

# UTERUSUN ATİPİK İMMUNOHİSTOKİMYASAL ÖZELLİKLERİ OLAN PERİVASKÜLER EPİTELOİD HÜCRELİ TÜMÖRÜ

## PERIVASCULAR EPITHELIOID CELL TUMOR OF UTERUS WITH ATYPICAL IMMUNOHİSTOCHEMICAL FEATURES

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### ABSTRACT

Perivascular epithelioid cell tumors (PEComa) are a rare type of mesenchymal tumor arising from perivascular epithelial cells. The prognostic classification of PEComas, the nature of their biological behaviour and the criteria determining their malignancy potential remain uncertain. PEComas usually show immunoreactivity for melanocytic (HMB-45 and/or melan-A) and smooth muscle (actin and/or desmin) markers. Surgery is the most recommended primary treatment. We reported an uterin PEComa with atypical immunohistochemical features.

**Key Words:** Immunohistochemistry, Perivascular Epithelioid Cell Tumors, Uterus.

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## Introduction

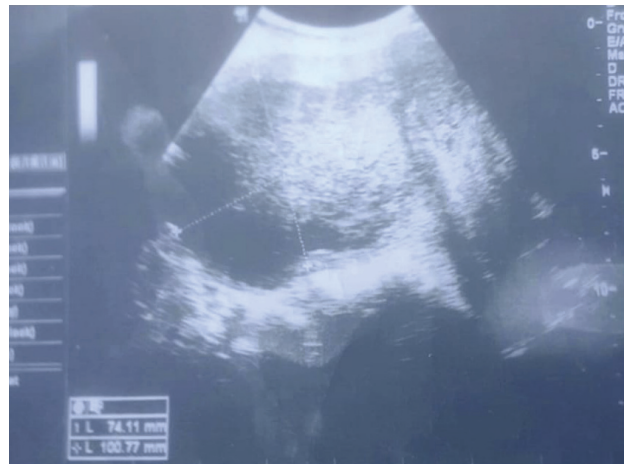
Perivascular epithelioid cells (PECs) were first defined in 1943 as anormal myoblasts in renal angiomyolipomas (Aritz 1943) In 1992, Bonetti et al. used the definition “perivascular epithelioid” for these abnormal epithelioid cells (Bonetti et al. 1994). Although the origins of PECs are uncertain, it is accepted that melanocytic cells, smooth muscle cells, perivascular or undifferentiated neural crest cells containing both melanocytic and myogenic antigens are their origins (Martignoni et al. 2008). Later, tumors from the same cell-type root have been included in this PEC differentiation tumor group, including renal or extrarenal angiomyolipomas (AMLs), lymphangioliomyomatosis (LAM), pulmonary clear cell “sugar” tumors (CCSTs), clear-cell myomelanotic falciform ligament tumors and other clear cell tumors (Folpe 2002).

The most widely accepted classification today is that established by the World Health Organisation in 2002. According to this, histologically, PEComas are tumors showing immunopositive for melanocytic markers, in particular for HMB-45, having transparent and /or eosinophilic cytoplasm and containing spindle and/or epithelioid cells. These tumors express both melanocytic (HMB-45, Melan-A and tyrosinase) and myogenic (e.g., desmin, SMA, muscle specific actin, caldesmon, calponin) antigens (Folpe 2002).

PEComas are mostly seen in middle-aged (average 38) patients and are seven times more frequent in females than in males (Yamada et al. 2011). In tumors predominantly seen in women, the possibility of stimulation by the hormone receptors comes to mind, but in the few previous studies of PEComa cases, oestrogen and progesterone expression was not determined. Gynecological PEComa is a rare pathology and its prognosis is variable and dependent on histological features (Musella et al. 2015). We reported a woman with uterin PEComa.

## Case Study

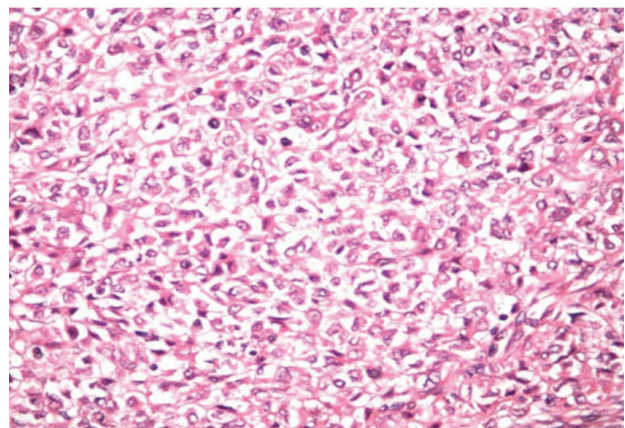
A 44-year-old multiparous woman presented in our clinic complaining of anormal uterine bleeding and a palpable mass in the abdomen. No remarkable features was in personal or family history. Physical examination revealed an 18-20 week size uterus. Transvaginally (TVUSG) showed a big leiomyoma displacing the endometrium 100 × 74 mm in size (Figure 1). Both adnexa were normal. Endometrium biopsy and smear showed no pathological findings. Preoperative chest X-ray was normal. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed and the material was sent to pathology. Macroscopic examination detected an white-coloured, moderately firm intra-



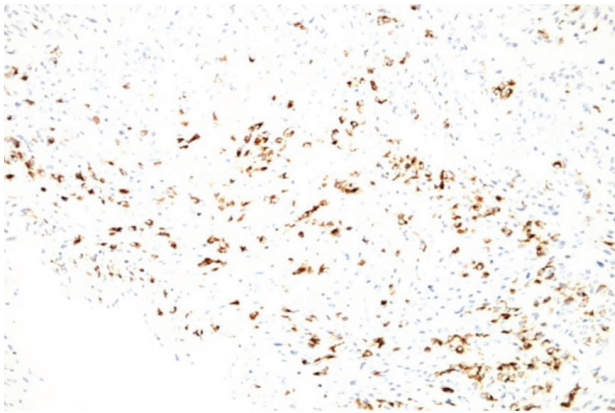
**Figure 1** • Presurgical sonographic view.

mural myoma nodule 12 × 11 × 6 cm in size, containing haemorrhaging in places. Microscopic examination of the mass showed its cellularity was elevated, with a mitotic activity of 3-4 in 10/HPF, having a moderate atypia; necrosis and lymphovascular space invasion was not observed. Sheet-like pattern of epithelioid tumor cells which has eosinophilic pale granular cytoplasm with round shaped nucleus was observed (Figure 2). Immunohistochemical examination revealed SMA positivity and CD34 vascular structures positivity and also CD10 focal positivity. In term of stain for melanocytic markers, HMB45 was positive and Melan-A negative (Figure 3). There were no pathological findings for the uterine cervix, endometrium, uterine tubes or ovaries. The enlarged tumor and elevated cellularity presented a high risk of malignancy.

Recurrence is not detected during routine 6-month-follow-up.



**Figure 2** • Sheet-like pattern of epithelioid tumor cells which has eosinophilic pale granular cytoplasm with round shaped nucleus (H&E, ×400).



**Figure 3** • Tumor positivity for HMB45 (H&E, immunostaining,  $\times 200$ ).

## Discussion

PEComas are rarely seen mesenchymal tumors having distinctive histological and immunohistological features (Folpe 2002). The prognostic classification of PEComas, the nature of their biological behaviour and the criteria determining their malignancy potential remain uncertain. The prognostic factors of tumor size, presence of coagulative necrosis, mitotic activity, cytological atypia, lymphovascular invasion and degree of infiltration have been evaluated. It has been suggested that a tumor having a mitotic rate of  $> 1/10$  HPF and/or with coagulative necrosis present can be viewed as aggressive. The distant metastasis rate in all uterine PEComas cases has been determined as 6.8%. The most common site of metastasis is the lungs, followed by the bones, ovaries, liver, adrenal glands and peritoneum. In addition to computerized tomography (CT) detection of multiple round nodules of different sizes spread over the entire lung in the costophrenic angles, its abnormal parenchyma is pathognomonic (Bleeker et al. 2012).

PEComas are often distinguished as tumors having pale eosinophilic and/or clear cytoplasm with a round or oval nucleus and containing a prominent capillary network. All HMB 45-positive epithelioid tumors, regardless of showing perivascular spread, are included in a diagnosis of PEComa (Bleeker 2012). HMB-45 immunoreactivity is not detected in epithelioid leiomyomas, or when positive, is regional; SMA and desmin are positive. While the HMB-45 positivity detected in 31-36% of leiomyosarcomas is often regional, leiomyosarcoma-free clear cell areas are HMB-45 negative (Vang et al. 2002). Nearly all PEComas show immunoreactivity for both melanocytic (HMB-45 and/or melan-A) and smooth muscle (actin and/or desmin) markers (Ying Y et al. 2014). On the other hand, the Melan-A was negative in our case.

Uterine PEComas are rare but they may arise from uterine tumors like leiomyomas, epithelioid leiomyosarcomas and endometrial stromal sarcomas (EES) (Folpe 2000). Microscopic examination of the leiomyoma showed its cellularity was elevated, with a mitotic activity of 3-4 in 10/HPF, having a moderate atypia and necrosis in our case.

Schoolmeester et al. studied 16 gynaecological PEComa cases, with an average follow-up period of 26 months. They reported that 4+ had adverse histological findings (tumor size  $\geq 5$  cm, mitosis  $\geq 1/50$  HPF, nuclear atypia, necrosis, lymphovascular invasion) and the tumors were classified as malignant. If all of these criteria were negative, the case was benign; if 1-3 of the criteria were present, they classified it as an uncertain malignancy potential tumor (Schoolmeester 2014). Folpe et al., in their study, reported on 26 cases of PEComa detected in the soft tissue and female reproductive system. Metastasis was detected in eight of the 24 patients who were followed up for a period of 30 months. In this study, a combination of epithelioid and spindle cells occurred in 38% of the cases, while in 27% epithelioid cells were present and in 35%, spindle cell preponderance was observed. Folpe et al. divided these tumors into three groups: benign, those with uncertain malignancy potential and malignant. They reported that the tumor size ( $>5$  cm), mitotic activity ( $>1/50$  HPF), necrosis, high nuclear grade and infiltrative growth pattern in tumors showed them to be aggressive (Folpe 2005). PEComa in our case had mitotic activity of 3-4 in 10/HPF, moderate atypia and necrosis. Also the tumor was bigger than 5 cm so we accepted this tumor aggressive PEComa.

A wide range of treatment approaches have been employed in the treatment of these tumours. Surgery is often undertaken to establish the diagnosis, although chemotherapy and radiotherapy have shown little efficiency in this disease (Ying Y et al. 2014). The significant response observed in these patients indicates that the activity of temsirolimus and other mTOR inhibitors in patients with PEComas (Italiano et al. 2010).

Uterine and cervical PEComas should be considered as rare tumors with uncertain malignancy potential, and because of the risk of local recurrence and metastasis, they should be monitored over a long period in order to determine the biological behaviour of the tumors. In order to determine the prognostic classification and appropriate treatment approach of the tumor, there is a need for studies involving a large number of cases and extended clinical monitoring.

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