

Case Report

Fertility sparing treatment of a malignant uterine perivascular epithelioid cell tumor: A case report[☆]Kristen Bunch^{a,*}, Jan Sunde^b^a Department of Obstetrics/Gynecology, Madigan Healthcare System, Tacoma, WA, USA^b Department of Gynecologic Oncology, MultiCare Tacoma General Hospital, Tacoma, WA, USA

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Introduction

Perivascular epithelioid cell tumors (PEComas) are a family of rare, poorly defined mesenchymal tumors of uncertain malignant potential found in various locations throughout the body. They are composed of epithelioid and spindle cells, have a perivascular distribution, and display immunoreactivity for melanocytic markers, most frequently HMB-45, and smooth muscle markers (actin and/or desmin) (Fadore, 2008; Folpe et al., 2005). A review by Bleeker et al. of all 234 published cases of PEComas identified the uterus as the most common site of origin comprising 20% of cases while the lung is the most common location for metastatic disease (Bleeker et al., 2012).

Treatment for PEComas has historically involved excisional biopsy or surgical resection. Neoadjuvant and adjuvant therapies with chemotherapy and/or radiation have also been described in a small number of cases with mixed results. The majority of chemotherapy regimens have typically used similar regimens for soft tissue sarcomas, utilizing an anthracycline backbone, however, no uniform regimen has been proposed or utilized (Folpe, 2002). Recently a class of medication that interferes with the mammalian target of rapamycin (mTOR), called mTOR inhibitors, has emerged as a promising therapy with the discovery that activation of the mTOR-signaling pathway occurs in PEComas.

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Experience with mTOR inhibitors in treating PEComas is limited, primarily for metastatic or recurrent disease. To our knowledge, there are no reports on the use of an mTOR inhibitor as adjuvant therapy in the setting of a malignant uterine PEComa. Small studies demonstrating tumor shrinkage and clinical response to mTOR inhibitors merit additional investigation (Gennatas et al., 2012; Italiano et al., 2010; Wagner et al., 2010). We present a case of a malignant uterine PEComa in a young, nulliparous patient treated with adjuvant chemotherapy followed by surgical excision.

Case

A healthy, 19-year-old nulligravida Caucasian woman presented to her primary provider with complaints of abdominal pain, vomiting, and dizziness. Her medical history was unremarkable to include no family history of cancer or tuberous sclerosis. Imaging studies revealed a large, hypervascular mass in the posterior cul de sac measuring approximately 8 cm in diameter. The patient subsequently underwent a diagnostic laparoscopy, which was converted to an exploratory laparotomy for removal of the mass. The large posterior uterine mass was resected at its base, however, resulted in a blood loss of 1100 cm³ secondary to its hypervascularity. Additional tumor located on the anterior uterine wall was not resected given concern for additional blood loss, and possible need for emergent hysterectomy to control bleeding. The final tissue pathology returned as aggressive/malignant perivascular epithelioid tumor (PEComa) which was confirmed by outside pathological consultation. The tissue characteristics included epithelioid and spindle cells with clear and granular cytoplasm, and prominent vasculature around which the tumor cells were arranged (Figs. 1 & 2). Nuclear atypia was identified, as well as mitotic activity of at least 1 mitosis/50 high-powered fields (HPF). Tissue stains were positive for HMB-45, smooth muscle actin, and desmin, and negative for S100 and melan-A.

Treatment typically involves surgical excision, which may have required a hysterectomy in this nulliparous patient who desired future fertility. Given the inability to remove the entire tumor during the initial surgery, she was considered suboptimally debulked. With her young age and future fertility desires, conservative management with adjuvant temsirolimus, an mTOR inhibitor, followed by interval surgical excision of remaining tumor was chosen after discussing available management options. Temsirolimus is currently approved by the Food and Drug Administration for advanced renal cell carcinoma and therefore, was used off-label in this patient. The patient was thoroughly counseled regarding the off-label use of Temsirolimus for her as well as the risks of

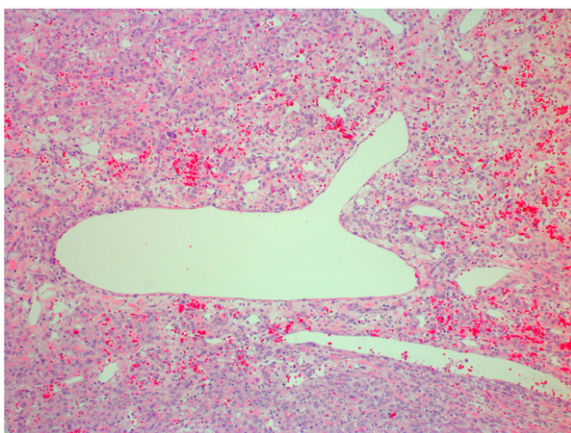


Fig. 1. Neoplastic epithelioid to spindled cells with a staghorn vessel in the background.

the medication, the most common serious adverse reactions (grade 3 or 4) being rash, dyspnea, pain, and asthenia (Kwitkowski et al., 2010).

The patient received 12 cycles of temsirolimus 25 mg IV weekly. A pelvic magnetic resonance image (MRI) performed following adjuvant therapy demonstrated interval reduction in the size of the uterine mass by approximately 65% compared to prior imaging, indicating a positive therapeutic response. Following completion of the adjuvant temsirolimus, the patient underwent laparotomy with resection of the remaining uterine mass, and various peritoneal and omental biopsies. There was no evidence of metastatic spread on surgical or pathologic evaluation. The patient's postoperative course was uncomplicated. Follow-up at fifteen months post-treatment was encouraging with no evidence of disease. Ongoing surveillance will be necessary to evaluate progression of disease in this patient treated with mTOR inhibitor therapy for malignant PEComa.

Discussion

Uterine perivascular epithelioid cell tumors are exceedingly rare mesenchymal tumors. The term "PEComa" was first introduced in 1996 by Zamoni and colleagues and in 2002 the World Health Organization (WHO) first recognized the perivascular epithelioid cell tumors as a distinct clinicopathologic entity (Fadore, 2008; Folpe, 2002). However, the concept of a family of perivascular epithelioid cell tumors dates back prior to 1996 when histologic and immunohistochemical associations were noticed between various soft tissue tumors. Other mesenchymal neoplasms that comprise the family of perivascular epithelioid

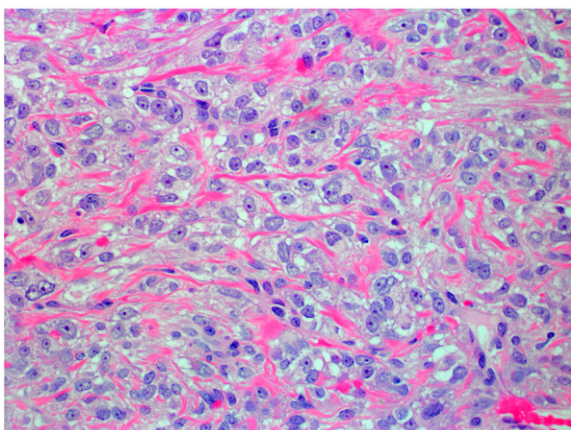


Fig. 2. Epithelioid and spindle cells with clear to eosinophilic, granular cytoplasm.

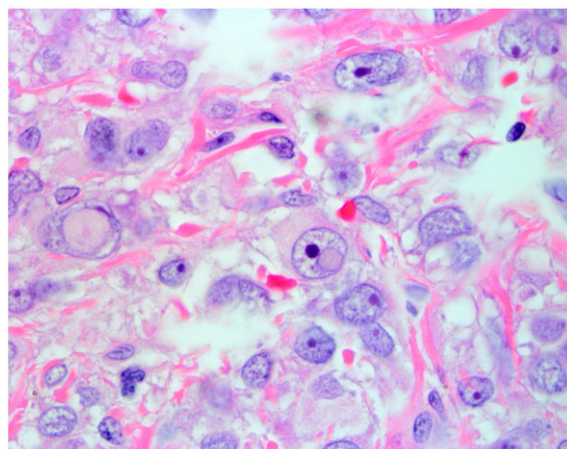


Fig. 3. Neoplastic cell with granular cytoplasm and intranuclear pseudoinclusion.

cell tumors include lymphangiomyomatosis (LAM), clear cell sugar tumor of the lung (CCST), and angiomyolipoma (AML) of the kidney, among other rare tumors characterized by perivascular epithelioid cells (Fadore, 2008; Folpe et al., 2005; Yamamoto et al., 2010).

The morphologic features of PEComas include epithelioid and/or spindled cells with clear to eosinophilic cytoplasm and a varying degree of growth around vessels as well as positive immunoreactivity for melanocytic and smooth muscle tumor markers. Perivascular epithelioid cell tumors may be confused with both smooth muscle tumors and carcinomas. Morphologic evaluation will demonstrate clear or lightly eosinophilic cytoplasm and round nuclei (Fig. 3) in PEComas in contrast to the diffuse cytoplasmic eosinophilia and cigar-shaped nuclei found in smooth muscle tumors. However, immunohistochemistry may be more useful in distinguishing a PEComa from a carcinoma by the presence of positive melanocytic marker expression found in PEComas, unlike carcinomas (Fadore, 2008; Folpe et al., 2005). The tumors also have a female predilection with a female-to-male ratio ranging from 4:1 to 9:1 which persists when gender-specific locations are excluded (Folpe et al., 2005; Bleeker et al., 2012).

A wide variety of treatment modalities have been utilized for PEComas. No treatment approach has been shown to be consistently effective, however, no randomized trials are available due to the rarity of the disease. Traditionally, therapy has involved surgical excision of the primary tumor. Neoadjuvant and adjuvant therapies have utilized chemotherapy, radiotherapy, chemoradiation, immunotherapy with interferon-alpha and hormonal therapy with tamoxifen. Chemotherapeutic regimens have included ifosfamide, doxorubicin, vincristine, cyclophosphamide, and platinum agents, among others (Bleeker et al., 2012). An association between tuberous sclerosis complex (TSC) and AML and LAM was previously established when it was observed that patients with tuberous sclerosis have a higher rate of AML and LAM compared to the general population. Tuberous sclerosis is an autosomal dominant disease caused by mutations in the TSC1 or TSC2 genes. A genetic association was demonstrated between TSC and the PEComa family with the discovery of germline mutations of the TSC locus in TSC-associated AML and LAM. Interest in the use of mTOR inhibitors for treatment of PEComas arose when further investigation revealed that TSC1 and TSC2 genes regulate cell proliferation via the mTOR pathway. Loss of the TSC locus, therefore, results in impaired activation of the mTOR complex and unregulated cellular proliferation (Folpe et al., 2005; Bleeker et al., 2012; Wagner et al., 2010). Treatment of PEComas with mTOR inhibitors, such as temsirolimus, has been reported in the literature, however, not for a malignant uterine PEComa (Gennatas et al., 2012; Italiano et al., 2010). The discovery that PEComas share activation of the mTOR pathway has presented the opportunity to investigate the use of mTOR inhibitors as a new treatment modality for these tumors.

The majority of PEComas are benign, however, a subset of these tumors have demonstrated malignant, invasive behavior with either local recurrences or distant metastases. In 2005, Folpe et al. proposed a classification scheme for categorizing the disease into three subgroups, “benign, malignant, or tumors of uncertain malignant potential.” Tumors were classified as malignant if they demonstrated two or more of the following features: tumor size >5 cm, high nuclear grade, necrosis, mitotic activity >1/50 HPF, and infiltrative growth pattern/vascular invasion. Tumors were classified as benign if the above features were absent, while those tumors >5 cm without the other features noted in the malignant category were labeled uncertain malignant potential (Folpe et al., 2005). Further analysis by Bleeker et al. demonstrated that tumor size >5 cm and a mitotic rate >1/50 HPF are the best predictors of tumor recurrence (Bleeker et al., 2012). In the case described, the tumor met the proposed criteria for a malignant tumor, and thus, higher potential for tumor recurrence, based on size, mitotic activity, and nuclear atypia.

Despite better characterization of PEComas over the last few decades, they remain a heterogeneous group of tumors with variable biologic behavior, which makes it difficult to define prognosis and provide treatment recommendations. Increasing recognition of this family of tumors will likely lead to improved characterization, and subsequently, management and treatment regimens. To date, there is no consensus regarding treatment that has shown consistent efficacy. Targeted therapy, such as with mTOR inhibitors, shows promise as a new treatment modality for this family of rare tumors, particularly for uterine PEComas, which has not been reported previously (Bleeker et al., 2012). As demonstrated in our patient who had multiple high-risk criteria on pathologic evaluation, the use of mTOR inhibitors may provide the best medical treatment currently available, as well as a fertility-sparing treatment option for young, female patients desiring future fertility.

Conflict of interest statement

The author(s) declare that there are no conflicts of interest. The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Madigan Healthcare System, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of Defense, or the U.S. Government.

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