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Uterine perivascular epithelioid cell neoplasm (PEComa) in a young woman: Case report, therapeutic considerations, and literature review

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ABSTRACT

Introduction: Perivascular epithelioid cell neoplasm (PEComa) is a rare tumor in woman's genital tract, mainly uterus. Its potential for malignancy, also the therapy, is still not clear. It frequently occurs in fourth decade of life and treatment is often surgical. When it occurs in young women desirous of fertility, it brings dilemmas as to which is the best treatment to guarantee the good chance of survival.

Case Report: A 24-year-old woman complaining of severe genital bleeding for four months and an ultrasound examination showing a 2.6 cm pathological growth in the uterine cavity, of endometrial polyp. She had a history of cesarean delivery. Colposcopy and Pap smear were normal. The lesion was completely resected from its base and the postoperative period had no complications. The result of the histopathological study showed a macroscopic lesion of 12 g, 3.0×0.6×0.3 cm, whose microscopy corresponded to a PEComa. As it was a rare tumor with risk of metastases, it was performed the hysterectomy with salpingectomy. The histopathology result showed a myometrium which had a residual lesion extended up to 0.3 cm short of the uterine serosa.

Conclusion: The authors propose is to perform hysterectomy with salpingectomy for primary uterus PEComas without estrogen and progesterone receptors. The patient has been in remission for 15 months and has maintained her ovarian activity.

Keywords: Female, Genital neoplasms, Hysterectomy, Immunohistochemistry, Rare tumor, Uterus

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INTRODUCTION

Perivascular epithelioid cell neoplasm (PEComa) is an extremely rare mesenchymal tumor originating from cells that involve vessels. These cells express immunoreactivity

for melanocytic as well as myogenic markers, present an epithelioid aspect and clear acidophilic cytoplasm, in addition to presenting perivascular distribution [1, 2].

This category of neoplasia is often confused with smooth muscle tumors, as they have overlapping morphological and immunohistochemical characteristics. However, an accurate diagnosis is crucial, mainly due to the possibility of using targeted therapy with mTOR (mammalian target of rapamycin) inhibitors when they behave adversely [3].

It occurs in any location, being more common in the kidneys, known as angiomyolipoma. There are reports of this neoplasm with locations in the liver, pancreas, rectum, abdomen, and gynecological tract [4]. Uterine PEComa is reported as the main type of PEComa outside the kidney. Few cases have been reported so far, mainly due to its rarity [3, 5, 6].

In this paper, we report a case of uterine PEComa and, in order to improve the understanding of this type of tumor by gynecologists and pathologists, we reviewed the relevant literature in recent years to discuss the clinical-pathological characteristics, determination of biological behavior, and differential diagnosis of uterine PEComas.

CASE REPORT

A 24-year-old woman complaining of severe genital bleeding for four months with an ultrasound examination showing a 2.6 cm pathological growth in the uterine cavity, suggesting endometrial polyp. She had cesarean section two years earlier without any history of hypertension nor diabetes mellitus. His routine tests, such as colposcopy and Pap smear, were normal. On physical examination, she was healthy, only with discolored mucous membranes suggesting mild anemia. She had hysteroscopic resection of the striated lesion with narrow base and atypical vessels corresponding to the image seen by ultrasonography scan at the Federal University of Pernambuco. The postoperative period had no complications. The result of the histopathological study showed a macroscopic lesion of 12 g, 3.0×0.6×0.3 cm, whose microscopy corresponded to a PEComa (Figure 1).

As it is a rare tumor, we sent the material for immunohistochemistry and requested the study of the pelvis with nuclear magnetic resonance imaging (MRI). Immunohistochemical panel applied include epithelial markers (cytokeratin AE1/AE3, cytokeratin CK7, CK20, vimentin, and epithelial membrane antigen – EMA), neuroendocrine (chromogranin, synaptophysin, inhibin, melan A, estrogen receptor, CEA and p53) mesenchymal (CD10, CD34, CD99, CD117, desmin, HMB-45, PAX-8, S100, WT-1, and smooth muscle actin) and cell proliferation (Ki-67). Figure 2 illustrates the positive results found.

The patient was also submitted to a tomography of the chest and abdomen in order to identify the presence of distant metastases. All of these tests were negative

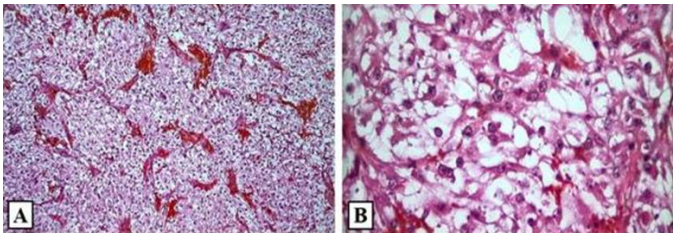

Figure 1: Microscopy of PEComa obtained by complete hysteroscopic resection, (A) 10× and (B) 40×.

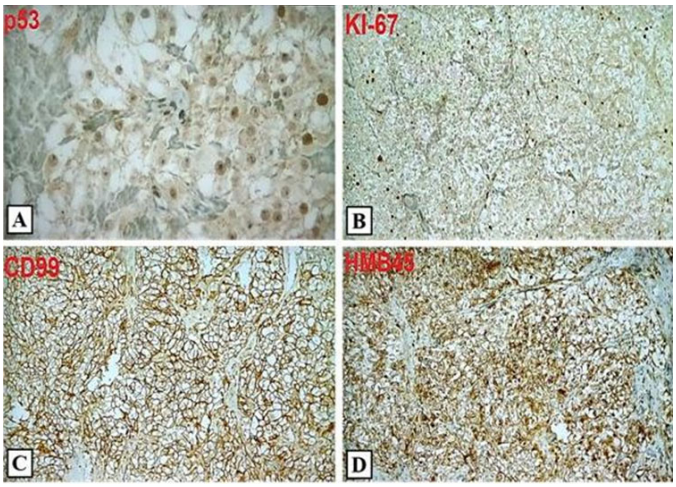

Figure 2: Positive results of immunohistochemistry panel of endometrial cavity lesion obtained by hysteroscopic resection. Positive immunohistochemical reaction is evidenced by brown staining of nuclei (p53 and Ki-67), cell membrane (CD99), or cytoplasm (HMB-45). The expression of apoptosis (p53) and cell proliferation (Ki-67) markers is illustrated by the brown staining of nuclei in (A) and (B), respectively. Spindle cell marker (C99) is identified by brown staining on the plasma membranes in (C). In (D), cells from the lesion obtained show strong expression of the cytoplasmic marker for melanoma. Immunohistochemistry 40× (A–D).

for residual uterine disease or metastasis. The case was submitted for discussion at a clinical meeting that decided to listen to the patient. Both the medical meeting and the patient opted for a hysterectomy. Hysterectomy was performed with salpingectomy and preservation of the ovaries. The result of the histopathological study showed an 87 g uterus with a disease-free cervix. In the myometrium there was a residual lesion that extended up to 0.3 cm short of uterine serosa, compatible with 2.2 cm PEComa. Its mitotic activity of 1/50 HPF (high power field) without necrosis, vascular invasion, perineural or necrosis. And then the material was once again sent to immunohistochemistry (Table 1).

The postoperative period was uneventful and she was discharged from the hospital 48 hours later. She had been in remission for 15 months, being followed up with images of the chest and abdomen every three months. She maintains her ovarian activity.

Table 1: Immunohistochemistry of uterine lesion obtained by hysterectomy

Antibody	Result
Ki-67	Positive less 1%
S100	Negative
HMB-45	Positive
AE1/AE3	Negative

DISCUSSION

In 2005, Fukunaga [7] observed that there were only 27 cases described in the literature, and presents 4 cases in which a negative outcome is observed in a patient whose size was more than 30 cm, and concludes that due to the heterogeneity of the presentation of this tumor, it must be considered of uncertain malignant potential. Bosincu et al. [8] presented two cases of PEComas in women aged 56 and 48 years, and performed a literature review. One of the cases died quickly and another was alive at 36 months of follow-up, without illness. This review brings to fore published cases up to that year where the youngest case was 19 years old but had no record of follow-up. Another 29-year-old patient died of ovarian metastasis at 12 months of follow-up. In another report in the same year [9], the author describes a case of a 9-year-old girl with vaginal disease and distant metastasis who was treated with multimodal chemotherapy, followed by radical surgical resection. The follow-up of this case was 15 months, without illness. Folpe et al. [5] review 26 cases described up to that year and propose a classification for aggressiveness in three categories: (i) Benign Tumors: >5 cm, without high nuclear grade, or high degree of cellularity, without tissue infiltration, mitosis ≤1/50HPF, without necrosis and without vascular invasion; (ii) End PEComas of uncertain malignant potential: nuclear pleomorphism/presence of giant cells only or size over 5 cm; and (iii) Malignant: if ones would have two or more of these findings.

However, the potential for malignancy, in a series that evaluated cases reported in the literature in 2008 [10], cannot be excluded due to the absence of metastasis, as well as the absence of mitotic activity, this was seen in a review of 41 cases, 31 of which were uterine PEComas. Zekry et al. [11] noted that cases of uterine body PEComas treated only with surgery had a longer survival, and those metastatic cases, regardless of treatment, had a similar prognosis.

Differently, Liu et al. [12] presented a case of a 33-year-old patient treated with surgery and chemotherapy, but whose follow-up was only eight months. This was similar to a case described by Bleeker et al. [13] in which a 50-year-old woman with uterine PEComa having four characteristics of malignancy opted for conservative treatment, even though recurrence in five weeks was evidenced, which had spontaneous resolution, seen at follow-up with image for 18 months.

Sikora-Szczésniak [14] reported the case of a 26-year-old patient with high Beta-HCG operated by a minimally invasive technique, which was found a 4 cm lesion in the uterine ligament, which is not followed up. In another report, Rego et al. [15] describe a case of the tumor in a 44-year-old in an oligophrenic woman, which had an extensively necrotic endometrium, concomitant with a finding of condyloma, and with a 15-month follow-up, asymptomatic. Both authors call attention to the fact that these tumors should be treated as having uncertain behavior.

PEComa is often mistakenly classified as sarcoma, which makes it difficult to know its pathogenesis. In a case review article [16] from 1990 to 2012 in women aged 28–60 years, of the 16 reported cases, 13 of these cases were primary in the uterus. One of the patients had multiple sclerosis. At 26 months, only 7 women were alive and without disease. That same article suggests as a criterion of poor prognosis in this population: tumor size ≥5 cm, high-grade histology, presence of invasion and ≥1/50 mitosis per field of high magnification.

In 2014, Yu et al. [17] published thee cases of PEComa of the female genital tract, two of which were primary in the uterine body. All patients were over 40 years old. The number of mitoses and tumor size were the most sensitive criteria for defining the prognosis. In that same year, other authors [18] presented two cases with similar characteristics. They point out that the delay in therapeutic management is mainly due to the lack of radiological definition of the tumor.

However, in 2015 another review [19] authors highlighted the efficiency of the PEComas classification systems. It was demonstrated the predominance in the uterine body in 78 described cases of reported uterine PEComas in English literature until that year, with an average survival of 20 months. Still compared the accuracy of the classification systems of Folpe [5] and Schoolmeester [20]. Fifteen percent of the cases classifiable as benign had malignant behavior. In the same year Musella et al. [16] demonstrated that surgery is the main treatment, with systemic treatments reserved for aggressive cases. However, it is not clear at that time which cases should be considered high risk.

Part of the cases reported in the medical literature is diagnosed through incidental findings, such as those reported by Kwon et al. [21]. In a 2018 review, Benenett et al. [3] reported 32 cases (01 case previously reported), with 77% of PEComas in the uterine body. They observed that even in PEComa classified as benign there was a recurrence in 65 months. The authors also observe the lack of report of the treatment instituted, and propose the elimination of the term benign, as well as a classification of malignancy based on three criteria: Size greater than or equal to 5 cm, high degree of atypia, and greater than 1 mitosis/50HPF.

PEComas are tumors whose rarity in their incidence poses a challenge to clinical practice. In the case presented in this paper, the therapeutic challenge was even greater.

The tumor was in a very young patient with only one child. In the first therapeutic approach, the entire lesion was removed under a hysteroscopic view. The MRI control examination did not show any residual disease. The literature review notes that the histological characteristics of this case, in the three proposed classifications (Bennett [3], Folpe [5], and Schoolmeester [20]), that it fits as having a benign behavior. But Fadare [10] demonstrates the great variability in his aggressiveness.

The lack of consensus on treatment and follow-up imposes a multidisciplinary discussion. PEComas cannot be distinguished from other uterine tumors, when seen in images, so Verbeeck et al. [22] call attention to a "snowstorm" that can be distinguished in this tumor but that is not valid for formation as small as that of our case.

To help in therapeutic decision-making Musella et al. [16] propose the construction of controlled clinical trials, but we believe that the rarity in the occurrence of PEComas makes the execution of this clinical tool unfeasible. We note that there is a small record of overall survival associated with the treatments offered in the reported cases. The use of mTOR inhibitors is still impracticable due to the scarcity of reported results, as well as the inaccessible costs for regions with low development rates. Positron emission tomography-computed tomography (PET-CT) can help diagnose metastasis or recurrence in treated tumors, but it is of low utility and high cost in early tumors.

After four weeks of the lesion resection surgery, our patient underwent a hysterectomy with salpingectomy and preservation of the ovaries. Then, only after the evaluation of the surgical specimen, we saw that she had a residual disease, with same proportion of the beginning of the treatment. It demonstrated the aggressive clinical behavior of the disease.

It is important to reinforce that the decision to hysterectomy perform was made with the complete consenting of the patient, after receiving all the scientific clarification, risks, and benefits. Despite all the risks, our case showed that it was a right decision to be made.

CONCLUSION

To know the pathogenesis of this tumor requires more consistent therapy in order to preserve life. The authors propose performing hysterectomy with salpingectomy for primary uterus PEComas without estrogen and progesterone receptors, and complementary resection of ovaries if positive for these receptors, especially if the patient has defined offspring. They emphasize the importance of involving the patient in decision-making, as well as supporting a medical consensus meeting. These measures plus molecular studies and the practice of reporting occurrences in scientific circles should clarify the knowledge about the pathogenesis of PEComas and define the most appropriate therapeutic approach for each case.

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Author Contributions

Iolanda Matias Gomes – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Lorena Magale Dantas Cirino – Conception of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Márcia Silva de Oliveira – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Edneide Florivalda Ramos Ramalho – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

José Reginaldo Alves de Queiroz Júnior – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Isadora Oliveira Melo – Design of the work, Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.