

## Perivascular epithelioid cell neoplasm of the uterine cervix: an unusual tumor in an unusual location

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### Abstract

A 46-year-old woman presented for a second opinion regarding a 3-4 cm mass of the uterine cervix. A prior biopsy had been interpreted as a malignant melanoma of the cervix, resulting in a radical hysterectomy with bilateral salpingo-oophorectomy. This was to be followed by external beam irradiation and immunotherapy; however, given the rarity of this diagnosis, the patient sought a second opinion at our institution. Further review of the pathological material from the hysterectomy revealed a morphologically benign perivascular epithelioid cell neoplasm rather than a malignant melanoma. Close monitoring of the patient was recommended; she is currently disease-free more than three years after her initial presentation.

### Introduction

Perivascular epithelioid cell neoplasms (PEComas) comprise a group of unusual visceral, soft tissue, bone, and skin tumors defined by both their unique morphological features and their characteristic "myomelanocytic" immunophenotype. These tumors co-express markers of melanocytic differentiation, such as gp100 protein (recognized by mAb HMB45) and markers of myogenous differentiation, such as smooth muscle actin isoforms.<sup>1</sup> Angiomyolipoma of the kidney represents the most common and "prototypical" PEComa, with much rarer tumors in different anatomical locations having been described under such names as lymphangioliomyomatosis, clear cell "sugar" tumor, clear cell myomelanocytic tumor, and abdominopelvic sarcoma of perivascular epithelioid cells, among others. The differential diagnosis of PEComas is broad and may include both benign tumors, such as leiomyoma or lipoma, as well as malignancies, including malignant melanoma, clear cell carcinoma, leiomyosar-

coma, and liposarcoma. Here we present a case of PEComa of the uterine cervix that was initially diagnosed and treated as a malignant melanoma. The differential diagnosis of this very rare neoplasm and its classification and treatment are reviewed.

### Case Report

A 46-year-old gravid-4, para-1 female presented to an outside provider in early 2007 for evaluation of intermittent vaginal bleeding, lasting for at least one year. The patient's medical history was significant for miscarriages, endometriosis, borderline hypertension, a grade 1/6 intermittent heart murmur, and malaria contracted while working in the Philippines in her twenties. Her family history was significant for a brother with multiple myeloma and a sister with leiomyosarcoma.

On examination by the outside provider, the patient was found to have a friable 3-4 cm mass arising from the uterine cervix. A biopsy of this mass was performed and diagnosed as malignant melanoma. Preoperative computer tomography (CT) and positron emission tomography (PET)-CT fusion scans were negative for regional or distant metastatic disease. A hysterectomy with bilateral salpingo-oophorectomy and regional lymph node dissection was performed.

The pathological specimen from the hysterectomy revealed a 2.5×2.0×0.9 cm cervical mass, which was considered by the pathologists at the outside institution to represent malignant melanoma. Thirty-three lymph nodes were negative for metastatic disease. On the basis of these findings it was recommended that the patient receive immunotherapy and external beam radiotherapy, possibly with additional brachytherapy. Following these recommendations, the patient presented to our institution for a second opinion regarding treatment options. On further review, the hysterectomy specimen was felt to represent a PEComa, rather than a malignant melanoma. This was based on its nested growth pattern, clear to lightly acidophilic cytoplasm, relatively low-grade cytological features, absence of mitotic activity or necrosis (Figures 1 and 2), and myomelanocytic immunophenotype, with expression of Melan A, gp100 protein, and smooth muscle actins, but not S100 protein (Figures 3-5). The tumor was considered to be morphologically benign, according to the criteria advanced by the most widely accepted classification scheme for PEComas.<sup>1</sup> We recommended that the patient receive no additional adjuvant therapy. The patient agreed to close observation and follow-up alone, and is currently without evidence of disease, 42 months after the initial diagnosis.

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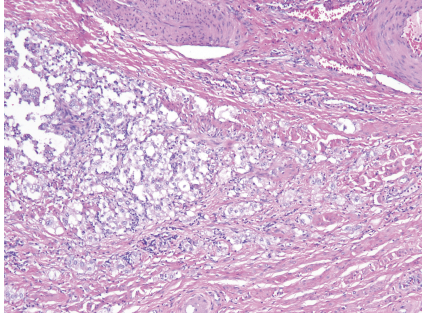
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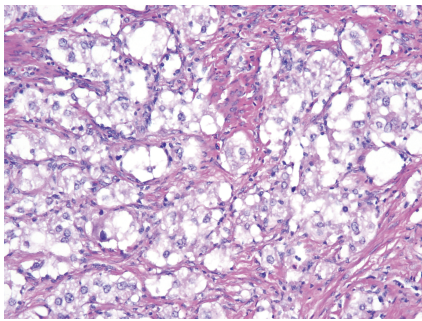
### Discussion

The PEComas comprise a family of related neoplasms defined both by morphology (characteristic clear to lightly eosinophilic, epithelioid to slightly spindle-shaped cells arranged in a perivascular distribution) and by immunohistochemistry (co-expression of melanocytic and myoid antigens). PEComas are rare with the most common member of this family, angiomyolipoma of the kidney, having an estimated prevalence of only 0.13% of the population.<sup>2</sup> PEComas have been reported in a wide variety of visceral, intra-abdominal, soft tissue, and bone locations, and occur with some frequency in the gynecological tract, including the uterine cervix and corpus.<sup>3,7</sup> PEComas of all types most often occur in middle-aged women (median age, 38 years), being seven times more common in women overall and four times more common even when gynecological sites of origin are excluded.<sup>1</sup> PEComas of all types have been associated with the tuberous sclerosis complex (TSC) and with inactivating mutations in the TSC-associated genes *TSC1* or *TSC2*, although this association is much stronger for angiomyolipoma and lymphangioliomyomatosis than it is for gynecological and soft tissue PEComas.<sup>8</sup>

The diagnosis of PEComa may be very challenging, owing to its rarity and its morphological and immunophenotypic overlap with other tumors, both benign and malignant. As emphasized by our case, PEComas may closely simulate malignant melanomas, particularly in the setting of limited biopsies. Important clues to the correct diagnosis of PEComa include lower nuclear grade as com-



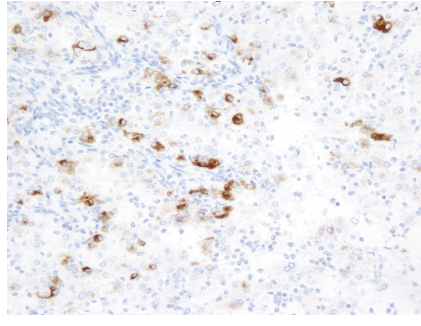
**Figure 1.** Hematoxylin-and-eosin stain of PEComa tissue slice at 100X magnification. Note the nested growth pattern, clear to lightly acidophilic cytoplasm, relatively low-grade cytological features and absence of mitotic activity or necrosis, which are consistent with a benign PEComa.



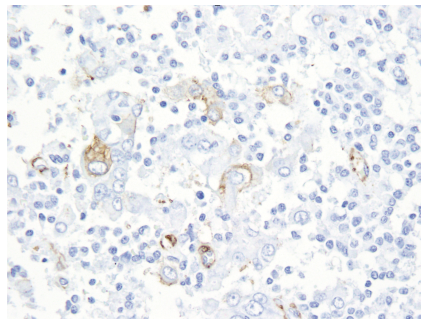
**Figure 2.** Hematoxylin-and-eosin stain of PEComa at 200X magnification.

pared with melanomas (without the prominent macronucleoli characteristic of melanomas), nested growth with a prominent associated capillary vasculature, and clear to lightly eosinophilic cytoplasm. Ultimately, however, immunohistochemistry is critical in the distinction between PEComa and melanoma. Although both tumor types express melanocytic markers, such as gp100 protein, Melan A, tyrosinase, and microphthalmia transcription factor, PEComas are typically negative for S100 protein, expressed in 98% or more of melanomas, and are positive for smooth muscle actin isoforms not expressed in melanomas.<sup>1,9,10</sup>

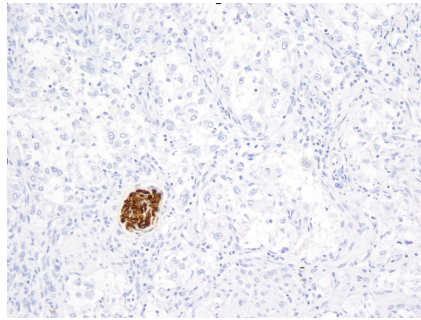
The behavior of PEComas remains to be fully elucidated, owing to their rarity. However, a histopathological classification scheme has been elaborated by Folpe and colleagues,<sup>11</sup> stratifying PEComas into “benign”, “of uncertain malignant potential”, and “malignant”. The present case was considered to be morphologically benign, based on its small size (<5 cm), intermediate nuclear grade, intermediate cellularity, low mitotic rate ( $\leq 1/50$  MF/HPF), and absent necrosis. Follow-up to date on PEComas classified as



**Figure 3.** Immunohistochemical staining demonstrates that the PEComa is positive for Melan A.



**Figure 4.** Immunohistochemical staining of the PEComa is positive for smooth muscle actin.



**Figure 5.** Immunohistochemistry demonstrates that this PEComa is negative for S100, a feature which can be used to distinguish between a PEComa and a melanoma.

morphologically benign has shown them to be clinically benign as well.

In the unlikely event of a recurrence of this patient's cancer, treatment options would include surgical resection, if feasible. The role of radiation therapy is presently unknown. Standard chemotherapy for sarcomas was not effective in a recent case report.<sup>12</sup> Another report suggests that PEComas may respond to inhibition of the mTOR signaling pathway using sirolimus or temsirolimus.<sup>13</sup> Owing to the rarity of these tumors and their mixed histological features, effective treatments are still being developed for malignant PEComas.

## References

1. Folpe AL, Kwiatkowski DJ. Perivascular epithelioid cell neoplasms: pathology and pathogenesis. *Hum Pathol* 2010;41:1-15.
2. Eble JN. Angiomyolipoma of kidney. *Semin Diagn Pathol* 1998;15:21-40.
3. Fukunaga M, Harada T. Pigmented perivascular epithelioid cell tumor of the kidney. *Arch Pathol Lab Med* 2009;133:1981-4.
4. Furusato E, Cameron JD, Newson RW, et al. Ocular perivascular epithelioid cell tumor: report of two cases with distinct clinical presentations. *Hum Pathol* 2010; 41:768-72.
5. Mitteldorf CA, Birolini D, da Camara, et al. A perivascular epithelioid cell tumor of the stomach: an unsuspected diagnosis. *World J Gastroenterol* 2010;16:522-5.
6. Rettenmaier MA, Zekry N, Chang M, et al. A heavily pigmented vaginal perivascular epithelioid cell neoplasm. *J Obstet Gynaecol* 2009;29:676-7.
7. Strzeiczzyk JM, Durczynski A, Szymanski D, et al. Primary perivascular epithelioid cell tumor (PEComa) of the liver: report of a case. *Surg Today* 2009;39:916-21.
8. Gomez MR, Sampson JR, Whittemore VH. Tuberosus sclerosis complex. 3rd ed. New York: Oxford University Press, 1999.
9. Nonaka D, Chiriboga L, Rubin BP. Differential expression of S100 protein subtypes in malignant melanoma, and benign and malignant peripheral nerve sheath tumors. *J Cutan Pathol* 2008;35: 1014-9.
10. Pea M, Bonetti F, Zamboni G, et al. Melanocyte marker HMB-45 is regularly expressed in angiomyolipoma of the kidney. *Pathology* 1991;23:185-8.
11. Folpe AL, Mentzel T, Lehr HA, et al. Perivascular epithelioid neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol* 2005;29: 1558-75.
12. Peng J, Yu B, Wang J, et al. An unresectable malignant perivascular epithelioid cell tumor resistant to multiple combined chemotherapies: a unique case report. *J Pediatr Hematol Oncol* 2010;32: e136-8.
13. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol* 2010;28: 835-40.