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Malignant perivascular epithelioid cell tumor in the female genital tract

Preferred reporting items for systematic reviews and meta-analyses

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Abstract

Background: Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal tumor, located at various anatomic sites, including the female genital tract. This study aimed to evaluate the clinicopathological characteristics of patients with PEComa arising from the female genital tract.

Methods: A retrospective study was conducted in Taipei Veterans General Hospital (Taipei VGH) between 2008 and 2018. All published English cases based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were also included in the current review.

Results: A total of 114 women from PRISMA and 3 women from Taipei VGH were identified. The uterus was the most commonly involved site (82/114, 71.9%), followed by the cervix (12/114, 10.5%). Immunohistochemical staining showed that nearly all gynecological PEComas were positive for human melanoma black 45(113/114, 99.1%). More than half of the gynecological PEComas were immunoreactive for desmin (50/85, 58.8%). Multi-modality treatment, including surgery and mammalian target of rapamycin (mTOR) inhibitors as targeted therapy, provided long-term disease-free survival (cure rate ranging from 50% to 100%, based on the different anatomic sites of the female genital tract).

Conclusion: Multi-modality treatment, including cytoreductive surgery and mTOR inhibitors with/without chemotherapy and/or radiation, should be considered for the management of women with PEComas in the genital tract.

Abbreviations: AML = angiomyolipoma, CCST = lymphangioma, pulmonary clear cell "sugar" tumor, CT = computed tomography, HMB-45 = human melanoma black 45, HPF = high power field, LAM = lymphangioleiomyomatosis, mTOR = mammalian target of rapamycin, mTORC1 = mammalian target of rapamycin complex 1, PEComa = perivascular epithelioid cell tumor, PRISMA = preferred reporting items for systematic reviews and meta-analyses, TFE-3 = transcription factor E3, TSC = tuberous sclerosis complex.

Keywords: female genital tract, immunohistochemistry, multi-modality, PEComa, targeted therapy

1. Introduction

Perivascular epithelioid cell tumors (PEComas) are a family of tumors and represent a unique diagnostic challenge with regard to distinguishing them accurately and reproducibly from more common entities, such as smooth muscle tumors.[1,2] The PEComa family of tumors is a complex disease group, which includes angiomyolipoma (AML), lymphangioma, pulmonary clear cell "sugar" tumor (CCST) and lymphangioleiomyomatosis (LAM), primary extrapulmonary sugar tumor, clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres, abdominopelvic sarcoma of perivascular epithelioid cells, and other tumors with similar features at various sites.[2,3]

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The authors declare that they have no competing interests.

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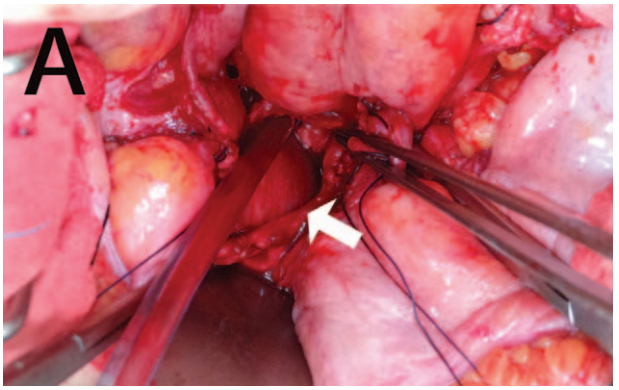

Figure 1. Operative image and specimen. (A) A significant vaginal tumor could be seen via the vagina cuff.

However, accurate diagnosis is very important, since mammalian target of rapamycin (mTOR) inhibitors as potential targeted therapy could be crucially used in tumors with aggressive behavior and an advanced stage.[3] PEComa of the gynecological tract was first recognized and diagnosed within the last 20 years.[2] To explore this rare disease and provide updated information, a retrospective study of cases between 2008 and 2018 from the Taipei Veterans General Hospital (Taipei VGH) and all published English cases based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was conducted. This study was approved by institutional review board and informed consents were obtained.

2. Methods

Three cases identified by Taipei VGH.

2.1. Case 1

A 51-year-old, gravida 2 para 2, menopausal woman was sent to the emergency department due to syncope and vaginal bleeding for several weeks. Abdominal computed tomography (CT) revealed an 8.3-cm mass in the right pelvis, suggesting that this tumor probably emerged from the vagina or uterine cervix, with involvement of the urinary bladder, rectum, and right ureter, and mild obstructive uropathy. A Foley or double-J catheter was inserted and a vaginal biopsy was performed. The initial report revealed sarcoma or malignant mixed müllerian tumor. As vaginal sarcoma was suspected, the patient underwent suboptimal debulking surgery with total vaginectomy. During the surgery, a significant vaginal tumor could be seen via the vagina cuff, and a very large vaginal tumor was excised (Fig. 1). Pathology showed that the cells were arranged in solid nests or lobules with round to ovoid nuclei, and clear to eosinophilic cytoplasm. Hypercellularity, marked nuclear pleomorphism with high mitotic features (65/50 high-power field [HPF]), tumor necrosis, and carcinoma-like feature were noted (Fig. 2). The cells were immunoreactive for melan-A, and were focally positive for

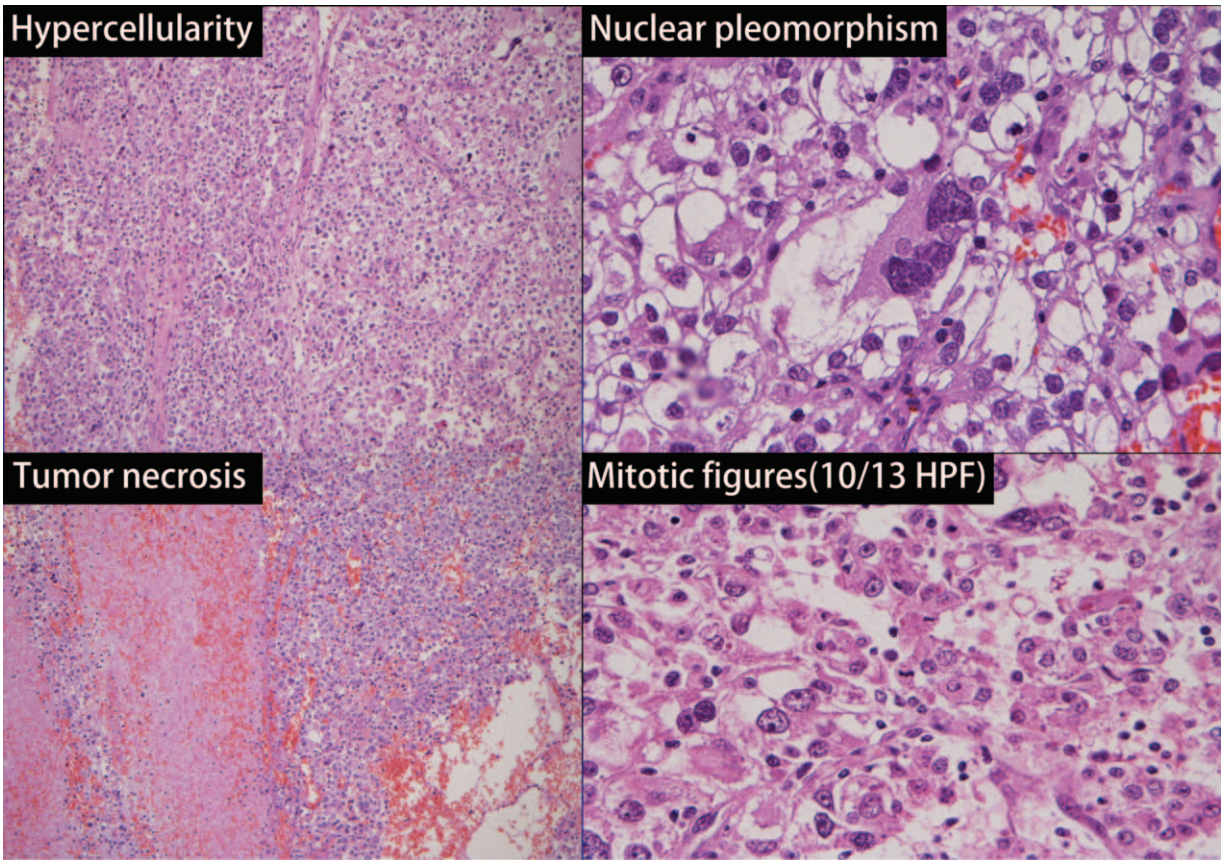

Figure 2. Hematoxylin–eosin staining. The neoplastic cells are arranged in solid nests or lobules with round to ovoid nuclei with clear to eosinophilic cytoplasm. Hypercellularity, marked nuclear pleomorphism, tumor necrosis, and carcinoma-like feature are noted. Frequent mitotic figures are found (13/10 high-power fields), × 200.

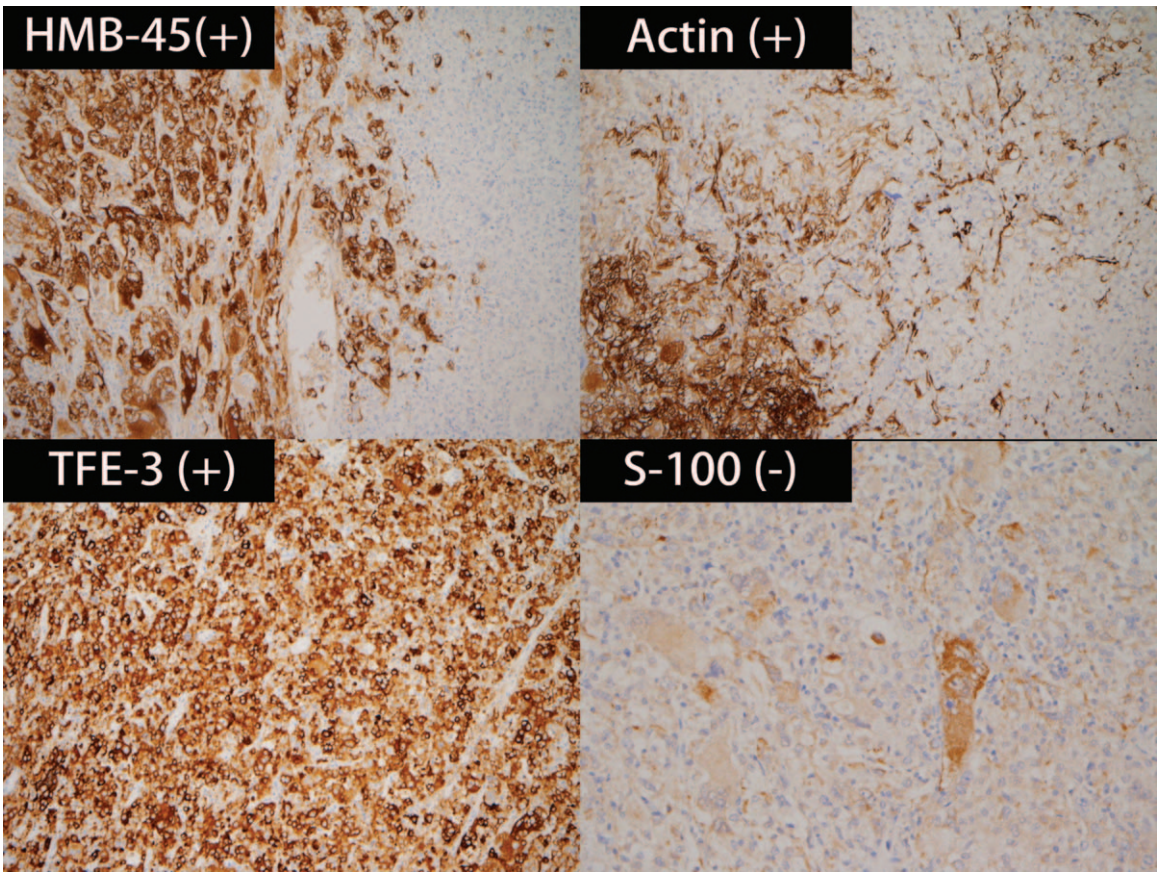

Figure 3. The neoplastic cells are immunoreactive for melan-A and focally positive for human melanoma black 45, actin, and transcription factor E3. The S-100, cytokeratin, and paired-box gene 8 immunostains are negative, × 4.

human melanoma black 45 (HMB-45), actin, and transcription factor E3 (TFE-3). S-100, cytokeratin, and paired-box gene 8 immunostaining was performed and the results were negative (Fig. 3). Based on these findings, the patient was diagnosed with PEComa of the vagina with aggressive behavior. Multi-modality treatment was administered, including mTOR inhibitors and radiotherapy. To date, the patient survived without the disease (more than 7 months).

2.2. Case 2

This 80-year-old woman with hypertension and arrhythmia on regular maintenance therapy had urinary incontinence for several weeks. Transvaginal ultrasound showed a 10-cm pelvic mass with rich flow. Magnetic resonance imaging showed a lobulated heterogeneous soft tissue mass, $10 \times 8 \times 8$ cm in size, arising from the right lateral posterior uterine body with an intermediate high signal on T2 weighted image, which indicates sarcoma. Complete staging surgery was performed. Pathology showed PEComa of the uterus, pT2bN0M0, with International Federation of Gynecology and Obstetrics stage IIB. Because the patient was elderly, no further treatment was administered. However, 1 month later, tumor recurrence resulted in vaginal bleeding and abdominal pain. Computed tomography examination confirmed tumor recurrence located at the right lower pelvis. Secondary complete tumor excision, including total vaginectomy and stump tumor resection, was performed, and pathology showed PEComa recurrence. Because of the aggressive behavior of this disease, postoperative multi-modality treatment, including the administration of mTOR inhibitors, and radiotherapy were initiated. To date, the patient has survived without the disease (more than 4 years).

2.3. Case 3

This 71-year-old woman, gravida 4, para 3, experienced menopause at the age of 50. She experienced intermittent lower abdominal pain for a month. Transabdominal ultrasound showed a 14-cm pelvic solid tumor. A computed tomography scan showed a pelvic mass with peritoneal seeding and ascites, which was suspicious of retroperitoneal uterine sarcoma. The patient underwent suboptimal debulking surgery. Pathology revealed broad ligament PEComa. For personal reasons, no further treatment was administered. Four months later, the patient experienced abdominal pain; a follow-up computed tomography examination was arranged and showed multiple mass lesions with heterogeneous enhancement, favoring persistent disease. Despite administration of mTOR inhibitor after disease progression, the patient died of disease 1 year after diagnosis.

Our experiences on gynecological PEComas were limited by the small case numbers and short follow-up period. However, we believe that with complete surgical resection of the tumor and early administration of mTOR inhibitors for aggressive disease behavior, patients might have the chance to achieve optimistic clinical outcomes and prolonged survival. The clinical and

Table 1

Summary of clinical features of Taipei VGH cases.

Case	Age	Tumor location	Tumor size (cm)	Surgery	Adjuvant therapy	Time to recurrence	Follow-up duration	Outcome
1	51	Vagina	9 × 9	Suboptimal debulking + total vaginectomy	Target therapy + IVRT	Disease free	7 months	SD
2	80	Uterus	10 × 9	Complete staging	Nil	1 month	50 months	Alive
3	71	Broad ligament	13 × 11	Suboptimal debulking	Nil	N/A	12 months	DOD

DOD = died of disease, N/A = indicates not applicable, SD = stable disease.

immunohistochemical characteristics of all patients diagnosed and treated at our institution are summarized in Tables 1 and 2.

3. PRISMA-driven systemic review for female genital tract PEComa

3.1. Literature search

To further understand the female genital tract PEComas, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to complete the searches and review. The final search was conducted in June 2018. Electronic medical database PubMed was searched for all related literature, using combinations of the following terms: ("perivascular epithelioid cell tumor" or "PEComa") and ("female genital tract" or "gynecological") in the title and abstract. Filters were set to find all human studies available in full-text and in the English language on PEComas that were published over the past 20 years. Inclusion criteria for the present systematic review included: case reports, case series, and case characteristic researches published from January 1997 to December 2017, concerning patients with a diagnosis of female genital tract PEComas. The definition of female genital tract includes the following pelvic structures: uterus, ovaries, fallopian tubes, cervix, vagina, broad ligament, and pelvic floor. Two independent reviewers (CHL. and WTC) selected the identified studies based on the title and abstract. The following data were collected from all included studies: first author's surname, publication year, sample size, treatment strategies, morphological and immunohistochemical characteristics of the PEComa, duration of follow-up, and clinical outcome. We present a flowchart in Fig. 4 that summarizes study identification and selection according to PRISMA. Ethics committee approval was not necessary for systematic reviews.

4. Results

Our search yielded 12 citations. A total of 114 cases were described in this report,[1,4–14] and the clinical characteristics of these cases are summarized in Table 3. The age of patients with gynecological PEComa ranged from 9 to 79 years, with a peak incidence around the mid-40 s. The uterus was the most commonly involved site (n = 82) followed by the cervix (n = 12). The median tumor diameter was 5 cm, and necrosis occurred in two-fifths of the cases. Epithelioid cells and thin and delicate vessels were present in nearly all histological examinations. Of the melanocytic markers, HMB-45 was most commonly expressed (113/114 positive, nearly 100%). Of the smooth-muscle markers, desmin was most commonly expressed (50/85 cases, 58.9%). Surgery was the main treatment. The patients showed favorable outcomes. At least half of the patients (some studies reported rates of 100%) were disease free, and only a few died of the disease. The majority of the remaining patients had stable disease.

5. Discussion

Among the patients with PEComa of the gynecologic tract, the uterus was reported to be the most commonly affected anatomic site (58.6%), followed by the cervix (10.5), while only 1 case occurred in the vulva (Table 3). Since PEComa primarily occurs in the uterus (either uterine body or uterine cervix), patients commonly experience vaginal bleeding, abdominal pain, and compression syndrome. A definite diagnosis is obtained through biopsy, and imaging is used to determine the location and staging. However, like our presented cases, gynecological PEComas could mimic uterine sarcoma because of their location and clinical presentations. PEComa is usually a circumscribed mass lesion containing solid and cystic components, seldom involving the adjacent organs or structures.[15] Avid enhancement is found in the solid components, and areas of high T1 signal intensity internally represent hemorrhagic or proteinaceous fluid content.[15–17] Therefore, an insufficient biopsy sample, and a rapidly enlarging uterus with a mass lesion containing solid and cystic components on an imaging study could easily be misdiagnosed as uterine sarcoma pre-operatively.

PEComa is classified as benign, of uncertain malignant potential, or malignant, based on the following 6 worrisome features: tumor size (>5 cm), infiltration, high nuclear grade, increased cellularity, high mitotic activity (≥2 mitotic figure/50 HPF), tumor necrosis, and vascular invasion.[5] According to the classification of PEComa of the gastrointestinal tract, benign PEComa had no worrisome features.[18] In contrast, PEComas with uncertain malignant potential exhibited 1 worrisome feature. When 2 or more worrisome features are noted, the

Table 2

Summary of immunohistochemical features of Taipei VGH cases.

Case	HMB-45	Melan-A	Actin	TFE-3	S-100	CK	PAX-8	H-caldesmon	HHF-35	CD-10	Desmin
1	Focally positive	Positive	Negative	Negative	Negative	Negative	Negative	N/A	N/A	N/A	N/A
2	Positive	N/A	Positive	N/A	N/A	N/A	N/A	Positive	Positive	N/A	N/A
3	Positive	Negative	N/A	N/A	Negative	N/A	N/A	N/A	Negative	Negative	Negative

CK = cytokeratin, HHF-35 = muscle actin antibody 35, HMB-45 = human melanoma black 45, N/A = indicates not applicable, PAX-8 = paired box gene 8, TFE-3 = transcription factor E3.

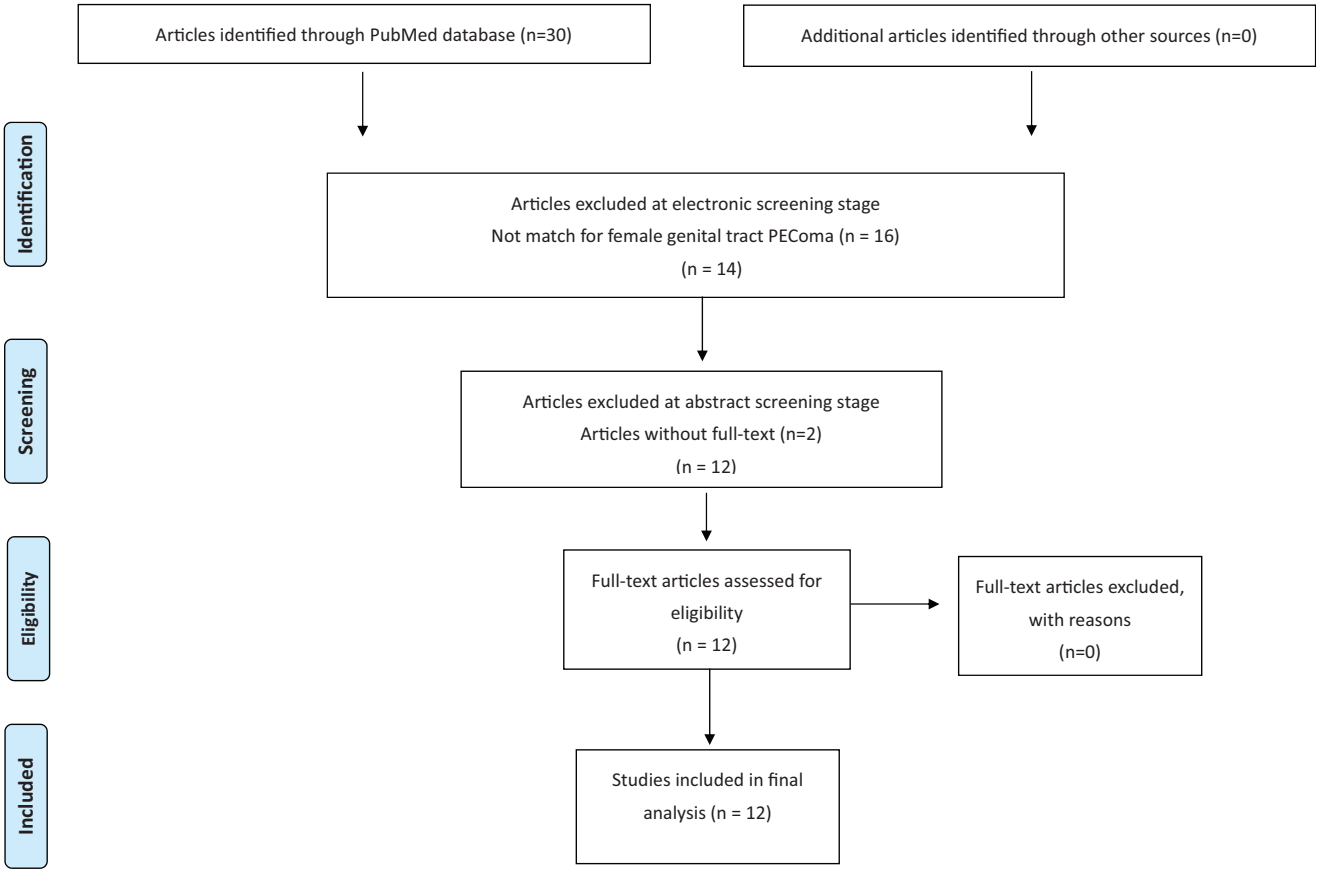

Figure 4. PRISMA flow diagram.

diagnosis of malignant PEComa is made.[18] However, an algorithm specific to gynecologic PEComa has been proposed to classify those that are malignant when a minimum of 4 worrisome features are present, and PEComa with fewer than 4 features is classified as benign and/or with uncertain malignant potential.[3]

Morphologically, most gynecological PEComas are similar to those that occur in other anatomical sites. The histological hallmarks of PEComa are as follows: the presence of a distinct cell type, known as "perivascular epithelioid cell," and the co-expression of smooth muscle and melanocytic markers.[19] PEComas exhibit an epithelioid appearance, which is characterized by a clear to eosinophilic and granular cytoplasm, with centrally located, round to oval nuclei with a nucleolus.[3] The tumor cells typically grow in nests or sheets, and the cells are often intimately associated with a prominent vascular component.[6]

Table 3

Summary of clinicopathological features of female genital tract PEComas.

	Uterine corpus	Cervix	Vagina	Adnexa	Broad ligament	Vulva	Total
Number	82 (58.6%)	12 (10.5%)	7 (6.1%)	7 (6.1%)	5 (4.4%)	1 (0.9%)	114
Age (years of age)	49 (9–80)	46 (25–61)	28 (6–57)	50 (33–63)	25 (24–57)	20	
Tumor size (cm)	5 (0.2–30)	3.8 (1–12)	3 (1.5–9)	3.9 (1.8–15)	11.5 (4–17)	2	
Necrosis	33/79 (42%)	5/11 (45%)	1/7 (14%)	3/7 (42%)	4/10 (40%)	0/1	46/114 (40.4%)
Mitotic activity	47/78 (60.3%)	12/12 (100%)	4/5 (80%)	3/6 (50%)	2/5 (40%)	1/1 (100%)	69/107 (64.5%)
(≤1 per 50 HPF)							
(≥2 per 50 HPF)	31/78 (39.7%)		1/5 (20%)	3/6 (50%)	3/5 (60%)		38/107 (35.5%)
HMB-45	76/77 (99%)	9/9 (100%)	6/6 (100%)	7/7 (100%)	4/4 (100%)	1/1 (100%)	113/114 (99.1%)
Melan-A	21/51 (41%)	5/6 (83%)	1/4 (25%)	4/4 (100%)	1/3 (33%)	NA	32/68 (47.1%)
Desmin	41/67 (61%)	4/6 (66%)	0/2 (0%)	4/7 (57%)	1/2 (50%)	0/1 (0%)	50/85 (58.8%)
Follow-up							
Duration (months)	19 (1.5–168)	25 (9–42)	14.5 (3–54)	9 (1–72)	13.5 (11–18)	48	
DOD	11/68 (16%)	1/10 (10%)	0	2/5 (40%)	0	0	
NED	47/68 (69%)	9/10 (90%)	6/7 (86%)	3/5 (60%)	2/4 (50%)	1/1 (100%)	
SD	11/68 (16%)	0	1/7 (14%)	0	2/4 (50%)	–	

Data are shown as median (range) or number (percentage).

DOD = died of disease, HMB 45 = human melanoma black 45, HPF = high-power field, NED = no evidence of disease, SD = stable disease.

This perivascular distribution is a distinctive feature, which prompted initial observers to speculate a probable origin from the blood vessel walls. Vascularization of PEComas often presented with characteristic features, composed generally of a network of small vessels (capillaries) distributed throughout the tumor.[6]

Immunohistochemically, a perivascular epithelioid cell is characterized by positivity for melanocytic markers, such as HMB-45, melan-A, tyrosinase, microphthalmia transcription factor, and NKI/C3, and smooth muscle markers, such as smooth muscle actin, desmin, h-caldesmon, pan-muscle actin, muscle myosin, and calponin.[4,11,12] In agreement with a previous systematic review published in 2015,[9] the most sensitive marker to diagnose PEComa is HMB-45, and nearly all PEComas were found to be positive staining for HMB-45 (Table 3).

Taken together, PEComas are a group of neoplasms, which share distinctive morphologic and immunohistochemical features, although some cast doubt as to whether PEComas are smooth muscle tumors with expression of melanocyte markers (eg, HMB-45).[19] We totally agree with the World Health Organization (2014) classification of tumors of the female reproductive organs, which lists PEComas as a distinct entity, owing to the particular morphologic features of the tumor and the frequent coexpression of melanocytic and smooth muscle markers,[20] suggesting that there are no markers available yet, which are specific to the diagnosis of PEComas. That is why Table 3 only demonstrates the positive rate of immunohistochemical markers (sensitivity rate) in the female genital organ PEComas.

There is currently no unanimous consensus regarding the treatment of female gynecological tract PEComa because of the small number of cases reported worldwide, a lack of randomized studies, and heterogeneous results with a variety of therapeutic strategies used, especially in patients who were not indicated for complete resection.[3,9] Moreover, the majority of female patients with genital tract PEComa are rarely diagnosed preoperatively. Surgery by complete resection is considered the primary treatment for PEComa, which aims to achieve a tumor-free margin.[9,21–23] In contrast, the role of chemotherapy and radiation therapy remains unclear. Different drugs, such as dacarbazine, ifosfamide, doxorubicin, and vincristine, as well as different combinations of these drugs, have been tested, but results were varied, contributing to the uncertainty of the value of cytotoxic agents. Furthermore, the optimal treatment for recurrence and/or distant metastases of PEComa remains uncertain.[4]

Targeted therapies,[24] especially administration of mTOR inhibitors, seem to provide promising results in recent case reports.[9] Tuberous sclerosis complex (TSC) is characterized by the development of tumors at various sites, including the brain, heart, and kidney. Genetically, TSC is associated with mutations in TSC1 or TSC2 (located on chromosomes 9q34 and 16p13, respectively), leading to impaired production of hamartin and tuberin, respectively.[14,25] TSC1 and TSC2 interact as heterodimers that inhibit the mechanistic mTOR pathway; inactivation leads to increased cell growth and proliferation.[26,27] Renal angiomyolipoma (AML) is the prototypical PEComa associated with TSC.[28–30] Thus, PEComas can be associated with TSC, and both sporadic and TSC-related cases demonstrate similar genetic alterations of the TSC1 or TSC2 locus.[31] The TSC1 and TSC2 gene products form a complex, which negatively regulates mammalian target of rapamycin complex 1 (mTORC1). TSC-associated loss of function of TSC1/TSC2 can lead to a phenotypic spectrum (classical AML-like PEComa, classical PEComa, sclerosing PEComa, and lymphangioleiomyomatosis) that is also recognized in sporadic PEComas.[14] Sirolimus is an allosteric inhibitor of the mTORC1 receptor, which blocks kinases that regulate growth and cell proliferation.[17,18,21] Gennatas et al described a patient who developed retroperitoneal PEComa with lung metastasis and was treated with an oral mTOR inhibitor.[15] The lung lesions disappeared and the abdominal mass significantly reduced after 12 weeks of treatment, without severe side effects.[15] Italiano et al reported promising results with the use of mTOR inhibitors in 2 patients with malignant PEComa.[16] Recently, sirolimus was used in the treatment of angiomyolipoma mimicking renal cell carcinoma in a transplanted kidney[17] and LAM in the abdominal cavity,[18] and the results were impressive. The effectiveness of sirolimus against TSC-related AML was also studied in open-label trials.[17,18,21,32–34] Sirolimus was prescribed for all documented case; however, the response varies due to the timing of the drug prescribed.

Only 3 cases of female genital tract PEComas have been diagnosed over the past 10 years in our hospital. The follow-up period is limited (50 months) and the case number was small. One patient with vaginal PEComa who received adjuvant target therapy after primary debulking surgery is still alive with stable disease at the 7-month follow-up. Two patients with uterus and broad ligament PEComas did not receive adjuvant therapy after primary resection; disease progressions were noted at 1- and 4-month follow-up, respectively, after primary surgery. We believe that the addition of adjuvant treatment should be considered to increase disease control in patients with malignant PEComa in the female genital tract. Moreover, close follow-up is necessary for all patients diagnosed with gynecological PEComas, especially for patients with high risk-features. There is currently no consensus on whether patients with gynecological malignant PEComas should receive post-operative radiotherapy. PEComas are extremely rare, and therefore, it is difficult to conduct randomized controlled trials to assess the outcome of each therapeutic approach.

6. Conclusion

PEComa arises from various anatomic locations, and PEComa of the female genital tract is a rare entity. Gynecological PEComa primarily occurs in the uterine body or cervix, and patients commonly experience vaginal bleeding, abdominal pain, and compression syndrome. The diagnosis is based on histopathological studies and immunostaining for melanocytic marker HMB-45. The diagnostic criteria for malignant PEComa were based on 6 high-risk features. Our study suggests that the primary treatment for gynecological malignant PEComa is complete surgical resection. Sirolimus as an adjuvant target therapy should be considered based on the extent of the disease and the trait of malignancy as high-risk features.

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