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Clinicopathological Analysis of Perivascular Epithelioid Cell Tumor in Female Genital Tract

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Abstract:

Objective: To explore the clinicopathological features, diagnosis, and differential diagnosis of perivascular epithelioid cell tumor (PEComa) of the female genital tract. *Methods:* The clinical data of four patients with PEComa of the female genital tract were collected, and their histomorphological characteristics were observed. Immunohistochemical staining was performed using the EnVision two-step method, and fluorescence *in situ* hybridization (FISH) was used to detect *TFE3* gene rearrangement. The clinicopathological features were analyzed, and relevant literature was reviewed. *Results:* None of the four patients were associated with tuberous sclerosis complex, and the lesions were located in the cervix, uterine body, and vaginal stump, respectively. The tumor was mainly composed of epithelioid cells arranged in solid sheets, nests, and bundles. The tumor cells had abundant cytoplasm, which was transparent or eosinophilic and granular. The nuclei showed mild or marked atypia with variable mitotic figures. Tumor necrosis, multinucleated giant cells, and rhabdoid cells were observed in some cases. Immunohistochemistry showed that HMB45, Melan A, MiTF, TFE3, desmin, SMA, and h-caldesmon were positive in three surgical specimens, while S-100 and SOX10 were negative. In one consultation case, HMB45, Melan A, desmin, and SMA were positive, while S-100 was negative. FISH detected no *TFE3* gene rearrangement in three cases. *Conclusion:* PEComa of the female genital tract is prone to misdiagnosis. Combining typical histological, immunohistochemical, and molecular genetic features can help improve diagnostic accuracy.

Keywords:

Perivascular epithelioid cell tumor
Female genital tract
Clinicopathological features
Immunohistochemistry
FISH

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1. Introduction

Perivascular epithelioid cell tumor (PEComa) is a mesenchymal tumor composed of perivascular epithelioid cells that are closely associated with blood vessel walls and express markers of melanocytes and smooth muscle cells. There are only about 100 cases of female genital PEComa reported in domestic and foreign literature [1], mostly as individual cases or small sample reports [2]. PEComa often occurs in the uterine body, and its histological and immunohistochemical phenotypes are similar to those of smooth muscle tumors, making it prone to misdiagnosis. This article explores the clinicopathological features, immunohistochemical phenotypes, and prognosis of female genital PEComa, aiming to provide more precise and effective methods for patient treatment.

2. Materials and methods

2.1. Clinical data

Four specimens of female genital tract PEComa diagnosed by the pathology departments of Peking University People's Hospital and Beijing Shijingshan Hospital from January 2017 to December 2019 were collected. Cases 1 to 3 were surgical patients, and Case 4 was a consultation patient. The patients' ages were 29, 31, 56, and 60 years old, respectively.

2.2. Methods

The surgical specimens were fixed with 10% neutral formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin and immunohistochemical EnVision two-step method. Antibodies including HMB-45, Melan A, MiTF, TFE3, desmin, SMA, h-caldesmon, S-100, SOX10, and Ki67 were purchased from Beijing Zhongshan Jinqiao Company.

2.3. Result interpretation

The sections were reviewed by two senior pathologists, and the diagnostic criteria were based on the WHO (2020) classification of female genital tract tumors [3]. The immune response of tumor cells was semi-quantitatively graded, with brown-yellow granular staining of the cell membrane, cytoplasm, or nucleus considered positive. No obvious positive cells were considered negative. Positive cell counts of 1–5% were (+), 6–25% were (++), 26–50% were (+++), and > 50% were (++++). The positive intensity of tumor cells was classified as strongly positive or weakly positive.

2.4. Fluorescence in situ hybridization detection

Fluorescence *in situ* hybridization (FISH) was performed to detect *TFE3* gene rearrangement in Cases 1 to 3. The *TFE3* (Xp11.2) gene break-apart probe kit was purchased from Guangzhou Anbiping Company.

3. Results

3.1. Clinical features

The clinical manifestations of patients in this group mainly included abdominal pain and uterine space-occupying lesions. Case 1 was preoperatively diagnosed with cervical polyp; Cases 2 and 4 were both preoperatively diagnosed with uterine leiomyoma by imaging; Case 3 underwent total hysterectomy at an outside hospital six years ago and pelvic tumor resection one year ago, and was misdiagnosed as leiomyosarcoma postoperatively. Cases 1 and 4 occurred in the cervix, Case 2 occurred in the uterine body, and Case 3 occurred in the vaginal stump; all four cases were not associated with tuberous sclerosis complex (**Table 1**).

3.2. Pathological examination

3.2.1. Gross examination

The maximum diameter of the tumors ranged from 2.0 to 10.0 cm, with relatively clear boundaries, soft to medium texture, and gray-white, gray-yellow, or gray-brown cut surfaces. Case 1 presented as polypoid; Case 2 had a tumor located in the uterine muscle wall with visible hemorrhage and necrosis (**Figure 1**); Case 3 appeared multi-nodular; Case 4 was a fragmented specimen of an intramuscular tumor.

3.2.2. Microscopic examination

Case 1 showed a well-defined pushing border; Cases 2 and 3 had partially compressive and infiltrative borders, with Case 2 showing tongue-like infiltrative borders similar to low-grade endometrial stromal sarcoma in some areas, along with contraction clefts (**Figure 2**); Case 4 was a fragmented specimen, making it impossible to evaluate the border. In all four cases, the tumor

Table 1. Clinical data of four cases of female genital tract PEComa

Case	Age (years)	Clinical manifestations	Clinical history	Tuberous sclerosis complex	Location of onset	Treatment method	Recurrence and metastasis	Follow-up
1	31	Physical examination revealed cervical polyp	None	None	Cervix	Polyp resection	None	30 months, survival without tumor
2	56	Fever, abdominal pain, and uterine mass	Multiple uterine fibroids for 20 years, untreated	None	Uterine body	Total hysterectomy + bilateral salpingo-oophorectomy + pelvic lymph node dissection	None	25 months, survival without tumor
3	60	Abdominal pain, abdominal distension, difficulty urinating and defecating	Total hysterectomy with bilateral salpingo-oophorectomy performed at an outside hospital six years ago, pelvic tumor resection performed at an outside hospital one year ago	None	Vaginal stump, sigmoid colon	Resection of vaginal stump and sigmoid colon lesions, chemotherapy with gemcitabine + docetaxel regimen	18 months at vaginal stump (lesion resection); 24 months at vaginal stump (untreated); 46 months in pelvis, sigmoid colon, and rectum (surgical resection followed by chemotherapy)	54 months, survival with tumor
4	29	Cervical and lower uterine segment masses	None	None	Cervix and lower uterine segment	Tumor resection (fragmented resection)	None	24 months, survival without tumor

tissue was arranged in solid sheets, nests, and bundles, with a rich network of thin-walled blood vessels in the stroma. Case 1 showed a radial arrangement of tumor cells around abnormal thick-walled blood vessels; Case 2 had antler-like blood vessels. The tumor cells were predominantly epithelioid, mixed with varying amounts of spindle cells. The epithelioid tumor cells had abundant cytoplasm that was transparent/eosinophilic and granular (**Figure 3**). A few rhabdoid cells were seen in Case 2, with deeply stained eosinophilic cytoplasm and eccentric nuclei (**Figure 4**). Cases 1 and 4 showed mild nuclear atypia; Cases 2 and 3 had significant atypia, with visible multinucleated giant cells (**Figure 5**), and Case 2 showed intranuclear inclusions. The mitotic count was 0–1/50HPF in Cases 1 and 4, and 3–10/50HPF in Cases 2 and 3, with visible tumor necrosis and intravascular tumor emboli. Varying degrees of hyalinization and myxoid changes were seen in the tumor stroma of all four cases. Cases 2 and 3 were malignant PEComas, while Cases 1 and 4 were PEComas with uncertain malignant potential.

3.3. Immunohistochemical phenotype

In this group, all four cases showed strong positivity for HMB-45, Melan A, desmin, and SMA (positive cell count ++ to ++++); two cases were strongly positive for TFE3 (positive cell count +++/++++), and one case was weakly positive for TFE3 (positive cell count ++++); three cases were strongly positive for h-caldesmon (positive cell count +++/++++); one case showed weak positivity for MiTF (positive cell count ++); all four cases were negative for S-100; three cases were negative for SOX10; the Ki67 proliferation index ranged from 5% to 70%.

3.4. FISH detection

No *TFE3* gene rearrangement was detected in Cases 1 to 3 (**Figure 6**).

3.5. Treatment and follow-up

Case 2 underwent hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection, while the other three cases underwent simple tumor resection; Case 3 received six courses of chemotherapy with gemcitabine and docetaxel postoperatively. Telephone follow-up was conducted in this group, with a follow-up period of 24 to 54 months as of December 31, 2021. Case 3 experienced recurrence and metastasis in the vaginal

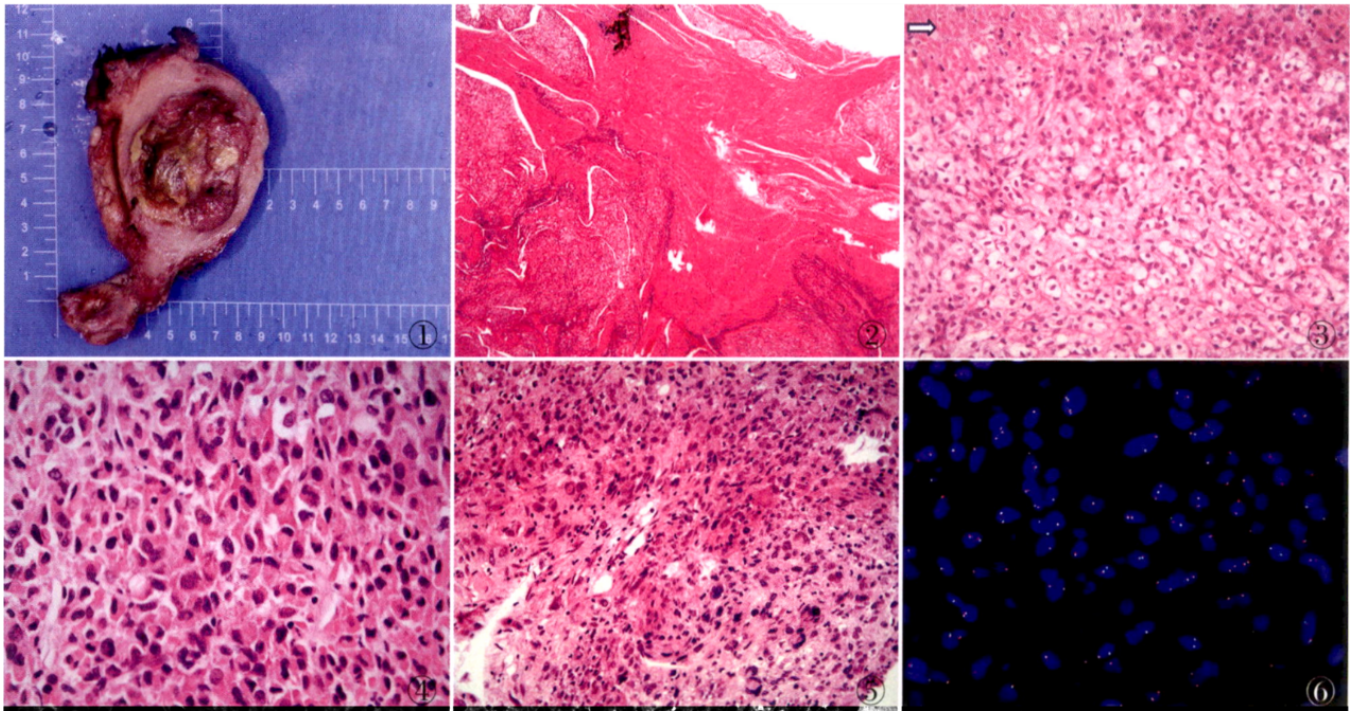

Figure 1. The tumor is located in the uterine muscle wall, showing hemorrhage and necrosis; **Figure 2.** PEComa of the uterine body with tongue-like infiltrative borders similar to low-grade endometrial stromal sarcoma, showing contraction clefts; **Figure 3.** The tumor tissue is arranged in solid sheets, with a rich network of thin-walled blood vessels in the stroma. The tumor cells are predominantly epithelioid, with abundant cytoplasm that is transparent/eosinophilic and granular. Tumor necrosis is visible (indicated by arrows); **Figure 4.** A few tumor cells show rhabdoid morphology, with deeply stained eosinophilic cytoplasm and eccentric nuclei; **Figure 5.** Malignant PEComa tumor cells show significant atypia and the presence of multinucleated giant cells; **Figure 6.** No *TFE3* gene rearrangement was detected in the tumor cells using FISH method.

stump, pelvis, sigmoid colon, and rectum at 18, 24, and 46 months postoperatively; the other three cases showed no tumor recurrence or metastasis (**Table 1**).

4. Discussion and conclusion

The WHO (2020) classification of soft tissue tumors recommends that PEComa includes angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), and unspecified type PEComa [4]. Among them, the unspecified type PEComa can occur in various locations, and the female genital tract (25%) is a relatively common site [1]. Currently, the cell origin of PEComa remains unclear and may originate from neural crest stem cells that differentiate into myoid and melanocytic cells during embryonic development [5].

PEComa of the female genital tract has nonspecific clinical manifestations and is often misdiagnosed as “uterine fibroids” before surgery [6]. According to literature reports, the uterine body is the most common site (about 71.9%), followed by the cervix (about 10.5%); the age of onset ranges from 6 to 79 years, with a peak age of 50 to 69 years [7]; about 10% of patients are associated with tuberous sclerosis complex [8]. The cases in this group occurred in the uterine body, cervix, and vaginal stump, respectively. The two patients with cervical lesions were younger, while the two patients with uterine body and vaginal stump lesions were older. Half of the patients were diagnosed with “uterine fibroids” before surgery, which is consistent with literature reports [6,7]. Uterine PEComa is usually located in the muscular wall and occasionally presents as a polypoid mass protruding into the uterine cavity [6]. In this group, two tumors were located in the muscular wall, and one presented as a polypoid mass protruding into the cervical canal, consistent with literature reports. Microscopically, the tumor margin can be compressive or infiltrative, and it can show a tongue-like infiltrative growth pattern similar

to low-grade endometrial stromal sarcoma [1,6]. The tumor tissue often arranges in solid sheets, nests, and bundles. The cells are mainly epithelioid, with clear boundaries, transparent/acidic cytoplasm, and granular appearance; spindle cells may also be present in varying proportions. Nuclear atypia can be mild or prominent, and there may be multinucleated tumor giant cells and coagulation necrosis. The stroma contains a rich network of thin-walled blood vessels, which may have collagen deposition with hyalinization. Rare features include rhabdoid cells, intranuclear inclusions, and antler-like blood vessels. The morphology of the cases in this group is consistent with literature reports [1,6,8].

PEComa characteristically co-expresses myogenic and melanocytic markers, but the positive range and intensity of each marker reported in the literature vary [8-10]. Bennett and Oliva [6] reported 87 cases of female genital tract PEComa. Melanocytic markers include HMB-45, Melan A, MiTF, CatK, and PLN2, with total positive rates of 99%, 67%, 83%, 100%, and 86%, respectively. Myogenic markers include SMA, desmin, and h-caldesmon, with total positive rates of 88%, 80%, and 76%, respectively. In this group, HMB-45 was positive in >50% of the tumor area in two cases and <25% in the other two cases, showing a large variation in the staining range. Melan A had a similar positive range and intensity to HMB-45 in three cases, but was significantly lower than HMB-45 in one case. MiTF showed focal weak positivity in one case and negativity in two cases, which is consistent with literature reports [6]. In summary, epithelioid tumor cells in PEComa show strong and diffuse positivity for melanocytic markers, while spindle cells show strong and widespread positivity for myogenic markers, but this is not absolute. In this group, there was a significant crossover in the positivity of melanocytic markers between epithelioid and spindle cells in four tumor cases. Schoolmeester *et al.* [9] reported that TFE3 protein was focally or diffusely positive in 38% of female genital tract PEComas, but no *TFE3* gene rearrangement was detected. Subsequently, they reported six cases of *TFE3* gene rearrangement-related lesions, where TFE3 was usually diffusely positive, and myogenic markers were often negative [11]. In this group, three tumor cases showed focal or diffuse weak to strong positivity for TFE3, and no *TFE3* gene rearrangement was detected, suggesting that *TFE3* gene rearrangement does not necessarily occur in PEComa with positive TFE3 immunohistochemistry. The myogenic markers in this group were all focally or diffusely strongly positive, suggesting that if female genital tract PEComa shows co-positivity for TFE3 and multiple myogenic markers, it is not a case of *TFE3* gene rearrangement, which is consistent with literature reports [9]. Additionally, S-100 and SOX10 were both negative in this group, consistent with literature reports [6,12]. There are three main molecular genetic features of female genital tract PEComa [6]: abnormalities in tuberous sclerosis complex (TSC1/TSC2); *TFE3* gene rearrangement; *RAD51B* gene rearrangement and other rare gene rearrangements. No *TFE3* gene rearrangement was detected in this group, and further analysis is needed.

Female genital tract PEComa needs to be distinguished from smooth muscle-derived tumors, as both can have similar preoperative imaging, histological features, and immunophenotypes [6]. In this group of PEComas, delicate thin-walled sinusoidal blood vessels were observed, while diffusely distributed thick-walled blood vessels were absent. The cytoplasm of tumor cells appeared granular, without diffuse eosinophilia or perinuclear vacuoles. Positive melanocytic markers (≥2) and strong positivity for TFE3 were present, distinguishing them from smooth muscle tumors. One patient in this group was misdiagnosed with leiomyosarcoma due to the absence of melanocytic marker detection such as HMB-45 and Melan A. Additionally, the presence of tuberous sclerosis complex or *TFE3* gene rearrangement further supports the diagnosis of PEComa [6]. PEComa also needs to be distinguished from alveolar soft part sarcoma, low-grade endometrial stromal sarcoma, and melanoma, which can be differentiated based on histological, immunophenotypic, and genetic features.

The WHO (2020) classification of female genital tract tumors predicts the biological characteristics of PEComa based on the following criteria: (1) tumor size ≥5 cm in maximum diameter, (2) high nuclear grade, (3) >1 mitotic figure per 50 mm^2, (4) tumor necrosis, and (5) vascular invasion [3]. Tumors with ≥3 of these features are classified as malignant, while those with ≤2 features are considered to have uncertain malignant potential. The diagnosis of "benign" should be avoided.

Currently, the treatment of female genital tract

PEComa often involves total hysterectomy with bilateral salpingo-oophorectomy, and radiotherapy and chemotherapy are administered for patients with recurrence and metastasis. Young patients with localized lesions undergo complete surgical removal of the tumor and follow-up. mTOR inhibitor targeted therapy has shown some efficacy in patients with malignant, recurrent, or incompletely resectable tumors [6]. In this group, there were two cases of malignant PEComa, with one patient experiencing multiple recurrences and metastases after surgery. The other two cases were classified as PEComa with uncertain malignant potential. These patients were young with localized lesions and underwent simple tumor removal without recurrence after surgery.

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Disclosure statement

The authors declare no conflict of interest.

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