed of epithelioid cells with less prominent clear cell features, smaller numbers of which are HMB-45 positive.\(^6\) The prognostic relevance of their subclassification remains to be demonstrated.

**Immunohistochemical Features**

The PEC is characterized by immunopositivity with both myoid (desmin [Figure 5], smooth muscle actin, muscle-specific actin/all-muscle actin/HHF-35, muscle myosin, and calponin) and melanocytic (HMB-45 [Figure 6], Melan-A/MART-1, tyrosinase, and microphthalmia transcription factor) markers. Desmin is less often positive, and cytokeratins and S100 protein are usually negative. Folpe and colleagues\(^8\) recently reviewed all reported cases of PEComa up to 2005 (61 cases). In their review, 100%
were HMB-45 positive, 59% were smooth muscle actin positive, 41% were Melan-A positive, 33% were CD117 positive, 31% were desmin positive, 11% were S100 positive, and 0% were cytokeratin positive. The spindle cells in PEComas are characterized by prominent smooth muscle–specific filaments, whereas the epithelioid component does not usually contain high numbers of such filaments. Most PEComas-NOS have been described in females, and therefore hormones may play a role in their pathogenesis and/or phenotypic cellular manifestations. Positive progesterone receptor (Figure 7) and estrogen receptor (Figure 8) expression, which has been reported primarily in the spindle cell component of PEComas, may play a role in the development of this morphologic pattern. Additionally, aggravation of LAM can occur during pregnancy or administration of estrogen, and estrogen receptor and progesterone receptor immunoreactivity has become negative in most cases of LAM after hormonal treatment.

The expression of CD117 has been evaluated in only 16 cases of PEComas to date. A total of 11 of these 16 cases showed consistently negative CD117 immunoreactivity. Of the 5 cases that showed positive CD117 immunoreactivity, 1 showed strong and diffuse expression, and 4 showed focal (20%–30% of tumor cells) expression. Strong and diffuse expression of CD117 in a reported case of PEComas highlights an important differential diagnostic problem between PEComa and gastrointestinal stromal tumor (GIST), since PEComa is a biphasic mesenchymal tumor with GIST–compatible morphology; hence, the suggestion that PEComa should be considered in the differential diagnosis of GIST. In cases of GIST with fewer than 50% of tumor cells being CD117 positive, the use of melanocytic markers is mandatory and might help to reach the correct diagnosis, since GISTs are negative for melanocytic markers. Negative immunoreactivity to CD99 and BCL-2 has been reported in a single case of PEComas to date. However, the clinicopathologic significance of the immunoreactivity status of CD117, myogenin, CD99, and BCL-2 in PEComa is not known. Malignant PEComas-NOS typically demonstrate a high proliferative index with Ki-67 immunostaining.

Electron Microscopic Features

Ultrastructural studies have documented abundant cytoplasmic glycogen, premelanosomes, thin filaments with occasional dense bodies, hemidesmosomes, and poorly formed intercellular junctions in PEComas.

Cytogenetic and Molecular Features

The cytogenetic features of PEComas have not been extensively studied to date. The few studies conducted have indicated loss of heterozygosity of the TSC2 gene on 16p13 to be the most common abnormality in both TSC-associated and sporadic cases of PEComa. The frequent deletion of 16p, in which the TSC2 gene is located, suggests an oncogenetic relationship of PEComas as a TSC2–linked neoplasm. From a molecular genetic perspective, the recurrent chromosomal alterations in both renal and extrarenal tumors further support the concept of PEComa as a distinctive tumor entity, regardless of anatomic location. Unlike the strong association between the TSC and AML, LAM, and CCST, only a few of the previously reported cases of PEComas-NOS were associated with TSC. Interestingly, 1 TSC patient with uterine PEComa-NOS had synchronous ovarian PEComa-NOS at presentation, and she was well without recurrence or metastasis at 6-month follow-up. Another TSC patient with uterine PEComa-NOS showed intra-abdominal “PEComatosis” with small foci of epithelioid cells detected in the lamina propria of the small intestine, myometrium, and ovarian hilum at surgery, but she was well without recurrence or metastasis at 35-month follow-up. These 2 rare occurrences in PEComa-NOS may be analogous to the multifocality and occasional lymph node involvement seen in renal AML and LAM.

Apart from the lack of association between the TSC and PEComas-NOS, which suggests that TSC1 and TSC2 genes do not appear to be important in the pathogenesis of most PEComas-NOS, little is known about the genes that may be involved in the pathogenesis of these tumors. Four malignant cases of PEComa-NOS arising in the colon and the thigh, elbow, and bladder have shown strong nuclear overexpression of cyclin D1 by immunohistochemistry. A total of 3 (colon, elbow, and bladder) of the 4 reported cases of PEComa-NOS that overexpressed cyclin D1 positivity showed a strong diffuse nuclear expression in both classic and overtly sarcomatous areas, whereas the other (thigh) was strongly positive only in the sarcomatous areas. Cyclin D1 is a cell cycle regulator necessary for the transition through the G1–S checkpoint. It is normally expressed transiently and may be constitutively expressed in other neoplasms, including lymphoma and melanoma. Sourcek and colleagues have shown that cyclin D1 abnormalities are associated with the loss of the TSC2 gene. However, the nuclear expression of cyclin D1 that was observed in more than 80% of neoplastic cells in the colonic PEComa-NOS case was not associated with the loss of heterozygosity of the TSC1 and TSC2 genes. This further supports the suggestion that TSC1 and TSC2 genes do not appear to be important in the pathogenesis of most PEComas-NOS. It suggests, however, that the overexpression of cyclin D1 may play a role in the tumorigenesis of PEComa, although the mechanism is not yet well understood and warrants further study.

DIFFERENTIAL DIAGNOSIS

The immunohistochemical and cytogenetic/molecular comparison of PEComa-NOS and its main differential diagnoses are summarized in the Table. The most difficult differential diagnosis of PEComa-NOS is epithelioid smooth muscle tumors (epithelioid leiomyosarcoma and epithelioid leiomyoma). Controversy exists regarding the minimum criteria for the diagnosis of malignant PEComa. In studies of uterine tumors demonstrating epithelioid morphology, clear cell areas, and HMB-45 positivity, some authors argued that these lesions represented epithelioid smooth muscle tumors with focal melanocytic differentiation and not PEComas. This view was based largely on the fact that the tumors looked like classic leiomyosarcomas with spindled and epithelioid areas, and stained with desmin. Nevertheless, some authors still advocated performing immunohistochemistry for HMB-45 in all uterine epithelioid smooth muscle tumors in order to identify patients who should be investigated for TSC. It is also noteworthy that only focal HMB-45 staining was seen in their cases, unlike the diffuse expression in nearly all of the reported cases of uterine PEComa. Other authors have reported uterine, cervical, and broad ligament epithelioid tumors with clear cell areas and HMB-45 pos-
cases labeling; with the TSC.6,7,9,10 Additionally, 31% of PEComas showed been described, tumors with S100 negativity, strong and diffuse melanocytic marker positivity, and actin immunoreactivity should be designated as PEComas based on morphology and immunophenotype. Pitfalls in the diagnosis of PEComas include aberrant staining of cells with melanocytic markers. However, diffuse and multiple melanocytic marker expression, which is not a finding in other sarcomas, is highly reliable for melanocytic differentiation and the diagnosis of PEComa. Focal or weak positivities can be disregarded, however, and do not warrant the diagnosis of PEComa. Angiomyolipoma can be ruled out because of a lack of lipomatous elements and biphasic cellular population. However, PEComa and monophasic epithelioid angiomyolipoma are probably very closely related, if not the same entity. Endometrial stromal sarcoma can be ruled out because of the presence of prominent perivascular accentuation of tumor cells and diffuse, rather than focal, positive staining of HMB-45. Perivascular epithelioid cell tumor can be distinguished from paraganglioma in that the former is negative for chromogranin A, synaptophysin, and S100 protein, and the latter shows more organoid growth. The expression of melanocytic markers (HMB-45 and MART-1/Melan-A) and the lack of immunoreactivity for cytokeratins and renal cell carcinoma marker argue against the diagnosis of carcinoma.

**CURRENT TREATMENT AND PROGNOSIS**

Clinically, most PEComas follow a benign course.1 Malignant PEComas-NOS are being increasingly reported, several originating in the uterus and others arising in the jejunum, prostate, pelvis, skull base, broad ligament, and somatic soft tissue.2 Specifically, 13 of the 38 reported cases

<table>
<thead>
<tr>
<th>Diagnostic Feature</th>
<th>PEComa-NOS</th>
<th>Epithelioid Smooth Muscle Tumor</th>
<th>Endometrial Stromal Sarcoma</th>
<th>Alveolar Soft Part Sarcoma</th>
<th>Malignant Melanoma and Melanoma of Soft Part</th>
<th>Carcinoma Undifferentiated NOS</th>
<th>Paraganglioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC marker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMB-45</td>
<td>+++</td>
<td>±</td>
<td>±</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Melan-A</td>
<td>+</td>
<td>±</td>
<td>−</td>
<td>NR</td>
<td>+++</td>
<td>−</td>
<td>±</td>
</tr>
<tr>
<td>S100</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>+++</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>MiTF</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>SMA</td>
<td>+++</td>
<td>+++</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>MSA/HHF-35</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Desmin</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Pancytokeratin</td>
<td>−</td>
<td>±</td>
<td>+++</td>
<td>−</td>
<td>−</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>EMA</td>
<td>−</td>
<td>±</td>
<td>+++</td>
<td>NR</td>
<td>±</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>AE1-AE3</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>CD31</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>−</td>
<td>NR</td>
</tr>
<tr>
<td>CD10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
<td>−</td>
<td>NR</td>
</tr>
<tr>
<td>CD117</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>+</td>
<td>−</td>
<td>±</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>±</td>
<td>NR</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chromogranin-A</td>
<td>−</td>
<td>NR</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characteristic cytogenetic finding</td>
<td>16p deletion</td>
<td>NCCF</td>
<td>NCCF</td>
<td>t(X;17)</td>
<td>t(12;22)†</td>
<td>NCCF</td>
<td>NCCF</td>
</tr>
</tbody>
</table>

* Compiled from cited references and Immunoquery (STATdx, PathIQ) database (http://www.immunoquery.com). IHC indicates immunohistochemical; MiTF, microphthalmia transcription factor; SMA, smooth muscle actin; MSA, muscle-specific actin; EMA, epithelial membrane antigen; +++, >75% of reported cases labeling; +, 50%–75% of reported cases labeling; + 25%–50% of reported cases labeling; ±, <25% of reported cases labeling; −, 0% of reported cases labeling; NR, not reported; and NCCF, no characteristic cytogenetic finding.

† Clear cell sarcoma of tendon and aponeurosis or melanoma of soft part only.
of uterine PEComas-NOS have exhibited locally aggressive behavior, and of these 13 showed distant metastases to liver, lungs, intestines, bone, and lymph nodes up to 7 years after resection of the uterine tumors.5–10,13 Since relatively few malignant PEComas have been reported, firm criteria for malignancy have yet to be established. However, Folpe and colleagues8 recently suggested criteria for malignancy, including a size greater than 8.0 cm, mitotic count of more than 1 per 50 high-power fields and necrosis, with benign, uncertain malignant potential, and malignant categories based on the presence of none, 1, or 2 or more of these 3 criteria, respectively. Infiltrative growth or edges, marked hypercellularity, and marked nuclear pleomorphism/atrophy may be secondary features suggesting aggressive behavior or malignancy.13,15 Isolated cases may show marked pleomorphism and overt sarcomatous areas and may mimic other sarcomas, especially pleomorphic myogenic sarcoma.14 These cases have the potential to behave in a malignant fashion.14 Most of the reported malignant PEComas contained areas of necrosis, and many showed a high mitotic index, although 2 cases (clear cell myomelanocytic tumor of the ligamentum teres15 and PEComa of the liver19) showing no histologic features of malignancy resulted in metastases. Perivascular epithelioid cell tumors with a Ki-67 labeling index of less than 1% have neither recurred nor metastasized.16 However, Ki-67 labeling of 5% of neoplastic cells has been observed in uterine PEComas that have behaved aggressively.7 Dimmler and colleagues have also reported late pulmonary metastases occurring 7 years after the diagnosis of a case of uterine PEComa.7 To our knowledge, the longest follow-up of a surviving patient with a malignant PEComa is 9 years.22 Additionally, there has been another report in which the PEComa was not recognized at initial presentation, and the diagnosis of PEComa was not made until the patient returned with a metastasis.7 Therefore, metastatic spread of PEComas may, in some cases, be a late complication, presenting after many years. This highlights both the need for criteria that more accurately predict the behavior of PEComas and the need for long-term follow-up of patients with PEComas, as widespread metastases may present as a late complication.

Optimal treatment for PEComas is not well established at this time. Currently, surgery is the mainstay of treatment for primary PEComa at presentation as well as for local recurrences and metastases, with the aim of obtaining clear resection margins. The role of adjuvant therapy remains unclear. Metastases have been successfully managed by resection alone. Primary excision is usually curative, as most PEComas are benign. However, locally advanced or metastatic disease portends a poor prognosis, and strategies incorporating chemotherapy and immunotherapy have been reported.10,20,21,30 Interferon α-2b therapy for the management of PEComa remains experimental.10 Partial, complete, and absent responses have also been noted for dacarbazine, vincristine, and imatinib mesylate (a tyrosine kinase inhibitor).10,20,21,30 Imatinib mesylate has been used as an effective treatment for chronic myelocytic leukemia and gastrointestinal stromal tumors. Additionally, there is continued interest in the testing of imatinib for such CD117-expressing cancers as ocular noma. However, a recent report demonstrated that this drug may not be effective in the treatment of malignant PEComa, despite CD117 expression.23 Admittedly, more investigations may be warranted, as 1 case is not sufficient to exclude an effect of imatinib mesylate in PEComa. A recent PEComa case report observed that the chemotherapy given did greatly reduce the vascularity but not the size of the tumor, making the subsequent definitive resection relatively bloodless.30 Given the uncertainty of PEComa tumor biology, adjuvant therapies, including chemotherapy and immunotherapy, may be considered for patients with locally advanced or metastatic PEComa.

References


25. Silva EG, Deavers MT, Bodurka DC, Malpica A. Uterine epithelioid leio-

myosarcomas with clear cells: reactivity with HMB-45 and the concept of PECo-


26. Simpson KW, Albores-Saavedra J. HMB-45 reactivity in conventional uter-


27. Hurrell DP, McCluggage WG. Uterine leiomyosarcoma with HMB45+


28. Harris GC, McCulloch TA, Perks G, Fisher C. Malignant perivascular epi-

