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Case Report

# Primary Ovarian Malignant PEComa: A Case Report

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**Summary:** Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal neoplasm characterized by expression of both melanocytic and smooth muscle markers. PEComas are rarely encountered in the female genital tract. We here report a case of malignant primary PEComa of the ovary, and discuss the differential diagnosis. This represents the first case of primary typical malignant PEComa of the ovary. **Key Words:** Perivascular epithelioid cell neoplasms—PEComas—Ovary—Malignant—Primary.

Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal neoplasm characterized by expression of both melanocytic and smooth muscle markers (1). PEComas are composed of nests or sheets of epithelioid or spindle cells with clear to granular eosinophilic cytoplasm. The cells are focally associated with blood vessels (2). PEComas have no known normal counterpart cell (3). Minute perivascular epithelioid cell nests occurring in lymph nodes have been proposed as a potential precursor lesion (4).

PEComas have been associated with tuberous sclerosis complex (TSC) and frequently harbor *TSC1* or *TSC2* mutations (5). These mutations have been found to regulate the Rheb/mTOR/p70S6K and hence tumors may in theory be amenable for treatment with mTOR inhibitors (6,7). Most multiple widespread PEComas, otherwise known as PEComatoses, occur in patients with TSC (4). Another mutation that has been associated with PEComa is *TFE3*, which generally occurs in the absence of the TSC mutations (8,9). It is important to make the distinction between these 2 sets of mutations as those with the absence of TSC mutations may not respond to mTOR inhibition (10).

PEComas are usually benign, but some cases are classified as malignant. Schoolmeester et al. (11), have proposed prognostic criteria that require 4 of the following features to be present for a malignant diagnosis: gross size $\geq 5$ cm, high-grade nuclear features, necrosis, vascular invasion, or a mitotic rate $\geq 1/50$ HPF. Another less stringent classification is represented by the modified Folpe criteria, which label any tumor with the presence of necrosis as malignant in addition to those with 2 of the following features: isolated marked atypia, size $\geq 5$ cm, mitotic count $\geq 2/50$ HPF, invasive edge, and lymphovascular invasion (12).

A number of tumors fall into the category of PEComa including lymphangioleiomyomatosis, renal capsuloma, angiomyolipoma, clear cell tumor of the lung, primary extrapulmonary sugar tumor, abdominopelvic sarcoma of perivascular epithelioid cells, and myomelanocytic tumor of the falciform ligament or ligamentum teres (3,13). These tumors arise most frequently within the abdominal and pelvic viscera with a particular predilection for the uterus and gastrointestinal system, but have been described in

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other visceral, cutaneous, retroperitoneal, and somatic soft tissues locations (14,15).

PEComas have been reported throughout most of the gynecologic tract including the uterine corpus, cervix, vagina, broad ligament, vulva, and the wider adnexa (16,17). Metastases of PEComa to the ovary and PEComatosis involving the ovary have been previously reported (18). However, only 2 cases have been previously reported as specifically arising in the ovary, both of which were benign, and 1 case of sclerosing PEComa with malignant transformation involving the ovary and fallopian tube (17–19). We report a case of malignant primary PEComa of the ovary.

## CASE REPORT

A 54-yr-old female who presented abdominal pain and investigations revealed a left ovarian mass. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and excision of a segment of small bowel with mesentery.

### Gross Features

The left ovary was replaced by a large mass which measured $20 \times 18 \times 10$ cm, with the fallopian tube stretched over the surface. The cut surface of the mass showed solid, necrotic, and friable tissue.

The uterus contained multiple fibroids. The right ovary and fallopian tube were normal.

The small bowel segment measured 7 cm in length and 3.5 cm in diameter. The serosal surface was congested, hemorrhagic, and the bowel wall was thinned out. An area of the mucosa was completely replaced by hemorrhagic necrotic tissue. There was a mesenteric nodule measuring 1.8 cm in diameter.

### Microscopic Features

Microscopic examination (Figs. 1A–F) showed a high-grade malignant tumor composed of sheets of markedly pleomorphic polygonal cells with indistinct cell borders, finely vacuolated cytoplasm, and enlarged nuclei with irregularly distributed coarse chromatin. There were bizarre and multinucleate cells present. Areas of necrosis were observed along with mitoses exceeding 20/10 HPF. The tumor cells showed perivascular distribution in areas and there was focal lymphovascular space invasion. No ovarian parenchyma was seen in the sections examined. The tumor appeared to extend to periadnexal tissue. The left fallopian tube was free of tumor.

The uterus contained intramural leiomyomata and the endometrium was inactive. There was chronic cervicitis. The right ovary and fallopian tube were normal.

The bowel and mesentery contained a viable nodule of tumor that showed similar features to the ovarian mass. Tumor tissue extended to focally invade the bowel wall.

### Immunohistochemistry

The tumor cells expressed H-caldesmon and SMA. There was focal positivity for Melan-A, HMB45, S-100, c-kit, and CD34. The tumor cells were negative for EMA, MNF116, and calponin (Fig. 1).

### Clinical Follow-up

Four months after the excision of the tumor, a CT scan showed 2 definite areas of recurrence. One of these measured 10 cm and was within the left iliac fossa and the other was within the small bowel mesentery. The patient was started on sirolimus. A month later, the patient presented with an acute abdomen and a second CT showed increased volume of disease. A decision was made to palliate and the patient died 5 weeks later.

## DISCUSSION

PEComas within different parts of the female genital tract have been reported, but are rare. Within this region, the main differential diagnosis is uterine smooth muscle tumors including leiomyoma and leiomyosarcoma. Differentiation between these entities remains a challenge due to the fact that they can both have epithelioid morphology and can express melanocytic markers focally (16).

In this case the principal differential diagnosis was leiomyosarcoma. However, the morphology and the immunoprofile favored PEComa. This was considered malignant because of the high mitotic rate ($>20$/10 HPF), a gross size of $>5$ cm, high-grade nuclear features, and necrosis. This was further substantiated by the presence of metastasis in the bowel mesentry. By these features the tumor qualified as malignant by both the prognostic criteria proposed by Folpe and Kwiatkowski (12) and by Schoolmeester et al. (11). To our knowledge this is, therefore, the first ovarian

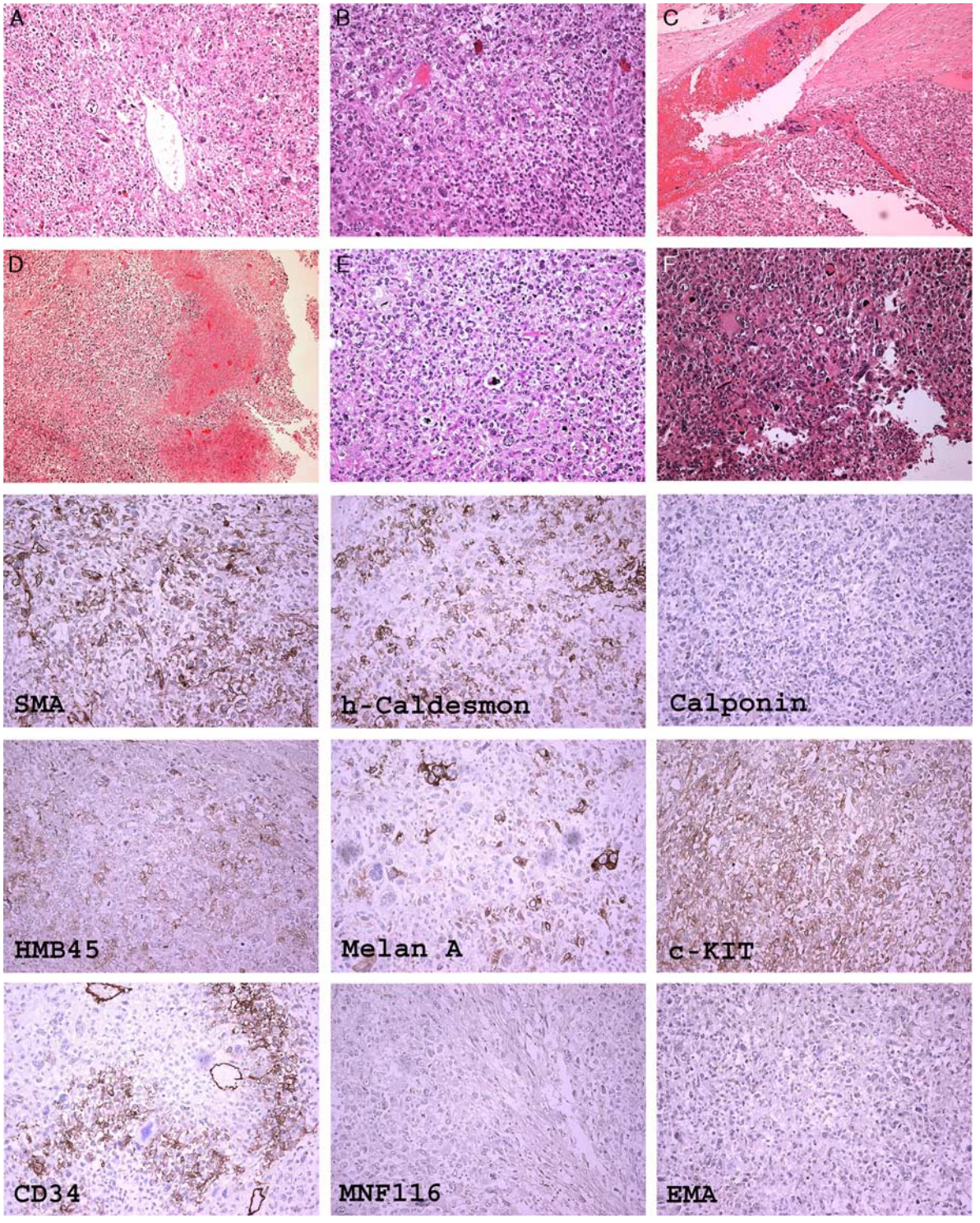


**FIG. 1.** Malignant PEComa: A, Sheets of tumor cells in a perivascular arrangement (100 ×). B, The cells show eosinophilic and clear cytoplasm ( × 200 ×). C, There is vascular invasion (100 ×). D, Areas of necrosis (200 ×). (E) Mitoses (200 ×) and (F) cytologic atypia and cellular pleomorphism, including giant cells (200 ×). The tumor cells express SMA, H-caldesmon, HMB45, Melan-A, c-KIT, and focally CD34. The tumor cells are negative for calponin, MNF116, and EMA (the magnification of all immunostaining slides is 200 ×).

PEComa to be classified as malignant in the English literature.

In our case there was a tumor mass in the ovary as well as a tumor nodule in the bowel mesentery. This raised the question as to which one represented the primary lesion. There are 9 cases of mesenteric PEComa in both small and large bowel mesentery reported within the English literature (20,21). These tend to be asymptomatic and can grow to a large size (range, 2–23 cm) before diagnosis. When symptoms occur they are often due to tumor size with palpable mass, abdominal pain, and distention being most common (20–23).

Given the relative size of our 2 lesions, and the fact that the PEComa was present in one of the ovaries, only a diagnosis of primary malignant ovarian PEComa with a mesenteric metastasis was made.

The only 2 previously reported ovarian PEComas were a small soft and tan to yellow papillary mass growing within a cystic cavity and a well-circumscribed solid yellow to brown septated mass (18,19) In comparison, ours was a far larger solid necrotic mass with metastasis.

Comparing microscopically, we did not have intermixed smooth muscle, thick-walled vessels, adipose tissue, or nests of tumor cells separated by fibrous stroma as found in other lesions. Pleomorphic polygonal epithelioid cells with multinucleate forms were present in ours and one other lesion, compared with cells with a clear cytoplasm, distinct cell borders, and round to oval nuclei found in the remaining case. Our lesion contained frequent mitoses, as opposed to the previously reported benign PEComas.

Immunohistochemical profiles were variable with ours and another lesion staining strongly for SMA, and the final case being negative. The previous lesions both stained strongly for HMB45 and one for Melan-A (not done in the other), whereas ours showed only focal expression for these markers. S-100 was focally positive in our lesion; however, 1 previous lesion was negative and it was not done in the other.

There is 1 previous malignant PEComa reported involving the adnexa, which completely replaced the ovary and fallopian tube (22). This was a sclerosing PEComa with malignant transformation. The tumor was composed of 2 distinctive components. One part showed regular epithelioid cells with clear cytoplasm arranged in clusters, trabeculae, and perivascular arrangements, separated by sclerosing hyalinized stroma. The cells showed mild cytologic atypia and low mitotic activity and no necrosis was identified. This bland component showed abrupt transition to a frankly malignant component composed of sheets of highly pleomorphic epithelioid cells with bizarre nuclei and atypical multinucleated giant cells. Mitoses were frequent (focally up to 5 mitosis in a single high-power field), including atypical forms and there was notable necrosis. One lymph node contained tumor metastasis with perinodal spread. The patient died within 4 months of surgery of metastatic tumor in the lungs and liver.

We here report the first case of primary typical malignant PEComa of the ovary, with distant metastasis at presentation and an aggressive clinical behavior.

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