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Primary Perivascular Epithelioid Cell Tumor (PEComa) of the Ovary: A Case Report and Review of the Literature

ANGIOLO GADDUCCI[1], CLARA UGOLINI[2], STEFANIA COSIO[1], FABIO VISTOLI[3], EMANUELE FEDERICO KAUFFMANN[3] and UGO BOGGI[3]

[1]*Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy;*
[2]*Department of Surgical, Medical, Molecular Pathology and Critical Area, Section of Pathology, University of Pisa, Pisa, Italy;*
[3]*Department of Translational Research and New Surgical and Medical Technologies, Division of General and Transplant Surgery, University of Pisa, Pisa, Italy*

Abstract. *Background: Perivascular epithelioid cell tumors (PEComa)s are mesenchymal neoplasms located at various anatomic sites, which usually express both melanocytic and myogenic markers. Case Report: A 60-year-old woman underwent laparotomy for a huge, heterogeneous, right ovarian mass. The histological examination of the surgical specimen revealed a neoplasm consisting of both cells with clear or eosinophilic cytoplasm and spindle cells in a myxoid stroma. Immunostaining was positive for human melanoma black-45, h-caldesmon, desmin, actin, and transcription factor 3. Cell atypias were moderate, mitoses were 4/ 10 high power fields (HPF) and margins were focally infiltrative. These findings pointed to a diagnosis of ovarian PEComa. Twenty-five months later, two subcutaneous lesions were surgically removed on the left trapezius muscle and the median subumbilical area, respectively. The former was a desmoid fibromatosis, whereas the latter was a recurrence of PEComa with greater nuclear pleomorphism and higher number of mitoses (26/50 HPF) compared to the primary tumor. The patient was free of disease 11 months later. Conclusion: A long-term follow-up of gynecological PEComas is strongly recommended.*

Correspondence to: Angiolo Gadducci, Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Via Roma 56, Pisa, 56127, Italy. Tel: +39 50992609, Fax: +39 50553410, e-mail: angiolo.gadducci@unipi.it

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Perivascular epithelioid cell tumors (PEComa)s include a family of different mesenchymal neoplasms with characteristic cells, which usually express both melanocytic and myogenic markers, such as human melanoma black (HMB)-45, human melanosome-associated antigen-1 (HMSA-1), MelanA/Mart1, microphthalmia transcription factor (MiTF), smooth muscle actin (SMA), pan-muscle actin, muscle myosin, calponin, sometimes h-caldesmon and, less commonly, desmin (1, 2). PEComa cells could arise from undifferentiated cells of the neural crest, from myoblastic cells harboring a molecular alteration leading to expression of melanocytic markers, or from pericytic cells. The majority of cases are benign, but a small subset behaves in a malignant fashion. Folpe *et al.* (3) classified PEComas as benign, of uncertain malignant potential or malignant on the basis of 6 worrisome findings represented by tumor size, infiltrative growth pattern, nuclear grade and cellularity, mitoses /50 high power fields (HPF), necrosis, and vascular invasion. Schoolmeester *et al.* (4) considered only 5 worrisome features, *i.e.*, tumor size >5 cm, high grade atypia, mitoses >1/50 HPF, necrosis and lymphovascular invasion. PEComas were defined as either benign/uncertain malignant potential or malignant according to whether there were <4 *versus* ≥4 worrisome features, respectively. Bennet *et al.* (5), who deleted the term benign in the benign/uncertain malignant potential category, classified a PEComa as either of uncertain malignant potential or malignant, if the tumor showed <3 or ≥3 worrisome features. Gynecological PEComas account for approximately 25% of all PEComas, and, in most cases, the primary site of the tumor is the uterine body (3-11). Adnexal PEComas are exceptional, with only 5 primary cases and 7 metastatic cases described in the literature (4, 7, 8, 11-20). This study aimed to report another case of primary malignant PEComa of the ovary.

Case Report

Because of abdominal pain and discomfort, a 60-year-old woman underwent clinical, gynecological and ultrasound examinations that revealed a huge pelvic mass. A computed tomography (CT) scan revealed a 25-cm heterogeneous mass of probable ovarian origin, extending from the pelvis to the celiac tripod, displacing small loops and the left colon. The lesion had a mixed structure with coexistence of liquid and solid areas. No suspicious or pathological radiological findings were detected in the liver, intrahepatic and extrahepatic biliary tracts, pancreas, adrenal glands, kidneys, urinary excretory tracts, pelvic and aortic lymph nodes, lungs, pleura, and mediastinal lymph nodes. The colonoscopy was negative. After prophylactic insertion of bilateral ureteral double-J stents, the surgical exploration showed a large polylobed neoformation that arose from the right ovary, which was non-cleavable from the right colon and a small segment (5 cm) of the sigmoid colon. En-block surgical removal of this mass, uterus, left adnexa, right colon and a small part of the sigmoid colon was performed, followed by latero-lateral isoperistaltic hand-sewn ileo-colic and colo-colic anastomoses. At gross examination, the neoformation measured 32×28×17 cm and showed a solid cut surface with myxoid and necrotic hemorrhagic areas. The intraoperative histological examination was suggestive of mucinous adenocarcinoma with non-cohesive signet-ring cells. An intraoperative esophago-duodenal-gastroscopy was negative. The accurate exploration of the omentum, parietal, visceral and diaphragmatic peritoneum, upper abdomen parenchymatous organs, and pelvic and aortic lymph nodes did not reveal any suspicious lesions. Radical omentectomy and multiple random biopsies of the paracolic gutters, diaphragmatic peritoneum, and root of the mesentery were performed. The definitive histologic examination showed that the right ovary was completely replaced by a mesenchymal neoplasm consisting of both cells with clear or finely granular eosinophilic cytoplasm and spindle cells in a myxoid stroma with a rich network of vessels and extensive areas of necrosis. Immunostaining was positive for HMB-45, h-caldesmon, desmin, actin, transcription factor 3 (TF3), CD10, estrogen receptor (ER) (weak) and progesterone receptor (PR) (weak) and negative for myogenin, MART, CD30, CD99, MUC4, p63, ALK, inhibin-α, MDM2, CD117, S-100, SOX10, CKpan, CKCAM5.2 and EMA. Cell atypias were moderate, mitoses were 4/ 10 HPF and margins were focally infiltrative. These findings pointed to a diagnosis of PEComa with morphological and immunophenotypic features of lymphangioleiomyomatosis (Figure 1). The tumor size, necrosis, number of mitoses and margin status were suggestive of a high–risk neoplasm according to the criteria of Folpe *et al*. (3) and Schoolmeester *et al*. (6). The endometrium, myometrium, cervix, right and left parametrium, left ovary, right and left fallopian tubes, omentum and multiple peritoneal biopsies were free of tumor. The walls of the resected intestinal tracts were affected by phlogistic processes that had tenacious adhesions with the tumoral ovarian mass. Postoperative course was uneventful and the patient was discharged in good general conditions on the eighth postoperative day.

Afterwards ureteral double-J stents were removed and the patient was followed with an intensive surveillance program, including clinical and gynecological examination and chest-abdomen pelvic CT scan every 4 months and brain CT scan yearly. Twenty-five months after surgery, two subcutaneous lesions of tense-elastic consistency were detected on the left trapezius muscle and in the median subumbilical area, respectively. At CT scan, these two lesions captured the contrast medium unevenly, whereas no other suspicious areas were detected in the chest, abdomen and pelvis, as well as in the brain. Both lesions were surgically removed. The lesion at the left trapezius muscle was a 1.6×1×0.7 cm white nodule, which showed spindled-shaped cells of monomorphic appearance, separated by abundant collagen with little cell-to-cell contact. The immunostaining was positive for actin and β-catenin and negative for desmin, S100, and SOX10. The morphological and immunophenotypic findings were suggestive of a desmoid fibromatosis. At gross examination the subumbilical lesion was a 2.8×2.8×2.8 cm polylobed neoformation with a gelatinous appearance. Microscopically, it consisted of epithelioid cells with a clear or eosinophilic cytoplasm and focal nuclear pleomorphism, and spindle cells in a mixoid stroma (Figure 2). Immunostaining was positive for HMB-45, h-caldesmon, desmin, actin, TF3, CD10, ER, MART1, myogenin (weak), and negative for PR, MDM2, SOX10, CKPan, CKCAM5.2, and EMA. The histological diagnosis was recurrence of PEComa with morphological and immunophenotypic features of lymphangioleiomyomatosis. Compared with the primary tumor, this neoplasm showed a greater nuclear pleomorphism and a higher number of mitoses (26/50 HPF). The patient was clinically and radiologically free of disease eleven months later.

Discussion

Only anecdotal cases of primary PEComas of the ovary have been described in the literature (13, 17-20). Anderson *et al*. (13) reported the case of a 39-year-old female with a history of tuberous sclerosis complex (TSC) and bilateral renal angiomyolipoma who underwent salpingo-oophorectomy for a 4.5 cm cystic ovarian mass detected at ultrasound. The histologic examination revealed an epithelioid angiomyolipoma of the ovary, characterized by admixture of HMB-45 positive epithelioid cells with eosinophilic cytoplasm and bizarre typical nuclei, and HMB-45 positive smooth muscle bundles with large thick-walled blood vessels. Follow-up data were not available.

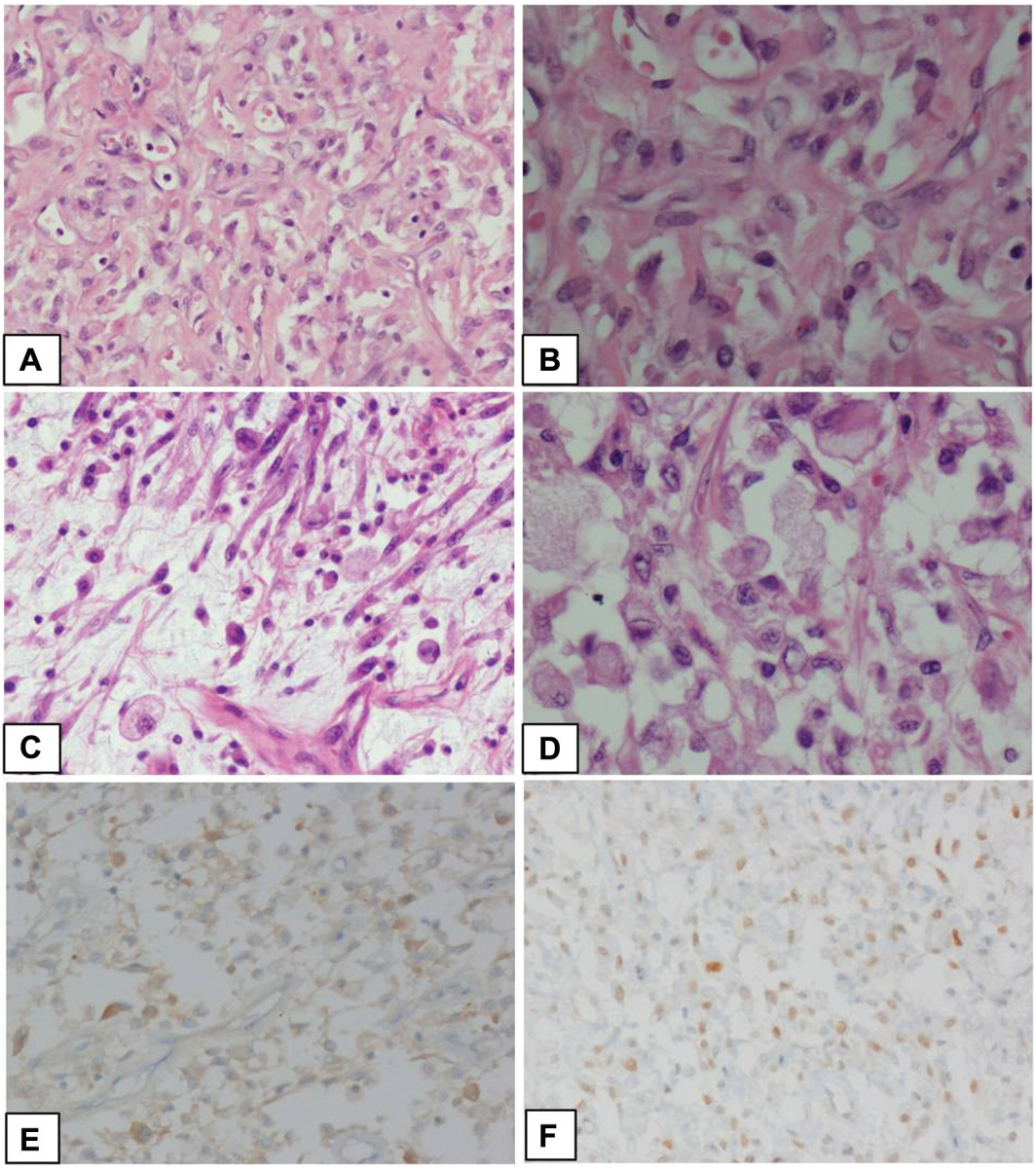

Figure 1. *Different aspects of primitive ovarian perivascular epithelioid cell tumor: A and B) Hematoxylin-eosin staining [20× (A) and 40× (B) magnifications]; cells with clear or finely granular eosinophilic cytoplasm. C and D) Hematoxylin-eosin staining [20× (C) and 40× (D) magnifications]; spindle cells in a myxoid stroma. E) Immunohistochemical positivity for HMB-45 (20× magnification). F) Immunohistochemical positivity for TF-3 (20× magnification).*

A sclerosing adnexal malignant PEComa was found in a 63-year-old woman who underwent total hysterectomy, bilateral salpingo-oophorectomy, omental biopsy and left pelvic lymph node biopsy for a huge pelvic mass (17). At microscopic examination the left ovary and fallopian tube were completely destroyed by a PEComa, and the excised lymph node contained a high-grade tumor with extra-nodal spread. The patient died 4 months after surgery with lung and liver metastases.

A 43-year-old, black female underwent hysterectomy with bilateral salpingo-oophorectomy for the presence of a multilocular complex cyst in the right ovary, a bilateral hydrosalpinx, and multiple uterine leiomyomas detected at ultrasound and magnetic nuclear resonance scan (18). The histologic examination revealed a PEComa composed of sheets of epithelioid cells with round to ovoid nuclei, prominent nucleoli, and eosinophilic cytoplasmic inclusions,

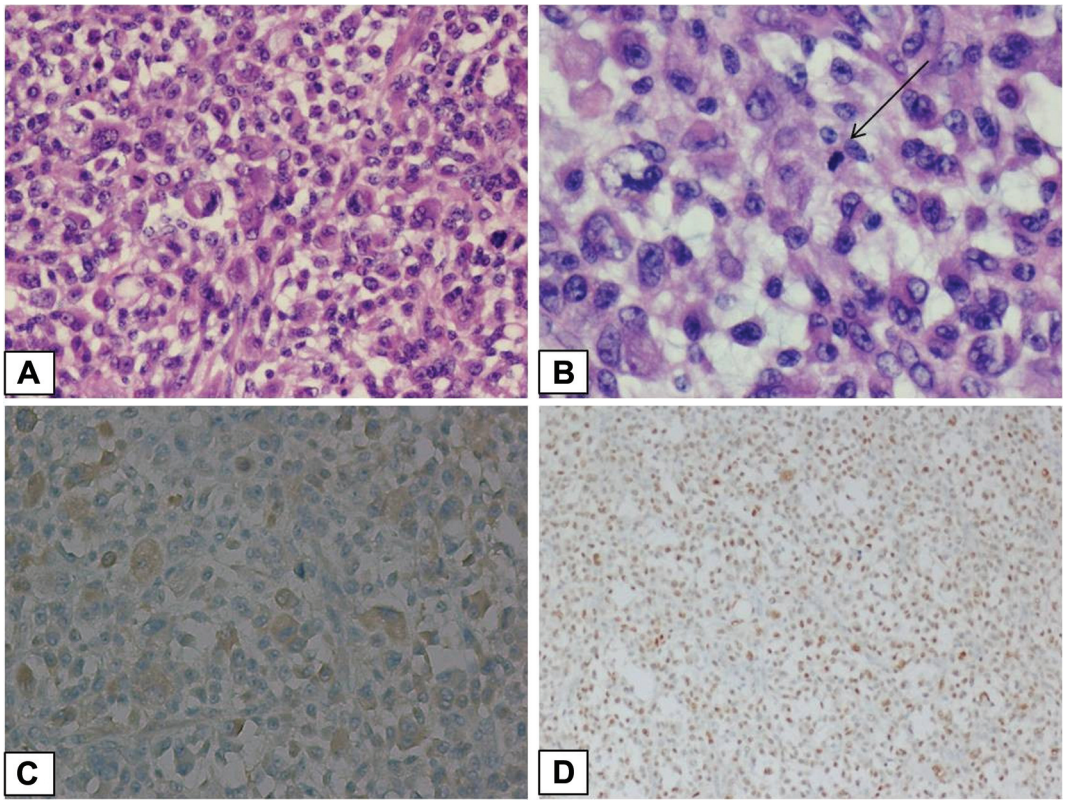

Figure 2. *Abdominal recurrence of ovarian perivascular epithelioid cell tumor (PEComa): A and B) Hematoxylin-eosin staining at 20× (A) and 40× (B) magnifications. Images from PEComa with a lymphoangiomyomatosis aspect. Note the epithelioid cells arranging in short fascicles around endothelium-lined spaces. The cells show abundant grainy eosinophilic cytoplasm and pleomorphic nuclei with mitotic activity (thin arrow). C) Immunohistochemical positivity for HMB-45 (20× magnification). D) Immunohistochemical positivity for TF-3 (10× magnification).*

that were divided into irregular groups by hyalinized fibrous bands. The neoplastic cells were strongly and diffusely positive for vimentin, SMA and desmin, positive for HMB-45, weakly or moderately positive for TF3, and sometimes strongly positive for h-caldesmon. The proliferation rate was minimal, with only 0.5% of the cells being Ki-67-positive, and necrosis was absent. The patient was alive with no evidence of disease 7 years after surgery.

A 48-year-old, previously hysterectomized woman was found to have two large, well-defined, multiloculated, solid and cystic masses in the pelvis and bilateral variable-sized lesions in the lungs at CT scan performed for long-lasting, mild abdominal discomfort (19). The patient underwent bilateral salpingo-oophorectomy and wedge resection of the lung, and the histological examination of both adnexal and lung tissues detected epithelioid cells with mild atypia and cleared-out cytoplasm, which were diffusely positive for SMA and strongly positive for HMB-45. These findings were consistent with PEComa in the ovaries and lung, but follow-up information was lacking.

Symptoms and signs of ovarian PEComas are not specific and the diagnosis emerges from an accurate histologic and immunohistochemical study of the surgical specimens, whereas the preoperative imaging examinations are unable to discriminate these tumors from other benign or malignant gynecological conditions (10, 11, 19). The treatment of choice is represented by a complete surgical resection with tumor free margins, whereas there are no data as for adjuvant radiotherapy or chemotherapy for the cases with histological features suggestive of malignant behavior (8, 9, 11, 21). Two distinct molecular groups have been described: PEComas with TSC mutations and TF3-translocation associated PEComas (22). As for recurrent or metastatic setting, the patients with TSC mutations might benefit from mammalian target of rapamycin (m-TOR) inhibitors (22-24), whereas those with TF3-translocation could be treated with the met-inhibitor crizotinib (25).

Our patient harbored a primary TF3 positive PEComa of the right ovary belonging to the family of lymphangio-leiomyomatosis. The tumor size (32 cm), the number of

mitoses (4/10 HPF), the extensive areas of necrosis and the focally infiltrative margins were suggestive of a high-risk neoplasm. Twenty-five months after surgery, the patient developed two distinct subcutaneous suspicious lesions, which were removed. One of these was a desmoid fibromatosis, and the another one was a recurrence of PEComa with greater nuclear pleomorphism and a higher number of mitoses compared to the primary tumor.

Although the prognosis of patients with gynecological PEComas is usually good, a long-term follow-up is advised (11).

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, Writing - original draft: AG; Data curation, Formal analysis, Methodology, Writing-review & editing: CU, SC, FV, EFK, UB.

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