

Malignant perivascular epithelioid cell tumor of the uterus

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Abstract

Perivascular epithelioid cell tumors (PEComas) are a rare collection of tumors arising in a wide array of anatomic locations and characterized by a myomelanocytic phenotype. PEComas which occur in non-classic anatomic distributions are known as perivascular epithelioid cell tumor-not otherwise specified (PEComa-NOS), and one of the most common primary sites for PEComa-NOS is the uterus. The risk of aggressive behavior of these tumors has been linked to a number of factors evaluable on pathologic review following initial surgical resection. We report a case of PEComa-NOS of the uterus with multiple high-risk features, including frank vascular invasion, with no evidence of recurrent disease 18 months following initial surgical resection.

Introduction

Perivascular epithelioid cell tumors (PEComas) are a collection of rare tumors defined by the World Health Organization as mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells.¹ Bonetti *et al.*, coined the term perivascular epithelioid cell (PEC) for these cells in 1992 and proposed the presence of this distinctive cell as a common link between a number of rare disorders in disparate locations, including angiomyolipoma (AML) of the kidney as well as clear cell sugar tumors (CCST) and lymphangiomyomatosis (LAM) of the lung.²

Further descriptions of tumors in multiple anatomic locations composed primarily of these cells has led to them being designated PEComas, as first suggested by Zamboni *et al.* in 1996.³ These tumors are notable for a myomelanocytic phenotype, with nearly all PEComas being immunoreactive for both melanocytic (HMB-45 and/or melan-A) and smooth muscle (actin and/or desmin) markers. The PEComa family of tumors is now felt

to be comprised of AML, CCST, LAM and less well-characterized PEComas of a variety of other anatomic origins, for which the term perivascular epithelioid cell tumor-not otherwise specified (PEComa-NOS) has been proposed.⁴

Multiple case reports and case series have described PEComa-NOS in a number of diverse anatomic locations including the colon, pancreas, heart and breast.^{3,5-9}

One of the most common primary sites for PEComa-NOS is the female genitourinary tract, and more specifically, the uterus,¹⁰ and patients with PEComa-NOS of the uterus have a demonstrated a wide variety of clinical outcomes.

Case Report

A 50 year old gravida 3, para 3 African-American female with a distant diagnosis of uterine fibroids presented to her local emergency department with acute worsening of chronic abdominal pain which had been present for 4-6 months. Her past medical history was otherwise unremarkable with no features suggestive of tuberous sclerosis, and initial evaluation revealed hypotension and anemia with a hematocrit of 32%. Physical exam revealed a moderately tender abdomen and unremarkable pelvic exam.

Subsequent imaging in the form of a computed tomography (CT) scan revealed a large and very vascular pelvic mass with extension into the lower and midabdomen...measuring 25 cm × 11 cm × 22 cm. Moderate intraperitoneal fluid, mesenteric fat stranding and an intraluminal filling defect of the right ovarian vein were also noted.

With a working diagnosis of bleeding uterine myomata, she was taken to the operative theater the following day. Upon opening, hemoperitoneum and a large, fungating, vascular mass arising from the uterus and adherent to the overlying omentum were noted. During the dissection of the adherent omentum from the underlying tumor, a number of markedly dilated mesenteric veins were noted, and one left parametrial vein was transected, yielding an approximately 4-5 cm worm-like mass felt to be tumor thrombus.

Pathology review of the surgical specimens revealed a multinodular 22×17×10.5 cm mass arising from the superior aspect of the uterine corpus and infiltrating the subserosa and >50% of the myometrium. On gross examination, the mass was described as having hemorrhagic, tan/yellow, softened cut surfaces with multiple finger-like projections into the myometrium (Figure 1). The parametrial soft tissue margins revealed residual disease, and both ovaries contained discrete tumor nodules.

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The mass extracted from the left parametrial vein was also consistent with tumor. One left pelvic lymph node was sampled without evidence of metastatic disease.

Microscopic review revealed predominantly epithelioid cells with a clear to lightly eosinophilic cytoplasm; in areas the neoplastic cells showed granular cell change. Extensive areas of hemorrhage, coagulative necrosis and prominent vascular invasion were also noted; the mitotic index was 2/50 high powered fields (HPF) (Figure 2).

Extensive pleomorphism and occasional giant cells were noted with some cells containing intranuclear inclusions. No spindle cells were seen and the vascular pattern was relatively inapparent. The neoplastic cells were positive for HMB-45, melan A, smooth muscle actin, desmin, and estrogen receptor, while they were negative for S100, pankeratin, inhibin alpha and tyrosinase (Figure 3). Given the myomelanocytic phenotype, a diagnosis of PEComa was made. Given the size of the primary mass and the presence of multiple high risk features as proposed by Folpe, *et al.*,¹¹ (Table 1) this was felt to represent a malignant or high-risk PEComa.

The patient made a full recovery, and CT of the chest, abdomen and pelvis 5 weeks following surgery revealed a small, subsegmental pulmonary embolus (PE), multiple bilateral

sub-cm pulmonary nodules and a tubular 9.0×2.4 cm mass within the right gonadal vein (Figure 4). The PE, small pulmonary nodules and likely gonadal vein thrombus all raised concern as potential sites of residual disease, so a Positron Emission Tomography/Computed Tomography (PET/CT) scan was performed. This demonstrated mild, indeterminate FDG uptake both within a mass located inside the right gonadal vein as well as in the post-operative field. No distant FDG uptake was noted. After a lengthy conversation regarding the potential utility of surgical assessment of the right gonadal vein and systemic therapy, the patient opted not to pursue further diagnostic evaluation or adjuvant therapy. She was started on systemic anticoagulation with warfarin and active surveillance was undertaken in the form of serial CT scans.

Over the course of the interim 18 months, serial CT scans have demonstrated initial shrinkage followed by complete resolution of both the right gonadal vein thrombus and the subsegmental PE. The multiple small pulmonary nodules have been unchanged on serial imaging exams and there has been no radiologic evidence of local recurrence.

Given the lack of evidence for residual or recurrent malignancy, her warfarin was discontinued after a 6 month course of therapy and she has returned to an active lifestyle without complaint.

Discussion

Given the rarity of PEComas and their relatively recent description, little is known in regards to risk factors for development of these tumors, epidemiologic patterns of disease or natural history following initial treatment. The bulk of what is known has been gleaned from a number of case reports and case series and thus descriptive in nature. Series consistently report a strong female predominance, with a female-male ratio as high as 9:1 noted in some case series,¹¹ likely at least in part to the large number of cases originating from the female genitourinary tract. Although the median age at diagnosis is typically in middle age in most series,¹⁰⁻¹² PEComa-NOS has been diagnosed in patients ranging from 3 to 97 years of age.^{11,13}

PEComas have an unpredictable biologic behavior, with some tumors being unresectable or metastatic at the time of diagnosis,^{14,15} a majority behaving in a benign fashion and apparently curable with surgical resection alone, and still others experiencing relapse after surgery, in some cases as long as 15 years postoperatively.¹⁶ In an effort to better define risk factors for aggressive behavior and relapse, Folpe, *et al.* proposed provisional risk

stratification criteria based on a number of pathologic findings in 2005.¹¹ When applying these criteria to 59 cases reported in the literature at that time, 71% (12/17) patients whose cases met the criteria for *malignant* disease demonstrated *malignant* behavior, defined as metastatic or recurrent disease. These criteria have been widely adopted in an effort to predict the natural history of these rare tumors, although they have not been validated, nor has their use been uniformly linked to recommendations for management at this point.

Given the fact that gynecologic PEComas are relatively common, a number of attempts to provide useful risk stratification criteria for this subset of patients have been undertaken over the past decade. Fadare¹⁰ reviewed 41 reported cases of uterine PEComas and concluded that a high mitotic rate (defined as >1/10 HPF) and presence of coagulative necrosis were the best predictors of malignant behavior in this subgroup of patients. Zekry, *et*

*al.*¹² reviewed 53 cases of gynecologic (cervical, uterine and ovarian) PEComa and focused on clinical rather than pathologic risk factors. The only significant risk factors predicting a poorer prognosis were increasing age, metastatic disease at presentation, and receipt of additional therapy (chemotherapy and/or radiation therapy) as a part of a multimodality strategy including surgical resection. The authors suggest that the association between poor prognosis and need for additional therapy is likely attributable to the fact that patients felt to be at higher risk for relapse were more likely to receive additional therapy as opposed to an intrinsic harm in undergoing such treatment.

Surgery remains the mainstay of therapy when possible in PEComas of nearly every anatomic site. Surgical resection of oligometastatic disease has also been of benefit, leading to long disease-free intervals in a number of cases of relapsed disease, especial-

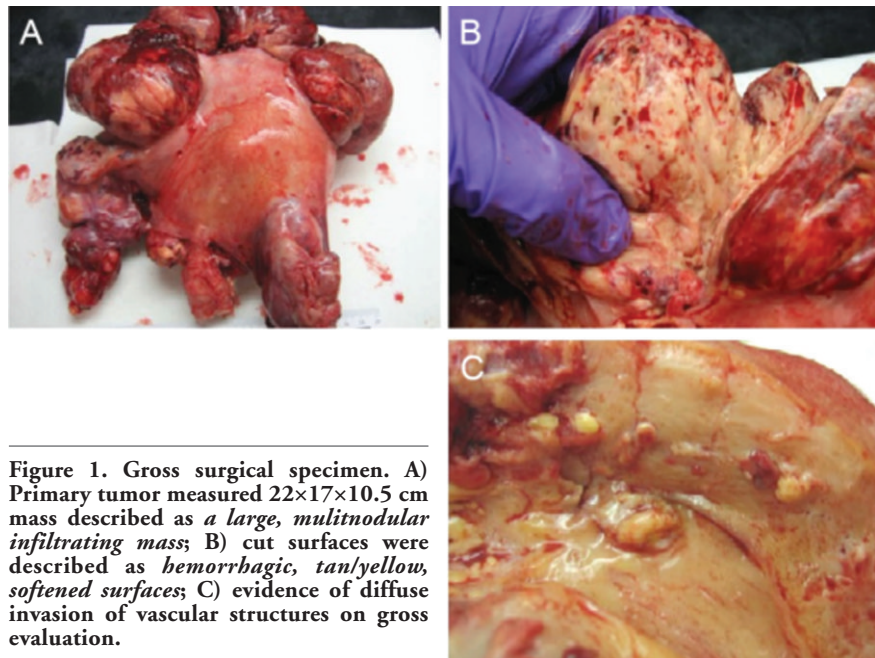


Figure 1. Gross surgical specimen. A) Primary tumor measured 22×17×10.5 cm mass described as a large, multinodular infiltrating mass; B) cut surfaces were described as hemorrhagic, tan/yellow, softened surfaces; C) evidence of diffuse invasion of vascular structures on gross evaluation.

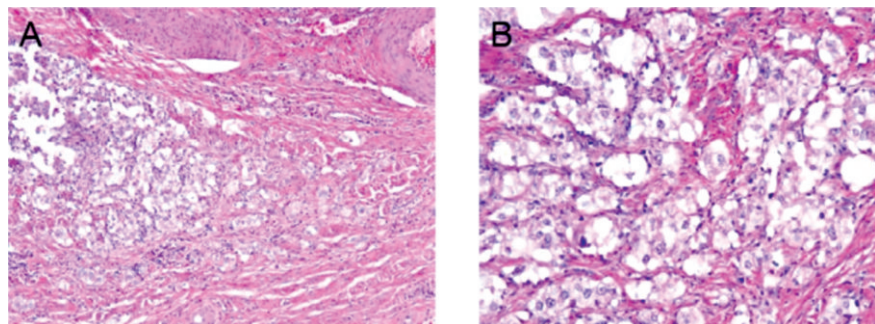


Figure 2. A) Uterine PEComa showing infiltrative growth into the myometrium; B) nests of perivascular epithelioid cells clear to slightly eosinophilic cytoplasm, moderate nuclear variability and small nucleoli.

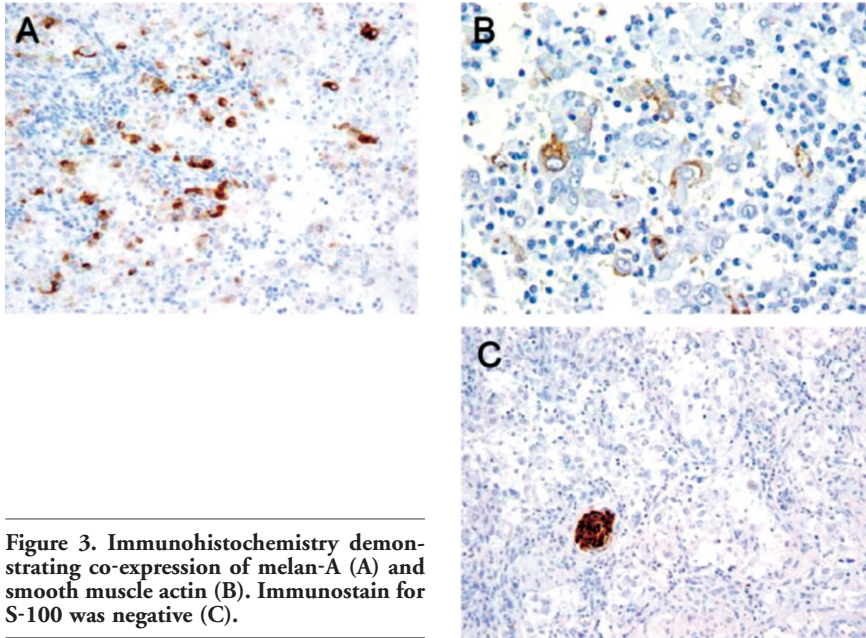


Figure 3. Immunohistochemistry demonstrating co-expression of melan-A (A) and smooth muscle actin (B). Immunostain for S-100 was negative (C).

Table 1. Proposed classification of perivascular epithelioid cell tumor (adapted from Folpe *et al.*¹¹)

High risk features	
a) Size > 5 cm	
b) Infiltrative growth pattern	
c) High nuclear grade and cellularity	
d) Mitotic rate >1/50 HPF	
e) Necrosis	
f) Vascular invasion	
Risk category	
1) Benign	<2 high risk features and size <5 cm
2) Uncertain malignant potential	Size >5 cm with no other high risk features OR nuclear pleomorphism/ multinucleated giant cells only
3) Malignant	2 or more high risk features

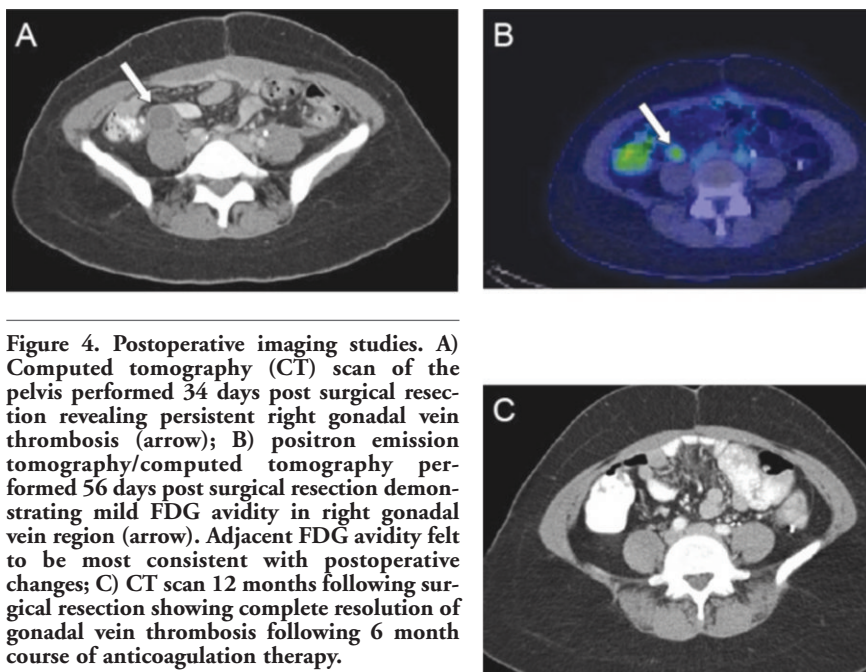


Figure 4. Postoperative imaging studies. A) Computed tomography (CT) scan of the pelvis performed 34 days post surgical resection revealing persistent right gonadal vein thrombosis (arrow); B) positron emission tomography/computed tomography performed 56 days post surgical resection demonstrating mild FDG avidity in right gonadal vein region (arrow). Adjacent FDG avidity felt to be most consistent with postoperative changes; C) CT scan 12 months following surgical resection showing complete resolution of gonadal vein thrombosis following 6 month course of anticoagulation therapy.

ly in late relapses.^{14,17} Radiation therapy has been utilized in a number of cases in both the neoadjuvant and adjuvant setting, without convincing results.^{11,14} Cytotoxic chemotherapy has similarly been integrated into multimodality therapy, with very few confirmed responses.^{17,18} A newer approach utilized primarily in the setting of recurrent or metastatic disease has been targeted therapy, namely mTOR inhibition.

The rationale behind mTOR inhibitor use in these tumors lies in the fact that both classic PEComas and PEComa-NOS have been shown to frequently harbor mutations in the *TSC1* and/or *TSC2* genes, which regulate cell proliferation via the mTOR pathway.^{19,20} Initial trials of these agents in the classic PEComas (AML, LAM) has led to a number of meaningful responses,^{21,22} sparking interest in their use for metastatic or recurrent PEComa-NOS. A number of case reports of mTOR inhibition in PEComa-NOS have now been published, with some long term responses,¹⁶ although these responses have not been uniform.²³

In conclusion, PEComa-NOS remains a rare diagnosis with a widely variant and difficult to predict natural history. This report demonstrates that even with multiple high risk features, patients can survive without recurrence for relatively long periods, as our patient had evidence of at least 4 high risk criteria on pathologic review and is without evidence of recurrence 18 months following surgical resection. Further investigation into potential predictors of poor prognosis must be undertaken in an effort to further clarify risk of aggressive behavior in patients with this diagnosis and, eventually, to help guide management decisions. Given the often indolent biologic behavior of this disease and reports of late recurrences as long as 15 years after initial surgical resection, continued vigilance will be of utmost importance in this case, especially given the history of positive surgical margins. Surgical resection of oligometastatic disease and/or mTOR inhibition would likely be the favored interventions should recurrence be detected, based on emerging data on the role of the mTOR pathway in the pathogenesis of these tumors.

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