

Perivascular epithelioid cell (PEC) tumors of the uterus: a clinicopathologic study of two cases with aggressive features

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We report the clinicopathologic, immunohistochemical and ultrastructural features of two unusual tumors of the uterus composed of spindle and epithelioid cells strongly positive for HMB45. The two patients of 56 and 48 years of age had, respectively, hemoperitoneum and abnormal uterine bleeding. Morphologically, both tumors showed atypia and extensive necrosis. The neoplastic cells express immunohistochemically both melanogenesis (HMB45) and smooth muscle markers (actin). Ultrastructural analysis showed the presence of intracytoplasmic membrane-bound granules. We viewed these neoplasms as perivascular epithelioid cell (PEC) tumors with aggressive features. Follow-up has shown the death of one patient whereas the other is alive without disease 36 months after the surgery. The two patients were evaluated for signs of tuberous sclerosis complex, and findings were negative.

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The recent literature has paid considerable attention to tumors exhibiting an immunophenotype consistent with a perivascular epithelioid cell (PEC) differentiation¹ characterized by actin and HMB45 immunoreactivity and its association with the tuberous sclerosis complex (TSC).² These neoplasms have a broad spectrum of morphology and behavior and may involve the kidney, lung, liver, pancreas, common bile duct, jejunum, rectum, falciform ligament of the liver, heart, urinary bladder, prostate, breast, bone, soft tissues^{3–10} and female genital tract organs,^{11,8} among which the uterus is the most frequently involved.^{3,4,12–19} In this site, most of these tumors are benign or of uncertain malignant potential,^{4,13,16,19} although rare malignant cases have been reported.^{3,12,14,15,17,18}

We report the clinicopathologic features of two perivascular epithelioid cell tumors ('PEComa')

of the uterus with aggressive features, including one malignant and one with uncertain malignant potential.

Case reports

Case 1

A 59-year-old female without clinical or family history of TSC was admitted to the hospital for abdominal pain and hemorrhagic shock. Abdominal ultrasonography revealed the presence of a uterine tumor. Surgical findings included evidence of uterine rupture and hemoperitoneum with some necrotic neoplastic fragments free in the abdominal cavity. The patient was treated with total abdominal hysterectomy, bilateral salphingo-oophorectomy and omentectomy. Exploration of the upper abdominal cavity was negative. At 6 months after surgery, the tumor recurred as a 5 cm left pelvic mass and a fine-needle biopsy of the lesion was performed. At 1 year after diagnosis, the patient developed neoplastic cachexia and died. Autopsy was not performed.

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Case 2

A 48-year-old female without clinical or family history of TSC with frequent menometrorrhagia, which was considered due to a leiomyomatous uterus on the base of clinical and ultrasonographic findings. Endometrial curettage was unremarkable. Subsequently, the patient underwent therapy with GnRH analogues for 9 months and 3 months later she was readmitted to the hospital because of a further vaginal bleeding and a total abdominal hysterectomy was performed. Tamoxifen therapy was performed and the patient is alive and well without evidence of disease 36 months after surgery.

Materials and methods

Histopathology and Immunohistochemistry

The two cases we describe are from the files of the Istituto di Anatomia Patologica of Sassari University, Italy. Tissue specimens were fixed in formalin (10%) for 24–48 h and routinely processed for paraffin embedding. The original sections were examined, and new sections were prepared from the blocks and stained with hematoxylin–eosin and immunohistochemically with the avidin–biotin method and a panel of antibodies recognizing the following molecules: vimentin (Amersham, Buckinghamshire, England; dilution 1:10), CD34 (Biogenex; 1:50), CD31 (Dakopatts; Denmark, 1:60), cytokeratin AE1/AE3 (Boehringer, Mannheim, Germany; 1:500), cytokeratin CAM5.2 (Becton Dickinson, Mountain View, CA, USA; 1:10), Epithelial Membrane Antigen (EMA) (Dakopatts; Denmark, 1:100), Chromogranin (Dakopatts; Denmark, 1:300), HMB-45 (gp100 protein; Dakopatts; Denmark, 1:40), Melan A (Dakopatts; Denmark 1:25), S100 protein (Dakopatts; Denmark, 1:500), Calretinin (Swant; Switzerland, 1:4000), desmin (D33; Dakopatts; Denmark, 1:500), smooth muscle actin (1A4; Dakopatts; Denmark, 1:100), estrogen receptor (Abbot Lab, Wiesbaden, Germany, undiluted) and progesterone receptor (Abbot Lab, Wiesbaden, Germany, 1:5).

Sections of the two tumors were immunostained using multiple marker procedures. They were consecutively tested for HMB45 and actin and for Melan A and CD34, utilizing double peroxidase immunostaining, followed by alkaline-phosphatase immunostaining.

A total of 34 mesenchymal tumors of the uterus from the files of the Istituto di Anatomia Patologica of Sassari University were compared with the study tumors.

Ultrastructure

Formalin-fixed tissue from case 2 was washed extensively in phosphate buffer, fixed in 2%

glutaraldehyde in phosphate buffer for 2 h, postfixed in 1% aqueous osmium tetroxide supplemented with 1% potassiumferryanide for 1 h, dehydrated through graded alcohols, and embedded in a mixture of Epon and Araldite.

Ultrathin sections were obtained with an Ultracut E ultramicrotome (Reichert-Jung, Wien, Austria) and diamond knife, stained with uranyl acetate and lead citrate, and evaluated with a Zeiss EM 109 (Oberkochen, Germany) electron microscope.

DNA Extraction and LOH Analysis

DNA from 5 μ m histologic sections of the paraffin-embedded PEC tumor of the uterus of patient 2 was extracted as previously described²⁰ (Carbonara *et al*, 1996). DNA from peripheral blood leucocytes was extracted according to standard methods (Sambrook and Russel, 2001).²¹ The chromosome 16 *TSC2*-linked markers tested were HBAP1, D16S525, D16S3024, KG8 and D16S291 (*TSC2* lays between D16S3024 and KG8). On chromosome arm 9q, the *TSC1*-linked markers used from centromere to telomere were D9S149, D9S2127, D9S1830 and D9S1998 (*TSC1* lays between D9S1830 and D9S1998). References for the microsatellite markers used can be found in the genome data base (GDB). Polymerase chain reaction (PCR) was performed by using fluorescent primers. In all, 5 μ l aliquots were amplified in a 30 μ l reaction containing 10 mM Tris, pH 8.3, 50 mM KCl, 200 μ M of dNTP, 1–2 mM MgCl₂, 12 pmol of each primer and 1 U AmliTaq Gold polymerase. All fluorescent PCR products were analyzed by electrophoresis on 377 automated DNA sequencer (Perkin Elmer/Applied Biosystems). Microsatellite analysis was performed using the GENSCAN software (Perkin Elmer/Applied Biosystems).

Pathologic findings

Gross Pathology

Case 1

The uterus measured 13 × 8 × 9 cm³ and showed a 6 cm ruptured subserosal mass. On cut section, the tumor was spongy, hemorrhagic, ill defined, with necrotic areas and involved the myometrium. The cervix, both ovaries and fallopian tubes were grossly unremarkable.

Case 2

The uterus measured 11 × 9 × 5 cm³ and displayed a polypoid, intracavitary, ulcerated, mass of 7 cm in diameter. On cut surface, the tumor was white–grey with central necrosis and hemorrhagic areas and infiltrating the myometrium (Figure 1).

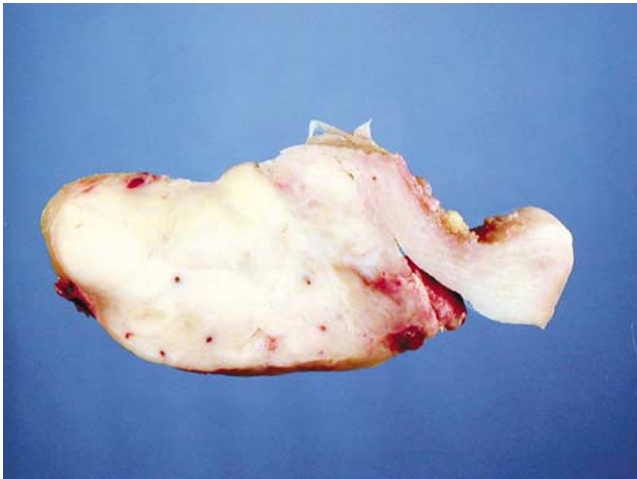


Figure 1 Grossly the tumor of case 1 was a polypoid, ulcerated mass white-gray in color.

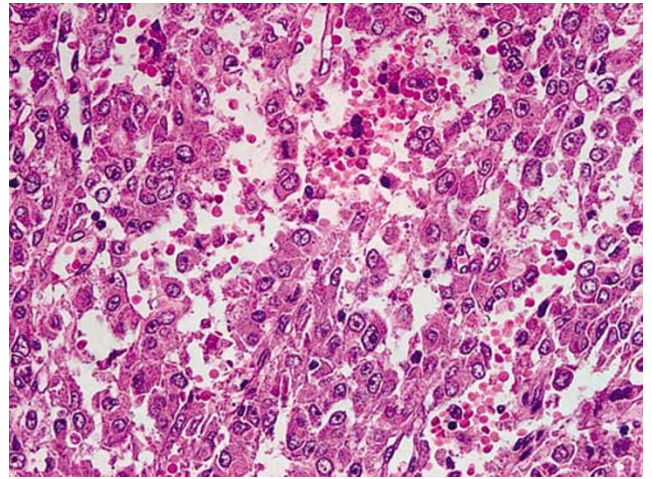


Figure 2 Case 1. Area of epithelioid cells with large eosinophilic cytoplasm and evident nucleoli.

Microscopic Pathology

Case 1

The tumor had areas of dense cellularity organized in short fascicles of epithelioid and spindle cells with a large eosinophilic or clear cytoplasm arranged around thin walled vascular structures with a prominent lymphangiomyomatous pattern. The nuclei of the neoplastic cells were round or oval, hyperchromatic and displayed evident nucleoli (Figure 2). Rare plurinucleated cells were seen. Mitotic figures were rare (1x10 HPF) whereas large areas of tumor cell necrosis were evident.

The fine-needle biopsy of the pelvic mass showed morphological features overlapping those of the uterine neoplasm.

Case 2

The lesion was composed of a solid epithelioid cell population showing eosinophilic cytoplasm and elongated nuclei with prominent nucleoli. Scattered plurinucleated cells were identified. Cytologic atypia, numerous mitoses (5x10 HPF), infiltration of myometrium and necrotic areas were present.

Immunohistochemical Findings

Immunohistochemical results were the same for both tumors and the pelvic recurrence of case 1. The neoplastic cells revealed a strong immunoreactivity ranging from 90% in case 1 to 30% in case 2 for HMB45, whereas Melan A was expressed in 80% of the cells of case 1 and was negative in case 2. The immunostaining for smooth muscle actin was found in 5% of the neoplastic cells of case 1 and in 40% of case 2. The double immunostaining for HMB45 and actin highlighted the coexpression of these markers in some neoplastic cells (Figures 3 and 4). Desmin, estrogen receptors and progesterone receptors were, respectively, expressed in 10, 50 and 60% of the

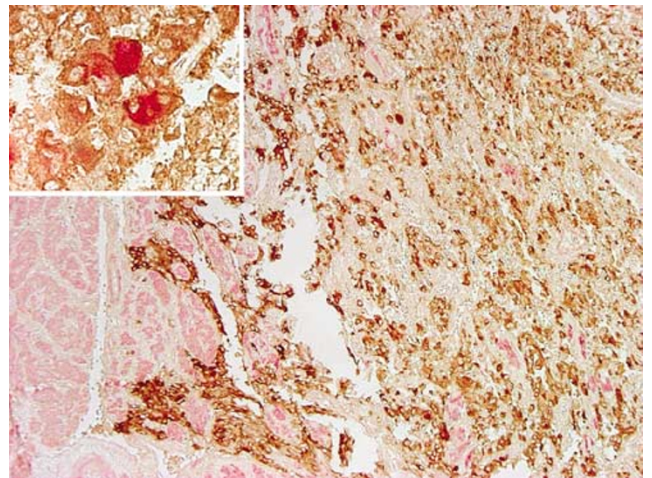


Figure 3 Case 1. A double immunostaining which showed in red (alkaline phosphatase) the actin immunoreactivity of the myometrium and in brown (peroxidase) the HMB45 granular positivity in the tumor. At high power, the coexpression of both markers in the cytoplasm of the neoplastic cells was evident (inset).

neoplastic cells of case 2, whereas AE1/AE3 and CAM 5.2 cytokeratins, EMA, chromogranin, vimentin, S100, CD31 and CD34 were consistently negative in both tumors.

The myometrium harboring the tumors was positive for actin and desmin, but negative for HMB45 and Melan A in both cases.

All the mesenchymal tumors including 16 leiomyomas (three classic, six highly cellular, two atypical, four epithelioid, one mixoid), 10 leiomyosarcomas (five classic, four mixoid, one epithelioid) and eight endometrial stromal tumors (two endometrial stromal nodules, three endometrial stromal sarcoma, low grade, two undifferentiated endometrial sarcoma and one mixed endometrial stromal and smooth muscle tumor) were negative for HMB45 immunostaining.

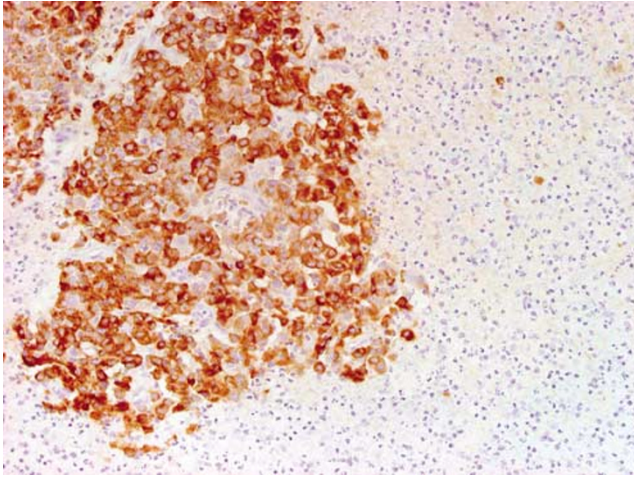


Figure 4 Fine-needle biopsy obtained from the pelvic recurrence of case 1. The HMB45 immunostaining was positive in all the fragments of the neoplastic tissue.

Ultrastructural Analysis

Ultrastructural analysis of case 2 performed in formalin-fixed material revealed the presence of numerous electron-dense, membrane-bound granules in the cytoplasm, some of which resembled premelanosomes and abundant microfilaments with dense bodies, suggesting a smooth muscle origin of the proliferating cells.

Genetic Findings

The PEC tumor of the uterus from patient 2 was analyzed for loss of heterozygosity at *TSC1* and *TSC2*-linked markers. DNA extracted from peripheral blood leucocytes and from normal endometrium was available as control of the germline genotype. All microsatellites analyzed on 16p were informative. No LOH was observed either at the *TSC1* or at the *TSC2* locus.

Discussion

The 'perivascular epithelioid cell' (PEC) is the descriptive term, first proposed by Bonetti *et al*¹ to identify a 'novel' cell type, which coexpresses melanogenesis and smooth muscle markers. Neoplasms with perivascular epithelioid cell differentiation are called PEComas and are defined as mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells.^{22,23} This family of tumors includes renal and extrarenal angiomyolipoma,^{23,9,5-7} pulmonary and extrapulmonary clear cell 'sugar' tumor^{25,4,8,10} pulmonary and extrapulmonary lymphangioliomyomatosis,²⁵⁻²⁷ clear cell myomelanocytic tumor of ligamentum teres⁴ and abdominopelvic sarcoma of PEC.³ Recently, these tumors

have been also described in the breast, urinary bladder, prostate gland, jejunum, common bile duct and in the soft tissues of the thigh.⁴

PEC proliferations can rarely involve the female genital tract. The first case reported by Pea *et al*¹⁶ was a polypoid tumor involving the endometrium, which showed morphological features closely related to the clear cell 'sugar' tumor of the lung. Vang and Kempson¹⁹ described eight examples of uterine perivascular epithelioid cell tumor ('PEComa') distinguishing 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 referred to as group B. A tumor with a strong and diffuse HMB45 expression morphologically corresponding to an epithelioid angiomyolipoma has been reported in the ovary.¹¹ Finally, one case described as primary extrapulmonary sugar tumor of the vulva has been reported by Tazelaar *et al*.⁸ Lesions considered to be uterine involvement of lymphangioliomyomatosis were usually asymptomatic and some of them corresponded to an incidental finding in patients bearing stigmata of TSC.²⁸⁻³⁰

The spectrum of the morphological features of the neoplasms with perivascular epithelioid cell differentiation is very broad with a great variation in the relative proportion of spindle and epithelioid cells arranged in a perivascular location with a solid or a lymphangioliomyomatous pattern. Both patterns of growth have been described in tumors arising in the uterus.^{15,17,19} The perivascular epithelioid cell tumors of the uterus have usually shown benign behavior.^{13,16,19} but eleven tumors, two of them associated with TSC, were aggressive (Table 1).

We consider our two cases as PEComas since one of them exhibited a lymphangioliomyomatous architecture and the other had an ultrastructural evidence of electron-dense membrane-bound granules associated with smooth muscle differentiation, characteristic of perivascular epithelioid cells. Moreover, both neoplasms were immunoreactive for HMB45 and actin. Both tumors showed aggressive histologic features such as severe cytologic atypia, the mitotic activity (case 2) and the large necrotic areas. We view case 1 as malignant because of the recurrences and death due to the disease, whereas we define case 2 as PEComa with uncertain malignant potential because of the aggressive histologic features previously described.

In regard to morphologic criteria of malignancy in PEComas, some features such as nuclear atypia, number of mitoses and presence of necrosis have been taken into consideration, although none of them seem to be significantly related to malignant behavior. Folpe *et al*¹² reported 24 cases of PEComas of soft tissues and gynecologic origin,

Table 1 Review of literature of malignant PEC tumors of the uterus

Cases	Age (years)	Symptoms	Site	Histology	TSC	Treatment	Follow-up
Gyure (95)	29	Pelvic mass	Myometrium	LAM-like	+	S, CH, RT	Died for metastatic ovarian carcinoma, 12 mo
Ruco (98)	56	Abdominal pain	Myometrium and right ovary	LAM-like	-	S	Alive with local recurrence, 84 mo
Bonetti (01)	19	Abdominal pain	Lower uterine segment	Epithelioid	-	S, CH, RT	NA
Bonetti (01)	41	Abdominal mass	Subserosal myometrium	Epithelioid	+	S	NED, 6 mo
Dimmler (03)	61	Abnormal uterine bleeding	Subserosal myometrium	Epithelioid	-	S	Alive with lung metastases, 84 mo
Greene (03)	79	Abdominal pain	Uterine fundus and pelvis	Epithelioid	-	S, CH	Local recurrence and DOD, 24 mo
Silva (04)	82	Abdominal pain, vaginal bleeding	Uterus and pelvis	Epithelioid	-	S	DOD 32 mo
Silva (04)	47	Abnormal uterine bleeding	Uterus	Epithelioid	-	S, CH, RT	Lung metastases and DOD, 30 mo
Silva (04)	76	Pelvic mass	Subserosal myometrium and pelvis	Epithelioid	-	S, RT	NED, 8 mo
Silva (04)	73	Abdominal pain	Uterus	Epithelioid	-	S, CH	Lung metastases and DOD, 9 mo
Silva (04)	43	Abnormal uterine bleeding	Uterus	Epithelioid	-	S, CH	Alive with lung metastases, 6 mo
Present	56	Hemoperitoneum	Subserosal myometrium	LAM-like	-	S	Local recurrence and DOD, 12 mo
Present	48	Abnormal uterine bleeding	Subendometrial myometrium	Epithelioid	-	S, TX	NED, 36 months

TSC = tuberous sclerosis complex; S = surgical; CH = chemotherapy; RT = radio therapy; TX = tamoxifen; NA = not available; DOD = died of disease; NED = no evidence of disease; mo = months.

concluding that these tumors can be benign or malignant and their malignancy is correlated with large size in the face of any level of mitotic activity and necrosis.³¹

Many entities should be considered in the differential diagnosis with neoplasms with perivascular epithelioid cell differentiation of the uterus. Clear and oxyphilic carcinomas show a characteristic positivity for cytokeratins, which is absent in PEComas. Endometrial stromal sarcomas are not immunoreactive for HMB45.^{32,19} Metastatic melanoma and the rare melanocytic differentiation found in carcinosarcomas³³ show S100 and HMB45 positivity in contrast with PEC tumors that are negative for the S100 protein. PEComas can be difficult to differentiate from clear and epithelioid smooth muscle tumors³⁴ but these entities are negative for HMB45.¹⁹ Leiomyosarcoma is usually negative for estrogen and progesterone receptors,³⁵ which can be expressed in PEComas as it occurred in our case 2.

Benign and malignant smooth muscle tumors have been described to arise spontaneously in Eker rats, which are considered the animal model of the TSC. Most of these neoplasms were typical leiomyoma whereas a subset of these were atypical showing an epithelioid morphology.³⁶ Although more cases need to be studied, the uterine HMB45-positive tumors that we describe in this study could

represent the human counterpart of the leiomyoma and leiomyosarcoma of the Eker rats.

We suggest that HMB45 immunostaining should be performed on uterine mesenchymal tumors with lymphangiomyomatous pattern or with clear and epithelioid features to identify PEC tumors and we believe that their identification warrants the examination of the patient for the stigmata of TSC.

The absence of LOH for TSC1 and TSC2 gene in the neoplastic cells of the case 2 is in accord with the fact that the 50% of tumors occurring in patients with TSC are negative with this analysis²⁰ and we think that other cases should be tested to accurately evaluate this issue.

Some authors suggest avoiding the use of the term PEComa and to maintain the old terminology, such as epithelioid leiomyosarcoma with clear cells, for practical reasons.¹⁸ We agree with them for lesions related to PEC, which have been extensively described in their clinicopathological features and are known with well-established names by clinicians and pathologists, for example, angio-myolipoma and lymphangioliomyomatosis; however, we think that the use of the term PEComa for all the other lesions should be encouraged to try to accumulate new clinicopathologic and genetic data regarding these peculiar lesions to better define them and their relationship with TSC.

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