**Primary Ovarian Malignant PEComa – A case report**

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**Abstract**

PEComa is a rare mesenchymal neoplasm characterised 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.

Keywords: Perivascular Epithelioid Cell Neoplasms, PEComas, ovary, malignant, primary

**Introduction**

Perivascular epithelioid cell tumour (PEComa) is a rare mesenchymal neoplasm characterised 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 harbour TSC1 or TSC2 mutations.5 These mutations have been found to regulate the Rheb/mTOR/p70S6K and hence tumours 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 two 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, have proposed prognostic criteria which require four of the following features to be present for a malignant diagnosis: gross size ≥5cm, high grade nuclear features, necrosis, vascular invasion or a mitotic rate ≥1 per 50HPF.11 Another less stringent classification is represented by the modified Folpe criteria, which label any tumour with the presence of necrosis as malignant in addition to those with two of the following features: isolated marked atypia, size ≥ 5cm, mitotic count ≥ 2 per 50HPF, invasive edge and lymphovascular invasion.12

A number of tumours fall into the category of PEComa including lymphangioleiomyomatosis, renal capsuloma, angiomyolipoma, clear cell tumour of the lung, primary extrapulmonary sugar tumour, abdominopelvic sarcoma of perivascular epithelioid cells and myomelanocytic tumour of the falciform ligament or ligamentum teres.3,13 These tumours arise most frequently within the abdominal and pelvic viscera with a particular predilection for the uterus and gastrointestinal system, but have been described in other visceral, cutaneous, retroperitoneal and somatic soft tissues locations.14,15

PEComas have been reported throughout most of the gynaecological 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 red.ported.18 However, only two cases have been previously reported as specifically arising in the ovary, both of which were benign, and one case of sclerosing PEComa with malignant transformation involving the ovary and fallopian tube.17,18,19 We report a case of malignant primary PEComa of the ovary.

**Case report**

A 54 year 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 x 18 x 10cm, 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 7cm in length and 3.5cm in diameter. The serosal surface was congested, haemorrhagic and the bowel wall was thinned out. An area of the mucosa was completely replaced by haemorrhagic necrotic tissue. There was a mesenteric nodule measuring 1.8cm in diameter.

Microscopic features

Microscopic examination (Figure 1A-F) showed a high grade malignant tumour 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 per 10HPF. The tumour cells showed perivascular distribution in areas and there was focal lymphovascular space invasion. No ovarian parenchyma was seen in the sections examined. The tumour appeared to extend to periadnexal tissue. The left fallopian tube was free of tumour.

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 tumour which showed similar features to the ovarian mass. Tumour tissue extended to focally invade the bowel wall.

Immunohistochemistry

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

Clinical follow up

Four months after the excision of the tumour, a CT scan showed two definite areas of recurrence. One of these measured 10cm 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 our patient sadly passed away five 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 tumours 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 favoured PEComa. This was considered malignant because of the high mitotic rate (>20 per 10HPF), a gross size of greater than 5cm, high grade nuclear features and necrosis. This was further substantiated by the presence of metastasis in the bowel mesentry. By these features the tumour qualifies as malignant by both the prognostic criteria proposed by Folpe et al and by Schoolmeester et al.11,12 To our knowledge this is, therefore, the first ovarian PEComa to be classified as malignant in the English literature.

In our case there was a tumour mass in the ovary as well as a tumour nodule in the bowel mesentery. This raised the question as to which one represented the primary lesion. There are nine 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 2-23cm) before diagnosis. When symptoms occur they are often due to tumour size with palpable mass, abdominal pain and distention being most common.20,21,22,23

Given the relative size of our two lesions, and the fact 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 two 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 mass18,19 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 tumour 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 to 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. S100 was focally positive in our lesion however one previous lesion was negative and it was not done in the other.

There is one 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 tumour 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 hyalinised 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 tumour metastasis with perinodal spread. The patient died within 4 months of surgery of metastatic tumour 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 behaviour.

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**Figure legend**

**Figure 1.** Malignant PEComa: **A,** Sheets of tumour cells in a perivascular arrangement (X100). **B,** The cells show eosinophilic and clear cytoplasm (X200). **C,** There is vascular invasion (X100), **D,** areas of necrosis (X200), **E,** Mitoses (X200) and **F,** cytological atypia and cellular pleomorphism, including giant cells (X200). The tumour cells express SMA, H-caldesmon, HMB45, Melan A, c-KIT and focally CD34. The tumour cells are negative for calponin, MNF116 and EMA. (The magnification of all immunostaining slides is X200).