American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2016; 17: 309-314
DOI: 10.12659/AJCR.896401

Received: 2015.10.22
Accepted: 2016.02.01
Published: 2016.05.06

Perivascular Epithelioid Cell Tumor of the Uterus with Ovarian Involvement: A Case Report and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 Megan Fitzpatrick
E 2 Tanya Pulver
E 1 Molly Klein
E 1 Paari Murugan
ADE 1 Mahmoud Khalifa
ABDE 1 Khalid Amin

1 Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, U.S.A.
2 Department of Obstetrics, Gynecology and Women's Health, University of Minnesota, Minneapolis, MN, U.S.A.

Corresponding Author: Khalid Amin, e-mail: kamin@umn.edu
Conflict of interest: None declared

Patient: Female, 61
Final Diagnosis: Uterine PEComa with ovarian involvement
Symptoms: Palpable abdominal mass
Medication: —
Clinical Procedure: Hysterectomy and bilateral salpingo-oophorectomy
Specialty: Obstetrics and Gynecology

Objective: Rare disease

Background: Perivascular epithelioid cell tumors (PEComas) are a rare group of neoplasms composed of epithelioid cells that express both melanocytic and myoid markers. When considering PEComas of the female genital tract, the uterus is the most common location. Involvement of the ovary in the context of a primary uterine PEComa, in the absence of systemic disease associated with tuberous sclerosis, however, has only been reported in 1 previous case.

Case Report: We report a case of a PEComa of the uterus with metastasis to the left ovary in a 61-year-old Caucasian woman. Gross examination of the uterus revealed a 10.7×10.5×10.2 cm tan-brown, mostly solid, partially cystic mass. Microscopic examination showed epithelioid cells with clear to eosinophilic cytoplasm, arranged in fascicles. Intranuclear pseudoinclusions were also noted. The tumor cells were smooth muscle actin, caldesmon, and desmin positive (diffuse); HMB-45 positive (focal); and Melan-A, AE1/AE3, CD10, and S100 negative by immunohistochemistry.

Conclusions: Distinguishing among mesenchymal neoplasms, including PEComas, endometrial stromal sarcomas, and leiomyosarcomas, can be difficult. Careful analysis of morphologic and immunohistochemical features is of the utmost importance. Differential diagnosis, including morphologic features and immunohistochemical patterns, is also discussed.

MeSH Keywords: Ovarian Neoplasms • Perivascular Epithelioid Cell Neoplasms • Uterine Neoplasms

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/896401

Background

Perivascular epithelioid cell tumors (PEComas) are a rare group of mesenchymal neoplasms composed of epithelioid cells, in a perivascular distribution, that express both melanocytic and smooth muscle markers and contain eosinophilic to clear granular cytoplasm. PEComas can occur at any anatomic site and include angiomyolipomas, lymphangioleiomyomatosis, clear cell "sugar" tumors of the lung, and PEComa not otherwise specified [1–5].

In the female genital tract, the uterus is the most common location for PEComas, with 78 reported cases to date [6]. Ovarian PEComas are exceptionally rare, with only 1 reported primary case [7] and 6 reports of PEComa metastatic to the ovaries [8–13]. Four of these 6 metastatic cases were associated with tuberous sclerosis and had multiorgan involvement including the ovary [8-11]. Of the 2 remaining cases that were not associated with tuberous sclerosis, one reported a jejunal PEComa with metastasis to the pelvic wall and ovary [12] and the other described a primary uterine PEComa with involvement of the ovary [13]. Here, we report the second published case of a primary uterine PEComa with involvement of the left ovary in a 61-year-old woman.

Case Report

A 61-year-old Caucasian woman presented with a 3-month history of a firm, nontender enlargement of the abdomen and a palpable abdominal mass in the absence of other gastrointestinal or genitourinary symptoms. At the time of her annual examination, 7 months previously, she had no symptoms and no palpable mass. The patient had no history of tuberous sclerosis. Her past medical history included leiomyomas with endometrial ablation at age 47. Her family history was significant for a mother with breast cancer diagnosed at age 59. Physical examination showed a firm, irregular, and enlarged uterus. A pelvic ultrasound identified a 10.5×9×12 cm mass adjacent to the superior aspect of the uterus, and computed tomography (CT) of the pelvis characterized the mass as complex, cystic, and with septations. Serologic evaluation, including a complete blood count, comprehensive metabolic panel, and CA-125 study, was remarkable only for a mild anemia with a hemoglobin of 11.6 g/dL.

The patient underwent hysterectomy and bilateral salpingo-oophorectomy. Macroscopic examination of the uterus showed a 10.7×10.5×10.2 cm solid, tan-brown mass in the fundus. The mass was partially filled with blood-tinged fluid and was coarsely trabeculated. No gross abnormalities of the fallopian tubes or ovaries were noted. The intraoperative diagnosis was determined to be a low-grade spindle-cell mesenchymal lesion.

A follow-up positron emission tomography/CT scan, performed approximately 6 months after tumor resection, was negative for tumor recurrence and metastatic disease.

On microscopic examination, the uterine tumor was densely cellular, with epithelioid cells arranged in fascicles. Moderate nuclear atypia was also present with 1 to 2 mitotic figures per 10 high-power field (HPF). The tumor was biphasic in nature and without necrosis. Some cells contained a clear-granular cytoplasm, whereas others had an eosinophilic cytoplasm. A vascular network was also evident, with cells arranged radially around blood vessels. Many intranuclear pseudoinclusions were also present (Figure 1). The tumor exhibited pushing borders into the myometrium. Tumor cells of the same morphology were also present in the left ovary (Figure 1).

Immunohistochemistry indicated that tumor cells were caldesmon, smooth muscle actin (SMA), and desmin positive (diffuse, Figure 1), as well as focally positive for melanoma-associated antigen (HMB-45). Tumor cells were cytokeratin AE1/AE3, CD10, Melan-A, and S-100 negative.

Discussion

In this study, we report a case of a uterine PEComa with left ovarian involvement in the absence of systemic disease associated with tuberous sclerosis. The patient had minimal symptoms and was found to have a uterine mass by CT scan. The tumor was characterized by epithelioid cell morphology, with cells radiating around a delicate capillary network and possessing a clear to eosinophilic cytoplasm. Cells with spider cell-like morphology and cells containing intranuclear pseudoinclusions were also identified. Tumor cells exhibited moderate atypia, including variability in size and shape, and frequent prominent nucleoli. Immunohistochemistry revealed expression of the melanocytic marker HMB-45 and the smooth muscle markers SMA, desmin, and caldesmon. These morphologic features and the immunohistochemical staining pattern supported a diagnosis of PEComa.

In the only other reported case of primary uterine PEComa with ovarian involvement, the patient had vaginal bleeding and was found to have a large uterine mass by CT scan [11]. The mass was significantly larger than in the current case, measuring 30×27×18 cm in comparison with 10.7×10.5×10.2 cm. On microscopic examination, tumor cells displayed similar morphology to cells in the tumor of the current case (Table 1). The tumor was also composed of epithelioid cells containing clear to eosinophilic cytoplasm and arranged in fascicules. Immunohistochemistry was similar as well, with cells showing positive reactivity to both melanocytic and smooth muscle markers including HMB-45, SMA, and caldesmon [11].

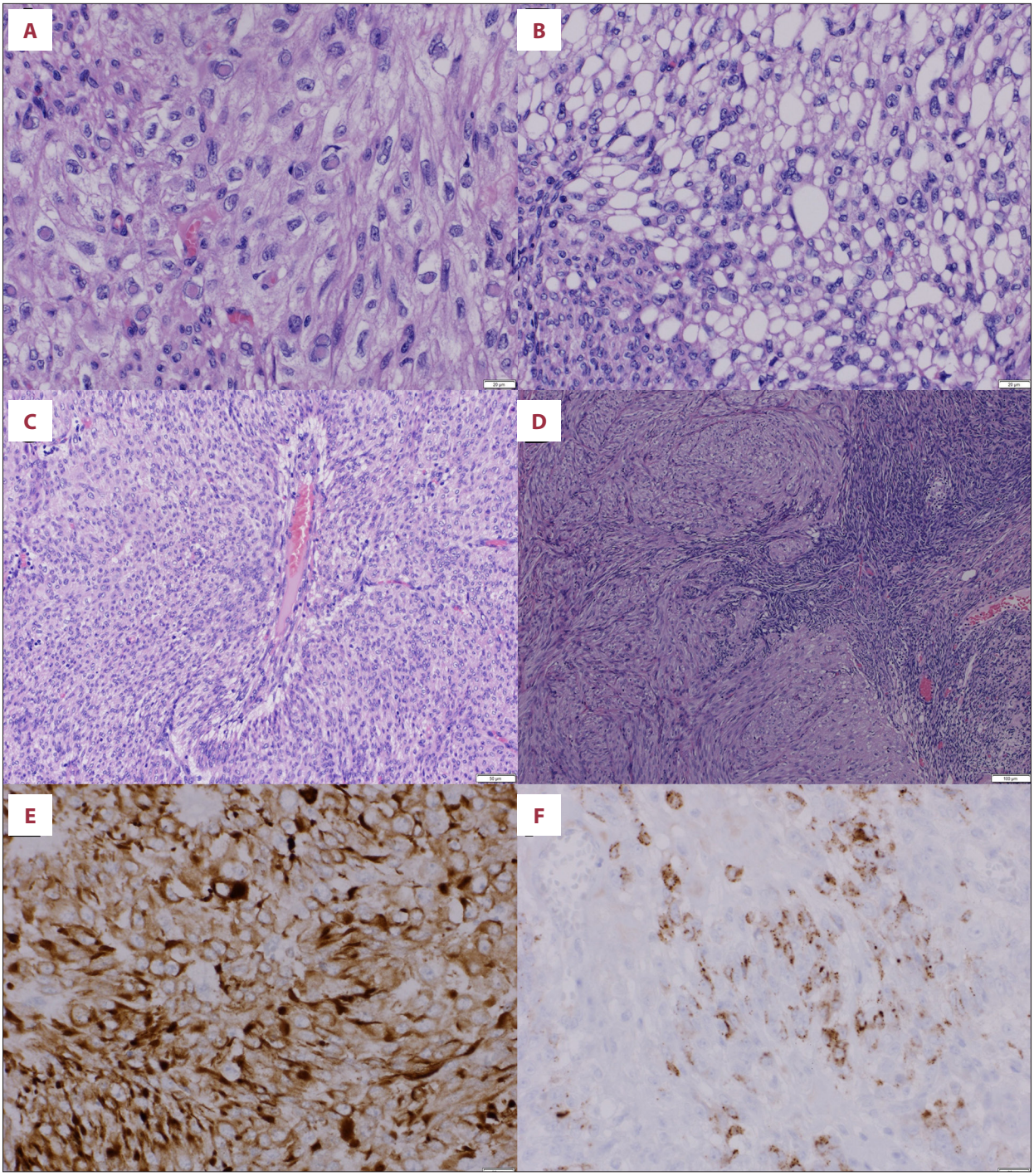

Figure 1. Histopathological features of a uterine perivascular epithelioid cell tumor. (**A**) Tumor is composed of epithelioid cells, with eosinophilic cytoplasm, prominent nucleoli, and mild to moderate variation in size and shape. Prominent nuclear pseudoinclusions are also present. *White bar=20 µm.* (**B**) Epithelioid cells with clear, granular cytoplasm. *White bar=20 µm.* (**C**) Tumor contained delicate capillary network with epithelioid cells radiating around lumen. *White bar=50 µm.* (**D**) Left ovarian involvement of epithelioid cell tumor. *White bar=100 µm.* (**E**) Diffuse positive reactivity for desmin. (**F**) Focal reactivity for HMB-45. *White bar=20 µm.*

Table 1. Summary of clinicopathologic features of primary uterine PEComas with ovarian involvement.

	Current case	Fukunaga (2005)
Age at presentation, y	61	40
Symptoms	Palpable abdominal mass	Vaginal bleeding
Size, cm	19.7×10.5×10.2	30×27×18
Location	Uterus, left ovary	Uterus, right ovary, omentum
Epithelioid cells	Present	Present
Spindle cells	Present	Present
Multinucleated giant cells	Present	Not noted
Capillary network	Present	Present
Clear cells	Present	Present
Eosinophilic cells	Present	Present
SMA immunopositivity	Diffuse	Focal
Caldesmon immunopositivity	Diffuse	Diffuse
HMB-45 immunopositivity	Focal	Focal

Table 2. Morphologic and immunohistochemical characteristics of mesenchymal neoplasms of the female genital tract.

Feature	PEComa	Leiomyosarcoma	ESS	References
Epithelioid cells	Usual	Rarely	+/–	[6,18,22]
Spindle cells	Usual	Usual	Usual	[6,18,22]
Multinucleated giant cells	Usual	Usual	Absent	[6,18,22]
Capillary network	Usual	Absent	Usual, but no radiation	[6,18,22]
Clear cells	Usual	Occasional	+/–	[6,18,22]
Eosinophilic cells	Usual	Usual	+/–	[6,18,22]
Islands of endometrial tissue	Absent	Absent	Usual	[18]
Desmin immunopositivity	63%	86%	50%	[6,21,24]
SMA immunopositivity	80%	100%	63%	[6,18,21]
HMB-45 immunopositivity	99%	36%	24%	[6,9,18]
CD10 immunopositivity	14%	50%	96%	[6,18,20,21]

The term *perivascular epithelioid cell tumor* was introduced in 1992 [14] and in 2002 the World Health Organization defined PEComas as mesenchymal tumors composed of perivascular epithelioid cells that express both melanocytic and smooth muscle markers [15]. The origin of PEComas is unknown, but it has been hypothesized that these tumors arise from neural crest stem cells and possess the ability to differentiate into both myoid and melanocytic cells [6,16]. To date, there have been 78 reported cases of uterine PEComas, the most common site in the female genital tract.

PEComas express both melanocytic and smooth muscle markers. In a recent review HMB-45 was found to be the most common melanocytic marker of uterine PEComas, with positive results in 99% (77/78) of reported cases [6]. Additionally, SMA was determined to be the most common smooth muscle marker, with positive results in 80% (53/68) of uterine PEComas. In the current case, the tumor was focally positive for HMB-45 and diffusely positive for SMA.

When considering a mesenchymal neoplasm of the uterus, leiomyosarcoma, endometrial stromal sarcoma (ESS), and

PEComas must all be considered. Distinguishing among these can be challenging and requires both morphologic and immunohistochemical evidence for diagnosis (Table 2). Morphologic features such as the identification of a capillary network are of particular importance in distinguishing between mesenchymal neoplasms. Leiomyosarcomas lack a capillary network, and although a capillary network is often present in ESS, the capillaries lack the radial appearance of epithelioid cells characteristic of PEComas [17]. Although PEComas are most commonly positive for melanocytic markers, cases of both leiomyosarcoma and ESS tumors expressing HMB-45 have been reported [18,19]. However, the absence of CD10 expression can provide evidence against ESS, which has been shown to express CD10 in 96% of cases. In contrast, CD10 expression is rare in both PEComas and leiomyosarcomas [6,18,20,21].

The age of patients affected by uterine PEComas varies widely from 9 to 79, with an average age of 45 [6]. Presenting symptoms are often vague and include postmenopausal or abnormal bleeding and abdominal pain. In the current case, the only presenting symptom was a palpable abdominal mass. Although PEComas are often benign, there have been reported cases of malignant tumors. To distinguish between benign and malignant uterine PEComas, the Folpe criteria are often used [22]. According to the Folpe criteria, a tumor is considered malignant if it contains at least 2 worrisome features, defined as size of at least 5 cm, high nuclear grade and cellularity, a mitotic rate of at least 1 per 50 HPF and necrosis or vascular invasion. In 2015, a modification of the Folpe criteria was proposed, defining malignant tumors as those containing any necrosis or at least 1 worrisome feature, defined as an invasive edge, size of at least 5 cm, a mitotic rate of at least 2 to 3 per 50 HPF, and lymphovascular invasion [6].

In the current case, we determined the PEComa to be of aggressive potential because moderate nuclear atypia was present, the size was greater than 5 cm, and the mitotic rate was greater than 1 mitotic figure per HPF, thus fulfilling both the Folpe and the modified Folpe criteria. The left ovarian metastasis also supported a diagnosis of malignancy. The most common sites of metastasis of PEComas are lung, followed by liver, lymph nodes, and peritoneum [23]. In contrast, PEComa metastasis to the ovaries is rare, with only 6 reported cases, the majority of which have been associated with multiorgan involvement in the context of tuberous sclerosis [8–13]. To our knowledge, this is only the second reported case of a primary uterine PEComa with ovarian involvement in the absence of tuberous sclerosis. The clinical consequences of ovarian involvement are still unknown. In the current case, the patient underwent resection of all gross disease by total hysterectomy and bilateral salpingo-oophorectomy; however, recurrence may still be a possibility.

There is no established treatment protocol for uterine PEComas. Hysterectomy is the current treatment of choice, but long-term outcomes remain unclear. As a result, close follow-up is necessary for all patients diagnosed with PEComas and is especially important for those diagnosed with PEComas of malignant potential.

Conclusions

PEComas are a rare group of neoplasms that are difficult to differentiate from other mesenchymal tumors. Careful examination of morphologic features and immunohistochemistry are necessary for accurate diagnosis. Of PEComas occurring in the female genital tract, the uterus is the most common location; involvement of the ovaries is quite rare. No established therapy protocol exists, and additional research is needed to determine the best treatment for these neoplasms.

Statement

Sources of funding: No grants funded this work. Conflicts of interest: None.

References:

1. Pea M, Bonetti F, Zamboni G et al: Melanocytic-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney. Pathology, 1991; 23: 185–88
2. Ashfaq R, Weinberg AG, Albores-Saavedra J: Renal angiomyolipomas and HMB-45 reactivity. Cancer, 1993; 71: 3091–97
3. Bonetti F, Pea M, Martigoni G et al" Clear cell ("sugar")" tumor of the lung is a lesion strictly related to angiomyolipoma – the concept of a family of lesions characterized by the presence of the perivascular eptihelioid cells (PEC). Pathology, 1994; 26: 230–36
4. Zamboni G, Pea M, Martignoni G et al: Clear cell "sugar" tumor of the pancreas. A novel member of the family of lesions characterized by the presence of perivascular epithelioid cells. Am J Surg Pathol, 1996; 20: 722–30
5. Pea M, Martignoni G, Zamboni G, Bonetti F: Perivascular epithelioid cell. Am J Surg Pathol, 1996; 20: 1149–53
6. Conlon N, Soslow RA, Murali R: Perivascular epithelioid tumours (PEComas) of the gynaecological tract. J Clin Pathol, 2015; 68: 418–26
7. Lee SE, Yoon-La C, Junhun C et al: Ovarian perivacular epithelioid cell tumor not otherwise specified with transcription factor E3 gene rearrangement: a case report and review of the literature. Huma Pathol, 2012; 43: 1126–30
8. Bonetti F, Martignoni G, Colato C et al: Abdominopelvic sarcoma of perivascular epithelioid cells. Report of four cases in young women, one with tuberous sclerosis. Mod Pathol, 2001; 14: 563–68
9. Froio E, Piana S, Cavazza A et al: Multifocal PEComa (PEComatosis) of the female genital tract associated with endometrosis, diffuse adenomyosis, and endometrial atypical hyperplasia. Int J Surg Pathol, 2008; 16: 443–46
10. Liang SX, Pearl M, Liu J et al: "Malignant" uterine perivascular epithelioid cell tumor, pelvic lymph node lymphangioleiomyomatosis, and gynecological pecomatosis in a patient with tuberous sclerosis: A case report and review of the literature. Int J Gynecol Pathol, 2008; 27: 86–90
11. Anderson AE, Yang X,Young RH: Epithelioid angiomyolipoma of the ovary: A case report and literature review. Int J Gynecol Pathol, 2002; 21: 69–73

12. Yanai H, Matsuura H, Sonobe H et al: Perivascular epithelioid cell tumor of the jejunum. Pathol Res Pract, 2003; 199: 47–50
13. Fukunaga M: Perivascular epithelioid cell tumor of the uterus: Report of four cases. Int J Gynecol Pathol, 2005; 24: 341–46
14. Bonetti M, Pea G, Martignoni G, Zamboni G: PEC and sugar. Am J Surg Pathol, 1992; 16: 307–8
15. Folpe AL: Neoplasms with perivascular epithelioid cell differentiation (PEComas). In: Fletcher CDM, Unni KK, Mertens F (eds.), World health classification of tumors: Pathology and genetics of tumors of soft tissue and bone. Lyon: IARC Press, 2002; 221
16. Fernandez-Flores A: Evidence of neural crest origin of PEComas. Rom J Morphol Embryol, 2011; 52: 7–13
17. Fadare O: Uterine PEComa: Appraisal of controversial and increasingly reported mesenchymal neoplasm. Int Semin Surg Oncol, 2008; 5: 7–18
18. Albores-Saavedra J, Dorantes-Heredia R, Chable-Montera F et al: Endometrial stromal sarcomas: Immunoprofile with emphasis on HMB45 reactivity. Am J Clin Pathol, 2014; 141: 850–55
19. Simpson KW, Albores-Saavedra J: HMB-45 reactivity in conventional uterine leiomyosarcomas. Am J Surg Pathol, 2007; 31: 95–98
20. Deniz K, Coban G, Okten T: Anti-Cd10 (56C6) expression in soft tissue sarcomas. Pathol Res Pract, 2012; 208: 281–85
21. Masand RP, Euscher ED, Deavers MT, Malpica A: Endometrioid stroma sarcoma: A clincopathologic study of 63 cases. Am J Surg Pathol, 2013; 37: 1635–47
22. Folpe AL, Mentzel T, Lehr HA et al: Perivascular epithelioid cell neoplasms of soft tissue and gynecological origin: A clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol, 2005; 29: 1558–78
23. Tirumani SH, Shinagare AB, Hargreaves J et al: Imaging features of primary and metastatic malignant perivascular epithelioid cell tumors. Am J Radiology, 2014; 202: 252–58
24. Nicolos MM, Tamboli P, Gomez JA, Czerniak BA: Pleomorphic and dedifferentiated leiomyosarcoma: A clincopathologic and immunohistchemical study of 41 cases. Hum Pathol, 2010; 41: 663–71