

Case Report

Endometrial polyp-like perivascular epithelioid cell neoplasm associated with TFE3 translocation: report of one case

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Abstract: This article reports the pathologic features and malignant biological behavior of a perivascular epithelioid cell neoplasm (PEComa) with the clinical manifestation being endometrial polyps. The case was cured with curettage in a local hospital one year ago. The postoperative diagnosis was “endometrial polyps”. This time, due to “irregular bleeding”, we carried out another curettage in our hospital. After the operation, 3 pieces of polyps were inspected with diameters of 0.3 cm, 0.5 cm and 0.6 cm, respectively. The tumor consisted of epithelioid cells with alveolar and nesting pattern and showed a diffuse strong expression of HMB45, Melan-A and TFE3. The patient then underwent a hysterectomy and the “polyps” were sent for pathological examination. The result showed that tumor cells infiltrated the deep muscle layer, close to the outer membrane, suggesting a malignant biologic behavior. TFE3-related PEComa is different from general PEComa. This neoplasm and Melanotic Xp11 renal carcinoma have similar clinicopathologic features, histology, immunity and molecular phenotypes, belonging to the same type of tumor. It has been suggested in the literature naming this neoplasm as ‘Xp11 neoplasm with melanocytic differentiation’ or ‘melanotic Xp11 neoplasm’. Our case has expanded our understanding of PEComa characteristics and increased data for TFE3 translocation-related PEComa, reminding us to avoid misdiagnosis when PEComa manifests as small polyps.

Keywords: Endometrial polyp, perivascular epithelioid cell neoplasm, TFE3 translocation

Introduction

Perivascular epithelioid cell neoplasm (PEComa) is a rare type of mesenchymal tumor with unique phenotypes by histology and immunohistochemistry. PEComa family tumors consist of angiomyolipoma (AML), lung clear cell glycoma (CCST), lymphangioliomyomatosis (LAM), hepatic clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres (CCMMT), and non-specific PEComa [1-7].

In the PEComa family, AML and LAM are associated with the tuberous sclerosis complex (TSC) gene, i.e. conventional PEComas. TSC is a genetic disease caused by loss of the TSC1 (9q34) or TSC2 (16p13.3) gene. Dibble et al. [8] found that the protein products of TSC1 and TSC2 form a heterotrimer with TBC1 domain family member 7 (TBCID7). The activa-

tion of TSC1/TSC2/TBCID7 can inhibit cell proliferation and metabolism. In patients with tuberous sclerosis, the loss of functional TSC proteins prevents the formation of TSC1/TSC2/TBCID7 heterotrimers, which in turn activates mTOR, leading to cell growth and proliferation. The mTOR inhibitor Sirolimus has been shown to be effective in the treatment of PEComa [9-11].

Recent studies have found that a small portion of PEComas contain changes in the TFE3 gene, while the lack of TSC1/TSC2 gene is considered to be a unique subtype of PEComa [12-14]. TFE3 is a member of the microphthalmia-associated transcription factor (MITF) family. Other members cover MITF, TFEB and TFEC. The occurrences of many tumors are associated with high expression of MITF family genes, which are called MITF family tumors. Currently,

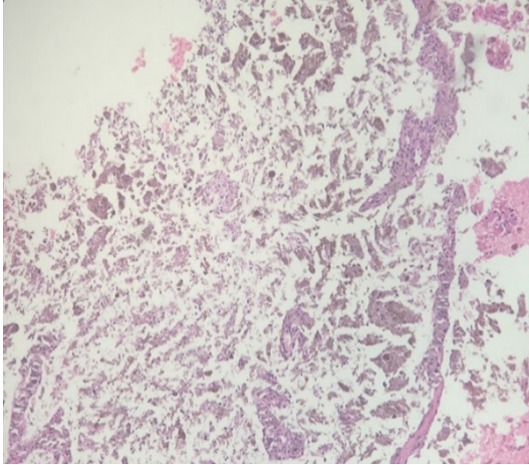


Figure 1. Postoperative pathology report from local hospital was “endometriosis” (H&E 50×).

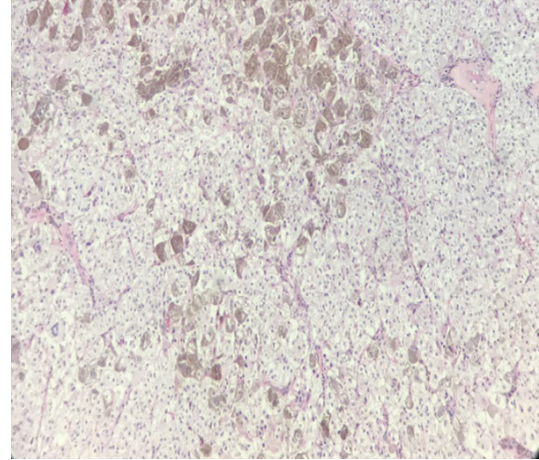


Figure 2. Most of the neoplastic cells were arranged in a nested or alveolar architecture supported by thin-walled vascular spaces (H&E 50×).

known MiTF family tumors have been reported as Xp11.2 translocation/TFE3 gene fusion-related renal cell carcinoma, t(6;11) translocation renal carcinoma, alveolar soft tissue sarcoma, malignant melanoma and soft tissue clear cell sarcoma.

This unique PEComa subtype is easily missed or misdiagnosed as a conventional PEComa because they are extremely rare, thus lack of understanding of their clinicopathologic features and also difficulty in predicting their clinical biologic behavior is a problem. Here, we report a case of TFE3 translocation PEComa and its malignant biological behavior, which was misdiagnosed as endometrial polyps a year ago and then relapsed. This study provides detailed clinical data, its histologic, immunohistochemical and molecular genetic characteristics, and follow-up data.

Case report

Clinical history

The patient, female, 53 years old, underwent left radical mastectomy in 2011, and was treated with tamoxifen for 4 years. In 2016, due to menstruation abnormality, curettage was undergone in a local hospital. The postoperative pathology report was “endometrial polyps” (**Figure 1**). In the past 1 year, the menstrual cycle was disordered. In the local hospital, ultrasonographic examination revealed that the thickness of endometrium was 13 mm, and a slightly higher echo of 23 mm * 17 mm was

observed in the intrauterine cavity. Clinically, this patient was treated as “endometrial polyps” and admitted to hospital. Under hysteroscopy, two polyps, 0.3 cm and 0.5 cm respectively, and a 0.6 cm black and brittle polyp on the right side of the uterus were seen. We diagnosed “TFE3 translocation PEComa”, and then the patient underwent laparoscopic hysterectomy. No space-occupying lesion was found in the uterine cavity. The tumor cells remained at the base of the “polyps”. No postoperative radiotherapy and chemotherapy was carried out and no recurrence and metastasis were observed during the 5 months follow-up period until now.

Histopathological and immunohistochemical findings

Morphologically, the tumor was mainly composed of epithelial-like cells that were, rich in cytoplasm and lightly stained. The tumor cells were arranged in a nested or alveolar architecture supported by thin-walled vascular spaces. Cell size was relatively uniform, and the cytoplasm was lightly stained and slightly eosinophilic. No necrosis and mitosis were observed in the cells. No obvious spindle cells existed (**Figure 2**). The nuclei were round or oval, and the nucleoli were obvious. High abundant melanin particles were found in certain cellular regions (**Figure 3**). The uterine whole-cut specimen showed that the tumor cells infiltrated the deep muscle layer and approached the outer membrane (**Figure 4**).

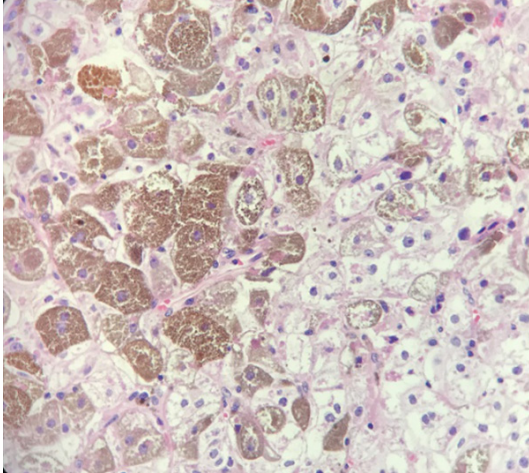


Figure 3. The tumor cells were rich in clear cytoplasm and lightly stained. The nuclei were round or oval, and the nucleoli were obvious. High abundant melanin particles were found in certain cellular regions (H&E 400×).

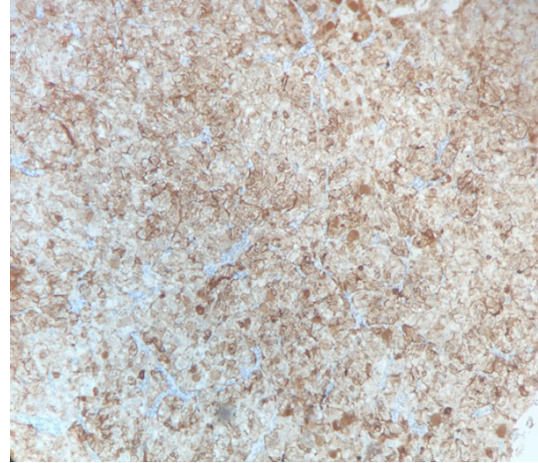


Figure 5. Strong expression of HMB-45.

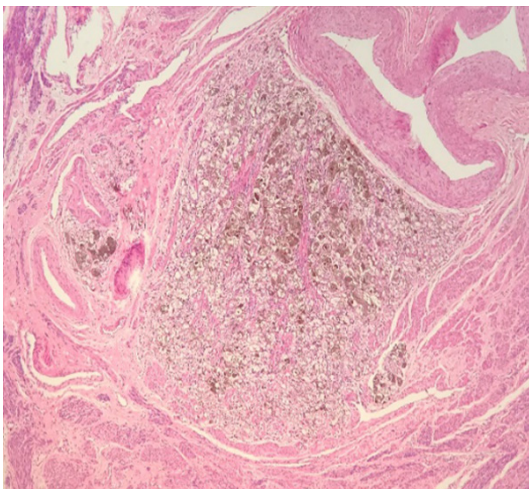


Figure 4. The tumor infiltrated into the muscular wall.

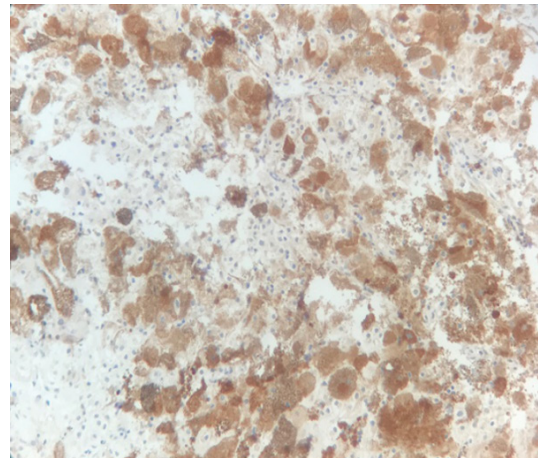


Figure 6. Strong expression of Melan-A.

The EnVision method was used for the immune reaction, and the positive signals of all antibody immunohistochemistry were brown-yellow granules. Immunohistochemistry showed that the tumor cells expressed HMB45 (**Figure 5**), Melan-A (**Figure 6**), Cathepsin K, and TFE3 (**Figure 7**), but SOX10, CK-PAN, S-100, PAX-8, DES (**Figure 8**) and SMA staining were all negative. Ki-67 protein showed a 5% proliferative rate (**Figure 9**).

Fluorescence in situ hybridization (FISH)

The FISH technique was used to detect the translocation and amplification of TFE3 gene.

The centromere sides were marked with green fluorescence, and the telomere sides were marked with red fluorescence. The measurement was performed according to the manufacturer's instruction: Under fluorescence microscopy, a pair of red-green fusion signals can be seen in the nucleus of normal female uterine cells. When the distance between red and green signals is greater than 2 signal diameters, the cell is considered a dividing cell. The positive result showed as one red-green fusion signal and one red-green separation signal can be seen in one nucleus. At least 100 nuclei were observed under fluorescence microscope with 1000× magnification, and only non-overlapping tumor nuclei were evaluated. When more than 10% of the tumor cells showed red-green separation signals, the specimen was considered a positive sample. In this

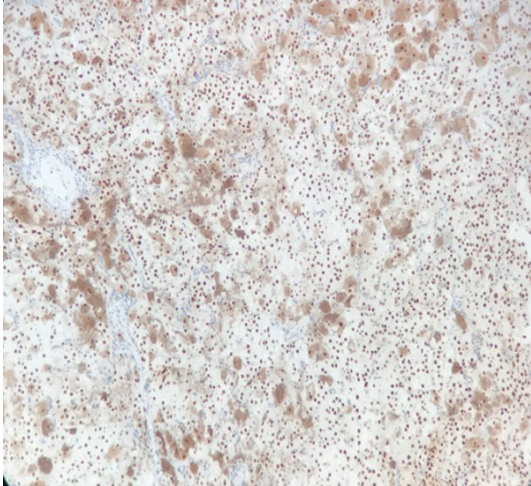


Figure 7. Strong expression of TFE3.

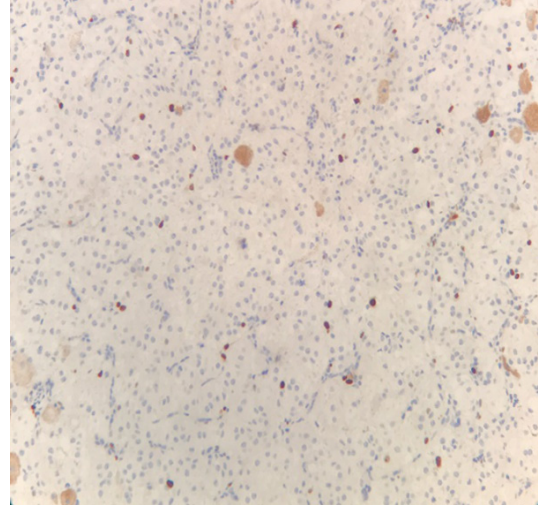


Figure 9. Ki-67 proliferation rate about 5%.

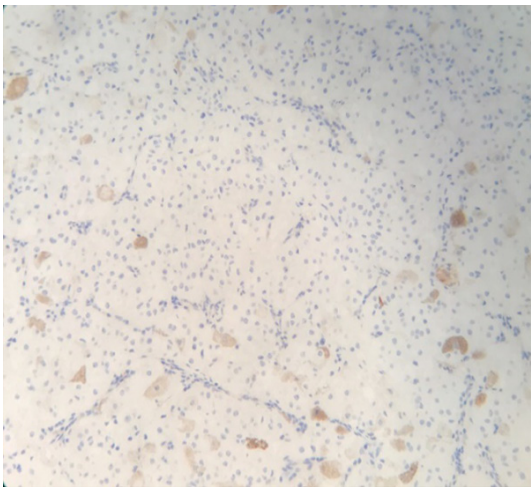


Figure 8. DES negative.

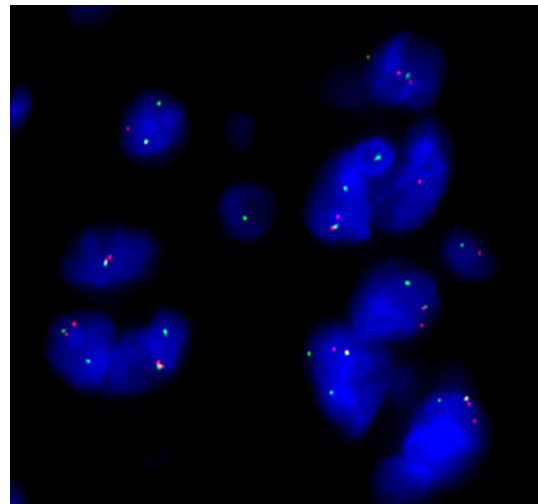


Figure 10. FISH showed abnormal splitting signal in TFE3.

case, more than 50% of the tumor cells showed red-green separation signals, indicating that the TFE3 genes have break translocations (**Figure 10**).

This study was approved by the Ethics Committee at Jinhua Central Hospital and the need for informed consent was waived (2019-174).

Discussion

In 1996, the concept of PEComa was first proposed by Zamboni et al. [15], who proposed to name all the tumors with perivascular epithelial-like cell differentiation as “PEComa”, including AML, CCST, LAM and other kinds of clear

cell tumors that could not be classified into the above three, which are called PEComa-NOS. In 2002, according to the soft tissue tumor histologic classification of WHO, PEComa was classified into differentiation-undefined soft tissue tumors [3], and female genital tract PEComas often occur in the uterus.

In recent years, many scholars have found that some PEComas have translocation of TFE3 gene. TFE3 fusion protein is highly expressed in such tumors, and has very high specificity and sensitivity. Cumulative evidence suggests that TFE3-related PEComa is a specific subgroup. Compared to conventional PEComa, TFE3-

translocated PEComas have several different clinical features, morphologic features, and immunophenotypes [16], such as relatively low patient age, no medical history of tuberous sclerosis; being completely composed of clear epithelioid cells morphologically, nested or alveolar architecture, with round or oval nuclei and clear nucleoli. TFE3-related PEComa share overlapping features with other TFE3 tumors (alveolar soft part sarcoma and Xp11.2 translocation renal cell carcinoma), strong expression of TFE3 and no-expression of smooth muscle actin or desmin according to immunohistochemistry. Moreover, such PEComas lack inactivating mutations of TSC1/TSC2. To our knowledge, only a few such cases have been reported. Our article reported a case of a malignant primary uterine PEComa with a TFE3 gene translocation detected by FISH, whose characteristics are consistent with those in this subgroup. Recently, there have been reports that TFE3-translocated PEComa and Melanotic Xp11 renal carcinoma have similar clinicopathologic features, histologic, immune, and molecular phenotype, belonging to a single clinicopathologic spectrum [17], and thus it is recommended to name this unique neoplasm as 'Xp11 neoplasm with melanocytic differentiation' or 'melanotic Xp11 neoplasm'.

The diagnosis of this case must exclude other morphologically similar tumors: (1) Alveolar soft tissue sarcoma which mainly occurs in adolescents, mostly in the limbs and trunk. Under microscopy, the tumor cells show organ- or acinar-like structures, which are divided by the sinusoidal vascular network and composed of eosinophilic polygonal epithelioid cells. In some cases, the cytoplasm is translucent or vacuolated, and the cytoplasm contains PSA-positive crystals. The cells are large, round or polygonal-shaped, containing 1 or 2 vacuolar nucleus, and the nucleoli are obvious. The tumor cells do not express HMB-45 or Melan-A, but can express the myogenic markers. The del(17)t(x; 17)(p11.2; q25) ASPL-TFE3 gene translocation fusion occurs, and the TFE3 protein is positive. (2) Metastatic Xp11.2 translocation/TFE3 gene fusion-related renal cell carcinoma mainly occur in children and adolescents, are rare in adults, and have morphologic features of papillary structures composed of clear cells, often accompanied by solid nest-

like structure composed of eosinophilic granules tumor cells, common in gravel bodies. These tumors are derived from several different translocations including the Xp11.2 chromosome. Currently, there are only 5 specific loci. The tumor cell nuclei highly express TFE3 protein, and PAX-8, PAX-2, CD10, but do not express HMB-45 and Melan-A. (3) Soft tissue clear cell sarcoma. Also known as soft tissue malignant melanoma, this is a malignant tumor with low incidence, and unclear tissue origin, mostly occurring in adolescents and middle-aged people, commonly in deep soft tissue of the distal extremities. Generally, it can be differentiated from PEComa by S-100 diffuse strong positivity. Clear cell sarcoma occasionally only express HMB-45 and can be confirmed by FISH detection of t(12;22)(q13;q13) (EWS;ATFI) gene fusion. (4) Epithelioid leiomyoma: Epithelioid cells and spindle cells can be seen under the microscope in both. The cytoplasm is acidophilic or clear, and it is bundled, nested, or dispersed-arranged, but epithelioid leiomyoma has no network-like thin-walled blood vessels, and TFE3, HMB-45, Melan-A show negative, while SMA, and desmin are positive.

Most PEComas showed good biologic behaviors and prognosis, with only a few poor prognoses, showing malignant behavior. In 2005, Folpe et al. [4] reported 26 cases of soft tissue and female genital tract PEComa, including 3 cases of recurrence, 5 cases of distant metastasis, 2 cases of death, and 18 cases of survival. In recent years, reports of recurrence and metastasis of PEComa have increased. There are currently no clear diagnostic criteria for malignant PEComa, because metastasis and recurrence are very rare for this kind of tumor, and there are always controversies on its clinical biologic behaviors. As described in WHO (2003): PEComa with invasive growth, abundant cells, enlarged nuclei and deep staining, increased mitotic figures, and atypical mitosis and coagulative necrosis should be considered malignant. Folpe et al. [4] proposed benign and malignant trial criteria for soft tissue and genital tract PEComa: (1) Benign: tumor diameter < 5 cm, non-invasive growth, no high nuclear grading and high cell density, mitotic $\leq 1/50$ HPF, no necrosis, no vascular infiltration. (2) The malignant potential is undetermined: only with nuclear polymorphic or mul-

tinucleated giant cells, or only with tumors > 5 cm in diameter. (3) Malignant: meeting the following two or more of the following criteria: tumor diameter > 5 cm, infiltrative growth pattern, high nuclear grade, mitotic activity > 1/50 HPF, necrosis, blood vessels infiltration. It has also been reported that the Ki-67 may be a reference value for the diagnosis of benign and malignant uterine PEComa, and Ki-67 > 5% may cause tumor metastasis [18]. Another study reported that the most important diagnostic indicator of uterine malignant PEComa is necrosis [19]. The results of Folpe et al. [4] revealed that PEComa with TFE3 gene fusion often showed invasive behavior and local recurrence rate and metastasis rates were 8.7% and 20.3%, respectively. An increasing number of TFE3-related PEComas demonstrated poor prognosis, and this finding seems to indicate that such tumors have malignant biologic behaviors [14]. Based on the above basis, our case should be malignant PEComa.

There are very few clinical cases and reports on TFE3-related PEComa. It is necessary to accumulate more cases and experience in the development of standardized diagnostic criteria between benign and malignant tumors as well as diagnosis and treatment plans. For a uterine malignant PEComa with altered TFE3 gene, there is no consistently accepted and effective treatment plan, and surgery is currently used. Complete resection of the tumor is currently recognized as a relatively direct and effective treatment method, but the scope of the surgery has not been unified. The role of adjuvant therapy is unclear and the protocol is not clear, either, and they are generally required to be comprehensively formulated combined with the patient's age, clinical manifestations, pathologic characteristics, and patient choice. Whether TFE3 is a driving gene for malignant uterine PEComa is still unclear and further researches are needed. For patients with uterine PEComa, we recommend detection of TFE3 gene, which may be another therapeutic target. Because its biologic behaviors are still unclear and the prognosis is difficult to estimate, patients should be followed up for long-term in clinical works.

Disclosure of conflict of interest

None.

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References

- [1] Folpe AL, Goodman ZD, Ishak KG, Paulino AF, Taboada EM, Meehan SA and Weiss SW. Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. *Am J Surg Pathol* 2000; 24: 1239-1246.
- [2] Matsui K, Tatsuguchi A, Valencia J, Yu Z, Bechtel J, Beasley MB, Avila N, Travis WD, Moss J and Ferrans VJ. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. *Hum Pathol* 2000; 31: 1242-1248.
- [3] Folpe AL. Neoplasms with perivascular epithelioid cell differentiation (PEComas) [M]. In: Fletcher CD, Unni KK and Mertens F, editors. *World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone*. Lyon: IARC Press; 2002. pp. 221-222.
- [4] Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL and Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol* 2005; 29: 1558-1575.
- [5] Doyle LA, Hornick JL and Fletcher CD. PEComa of the gastrointestinal tract: clinicopathologic study of 35 cases with evaluation of prognostic parameters. *Am J Surg Pathol* 2013; 37: 1769-1782.
- [6] Schoolmeester JK, Howitt BE, Hirsch MS, Dal CP, Quade BJ and Nucci MR. Perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: clinicopathologic and immunohistochemical characterization of 16 cases. *Am J Surg Pathol* 2014; 38: 176-188.
- [7] Conlon N, Soslow RA and Murali P. Perivascular epithelioid tumors (PEComas) of the gynecological tract. *Clin Pathol* 2015; 68: 418-426.
- [8] Dibble CC and Cantley LC. Regulation of mTORC1 by PI3K signaling. *Trends Cell Biol* 2015; 25: 545-555.
- [9] Wagner AJ, Malinowska-Kolodziej I, Morgan JA, Qin W, Fletcher CD, Vena N, Ligon AH, Antonescu CR, Ramaiya NH, Demetri GD, Kwiatkowski DJ and Maki RG. Clinical activity

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- of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol* 2010; 28: 835-840.
- [10] Sanfilippo R, Jones RL, Blay JY, Le Cesne A, Provenzano S, Antoniou G, Mir O, Fucà G, Fumagalli E, Bertulli R, Stacchiotti S, Brahmi M, Grosso F, Dufresne A, Hindi N, Sbaraglia M, Gronchi A, Collini P, Dei Tos AP and Casali PG. Role of chemotherapy, VEGFR Inhibitors, and mTOR inhibitors in advanced perivascular epithelioid cell tumors (PEComas). *Clin Cancer Res* 2019; 25: 5295-5300.
- [11] Gondran H, Thebaud E, Moreau A and Musquer N. First pancreatic perivascular epithelioid cell tumor (PEComa) treated by mTOR inhibitor. *Pancreatology* 2019; 19: 566-568.
- [12] Tanaka M, Kato K, Gomi K, Matsumoto M, Kudo H, Shinkai M, Ohama Y, Kigasawa H and Tanaka Y. Perivascular epithelioid cell tumor with SFPQ/PSF-TFE3 gene fusion in a patient with advanced neuroblastoma. *Am J Surg Pathol* 2009; 33: 1416-1420.
- [13] Argani P, Aulmann S, Illei PB, Netto GJ, Ro J, Cho HY, Dogan S, Ladanyi M, Martignoni G, Goldblum JR and Weiss SW. A distinctive subset of PEComas harbors TFE3 gene fusions. *Am J Surg Pathol* 2010; 34: 1395-406.
- [14] Williamson SR, Bunde PJ, Montironi R, LopezBeltran A, Zhang S, Wang M, MacLennan GT and Cheng L. Malignant perivascular epithelioid cell neoplasm (PEComa) of the urinary bladder with TFE3 gene rearrangement: clinicopathologic, immunohistochemical, and molecular features. *Am J Surg Pathol* 2013; 37: 1619-1626.
- [15] Zambone G, Pea M, Marignoni G, Zancanaro C, Faccioli G, Gilioli E, Pederzoli P and Bonetti F. Clear cell "sugar" tumor of the pancreas. A novel member of the family of lesions characterized by the presence of perivascular epithelioid cells. *Am J Surg Pathol* 1996; 20: 722-730.
- [16] Schoolmeester JK, Dao LN, Sukov WR, Wang L, ParkKJ, Murali R, Hameed MR and Soslow RA. TFE3 translocation-associated perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: morphology, immunophenotype, differential diagnosis. *Am J Surg Pathol* 2015; 39: 394-404.
- [17] Wang, XT, Xia QY, Ni H, Wang ZY, Ye SB, Li R, Wang X, Lv JH, Shi SS, Ma HH, Lu ZF, Shen Q, Zhou XJ and Rao Q. Xp11 neoplasm with melanocytic differentiation of the prostate harbouring the novel NONO-TFE3 gene fusion: report of a unique case expanding the gene fusion spectrum. *Histopathology* 2016; 69: 450-8.
- [18] Zhang C, Pan F, Qiao J, Jiang S, Du Y and Zhao C. Perivascular epithelioid cell tumor of the cervix with malignant potential. *Int J Gynaecol Obstet* 2013; 123: 72-73.
- [19] Fink D, Marsden DE, Edwards L, Camaris C and Hacker NF. Malignant perivascular epithelioid cell tumor (PEComa) arising in the broad ligament. *Int J Gynecol Cancer* 2004; 14: 1036-1039.