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A Rare Uterine Malignancy: A Case of High-Grade PEComa Defying Routine Immunohistochemistry

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ABSTRACT

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms that can arise in various anatomical locations, including the female genital tract, with the uterus being the most affected site. Malignant uterine PEComas are extremely uncommon and pose significant diagnostic challenges, particularly when they lack conventional immunohistochemical (IHC) marker expression. This report presents a rare case of a high-grade, *TFE3*-rearranged malignant PEComa of the uterus that defied routine diagnostic approaches.

This case underscores the diagnostic complexity of *TFE3*-rearranged PEComas, which can lack smooth muscle marker expression and mimic other high-grade uterine malignancies. Recognition of the nested vascular arrangement and utilization of melanocytic and *TFE3* markers are key for diagnosis.

Keywords: PEComa, TFE3 rearranged uterine malignancy, Immunohistochemistry

INTRODUCTION

The abbreviation PEComa stands for perivascular epithelioid cell tumours. PEComas are rare mesenchymal tumors that can occur in various anatomical sites, with the kidney, lung, and gynecologic tract being the most common locations. Within the gynecologic tract, PEComas primarily affect the uterus, although they have also been reported in the cervix, vagina, broad ligament, ovary, and, rarely, the vulva. The typical age range for patients with gynecologic PEComas is the fifth to sixth decade, although those affecting the vagina, broad ligament, and vulva tend to occur at an earlier age (1). Histomorphologically, these tumors display an epithelioid clear cell morphology arranged around blood vessels and on IHC express both melanocytic and smooth muscle markers. Most PEComas are benign and are managed by surgery. Malignant PEComas of the uterus are a rare occurrence and it is important to distinguish them from other types of uterine malignancies as the treatment approach for each type of cancer can vary significantly. We report a rare case of a malignant PEComa that posed a significant diagnostic challenge on biopsy and was found to be negative for a broad range of standard IHC including smooth muscle markers.

CASE REPORT

A 47-year-old female presented with bleeding per vaginum in the gynecology outpatient department. Clinical examination revealed a bulky uterus with the presence of a polypoidal mass. Clinical findings on per vaginum and per speculum revealed a fungating growth arising from the endocervix but the cervical lip was free. Ultrasonography revealed a hypoechoic polypoidal mass measuring 72 mm × 48 mm × 35 mm arising from the corpus and protruding into the endometrial cavity. Based on clinic-radiological evaluation, a clinical diagnosis of malignant/sarcomatous polyp was made and biopsy was done. The biopsy revealed a high-grade tumour present in solid sheets. The tumour cells were epithelioid to spindle and at places had abundant eosinophilic to clear cytoplasm with the presence of high-grade nuclear atypia, prominent nucleoli, bizarre tumour giant cells along with the presence of rich vascularity. Morphological differential diagnosis included choriocarcinoma, undifferentiated sarcoma, epithelioid leiomyosarcoma, undifferentiated carcinomas and malignant PEComa. We conducted a comprehensive basic IHC panel with relevant controls, including markers for cytokeratins, vimentin, smooth muscle actin, S100 protein, and desmin.

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To our surprise, the tumor was negative for all the markers. However, upon closer examination of the histopathology, we observed a nested arrangement of tumor cells around delicate vessels, suggesting a diagnosis of malignant PEComa. Our literature review revealed that *TFE3*-rearranged PEComas could show negative results for smooth muscle markers. Therefore, we performed immunohistochemistry with HMB-45, which showed strong and diffuse positivity. Based on these results, we proposed the possibility of a malignant PEComa on biopsy. Subsequently, a simple hysterectomy along with bilateral salpingo-oophorectomy was performed. The patient was lost to follow-up after the surgery.

Gross Findings

Uterus with cervix measured 10×8×5 cm. There was presence of a polypoidal mass measuring 7×5×4 cm arising from the near to the fundus and protruding into the cervical canal. On cut section the tumour was friable with large areas of necrosis with the presence of myometrial invasion (Figure 1A,B).

Histological Findings

Sections from the polyp showed a high-grade tumor arranged in nests and sheets around blood vessels (Figure 1C). The tumor cells were polygonal with the presence of clear to eosinophilic cytoplasm (Figure 1D,E). There were large areas of necrosis with the presence of a mitotic rate of 53/50 HPF (Figure 2A-D). Numerous tumor giant cells were present; the nuclei were hyperchromatic to vesicular with the presence of large macro nucleoli (Figure 2E). CK, Vimentin, SMA, S100 and Desmin were negative on IHC. HMB 45 was positive (Figure 2F). Melan A (Figure 1F) also showed positivity but SOX 10 was negative. TFE3 showed diffuse nuclear positivity in line with *TFE3* rearranged PEComas (Figure 1G).

DISCUSSION

The clinical presentation of gynecologic PEComas is often nonspecific and may include abnormal uterine bleeding, abdominopelvic pain, the misdiagnosis of "fibroids," or the identification of a mass on imaging. In the present case the patient had heavy menstrual bleeding (2,3). In rare cases, patients may present with uterine rupture and/or hemoperitoneum, particularly during pregnancy (4). A history of tuberous sclerosis is present in about 10% of patients (2). An accurate preoperative diagnosis is difficult as the findings on clinicoradiological grounds are non-specific. Hence a preoperative biopsy becomes important. Compared to the benign PEComas it is highly challenging to identify the malignant subtype in a biopsy. IHC too can be confusing if one is not aware of the *TFE3* rearranged

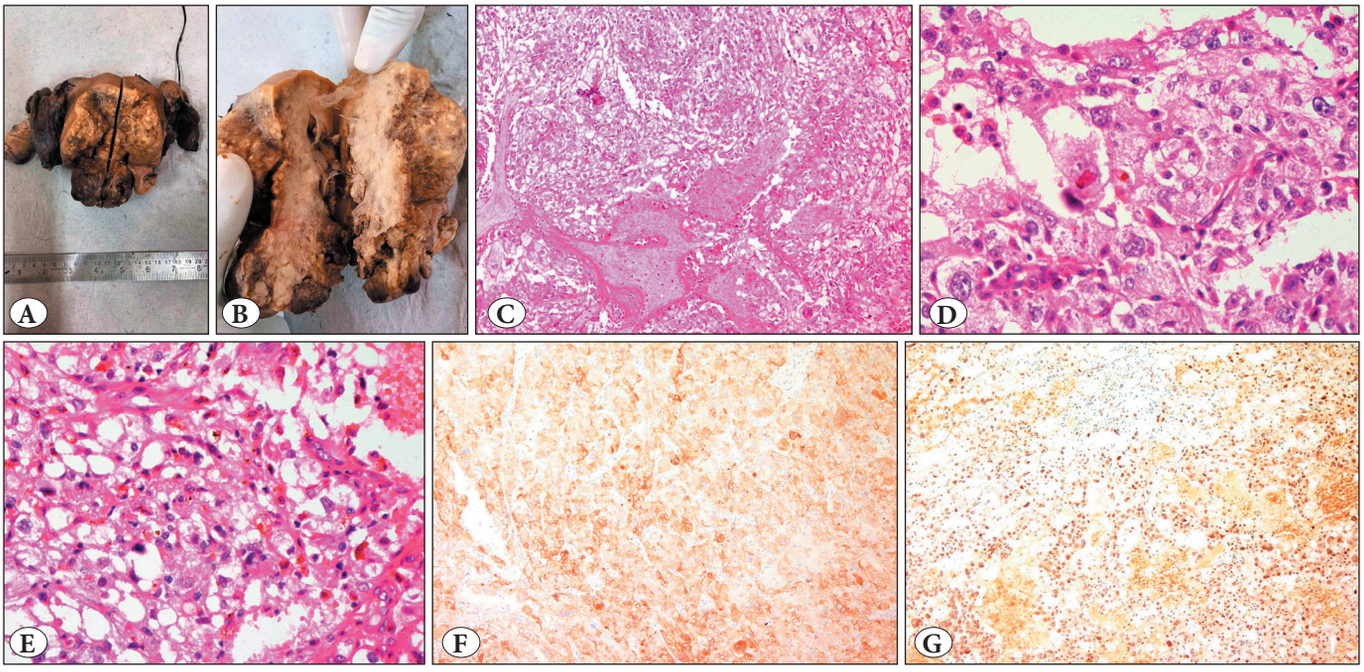


Figure 1: A) A polypoidal mass measuring 7×5×4 cm arising from the near to the fundus of the uterus and protruding into the cervical canal. **B)** Cut section of the tumor is friable with large areas of necrosis with the presence of myometrial invasion. **C)** High-grade tumor arranged in nests and sheets around blood vessels (H&E, 200x). **D, E)** Tumor cells are polygonal with the presence of clear to eosinophilic cytoplasm (H&E, 400x). **F)** Melan A - Positive (IHC, 100x). **G)** TFE 3 - shows diffuse nuclear positivity (IHC, 100x).

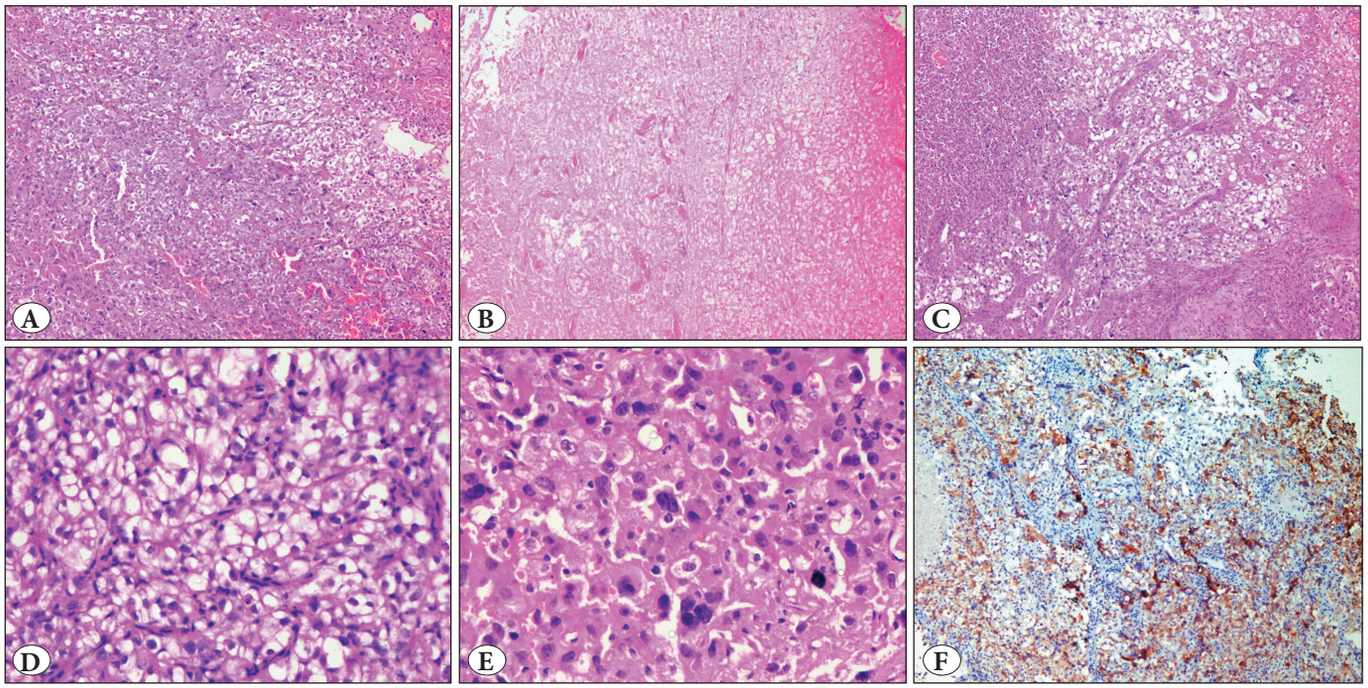


Figure 2: A-C) Tumor with large areas of necrosis with mitosis (H&E, 100x), **D)** Tumor arranged in nests with polygonal cells with clear to eosinophilic cytoplasm (H&E, 400x), **F)** HMB 45 - positive (IHC, 100x).

subtype. PEComas may present as a myometrial-based tumor, although in some cases, they may appear grossly as a polypoid or pedunculated mass that protrudes into the endometrial cavity. In our case, a friable polypoidal mass was observed protruding into the cavity (5).

PEComa is classified as benign, of uncertain malignancy potential, or malignant based on six key factors. These are tumor size (greater than 5 cm), infiltration, high-grade nuclei, high cellularity, high mitotic activity (more than 2 mitotic figures per 50 high-power fields), tumor necrosis, and vascular invasion. According to these criteria in general, a PEComa is classified as "benign" if it does not have any of these features, "of uncertain malignant potential" if it only shows nuclear pleomorphism or multinucleated giant cells, or if it is larger than 5 cm, and "malignant" if it exhibits two or more concerning features. However, for the female genital tract a PEComa is considered malignant if any 3 of the above atypical features are present. If less than 3 atypical features are present it is considered of uncertain malignant potential (6).

Schoolmeester et al. studied 6 cases of *TFE3* rearranged PEComas and found that 5 out of 6 cases had a pure clear cell morphology and all cases expressed diffuse HMB 45 and *TFE3* and had weak immunoreactivity for smooth muscle markers (3). In our case, the tumour showed a predominant clear cell epithelioid morphology and was negative for pan cytokeratin, vimentin, SMA, S100 and desmin. HMB45 and TFE3 were diffusely positive. Melan A showed focal positivity. Qin et al. reported eight cases of malignant PEComa, three of which exhibited features of malignancy, including bizarre nuclei, necrosis, and increased mitotic activity. All cases showed positive immunoreactivity for TFE3 (7). Table I summarizes the clinical, morphological and immunohistochemical characteristics of various malignant TFE3-rearranged PEComas reported in the literature. The majority of cases lacked expression of smooth muscle markers but showed positivity for melanocytic markers, similar to our case.

One of the challenging aspects of our case was the pre-surgical biopsy, which revealed cells with a high-grade morphology and tested negative for standard IHC markers. This emphasizes the significance of considering PEComa in the list of differential diagnoses and being knowledgeable about *TFE3* rearranged PEComas, which can exhibit negative results for smooth muscle markers. In conventional PEComas, both sporadic and syndromic types, *TSC2* mutation and loss of heterozygosity (LOH) are common, whereas *TSC1* mutation and LOH are rare. LOH at *TSC1/2* leads to upregulation of mTOR signaling, which is the basis of mTORC1 targeted therapy often used in PEComa treatment. However, *TFE3* rearranged tumors were found to lack *TSC2* inactivating mutations (8). Perivascular epi-

Table I: Clinicopathological and Immunohistochemical Features of Reported Malignant TFE3-Rearranged PEComas

Author	Clinical Details	Histomorphology	Immunohistochemistry	Treatment / Follow-up
Zhong and Yang (10)	53-year-old female with a uterine mass.	The tumour exhibited an epithelioid growth pattern arranged in nests and sheets surrounded by blood vessels. It showed high-risk features, including tumour size >5 cm, infiltrative growth pattern, necrosis, and a mitotic rate >1 per 50 high-power fields (HPFs).	**Positive:** HMB45, desmin, calponin, SMA (focally positive), focal TFE3 **Negative:** S100, MyoD1, myoglobin, myogenin, EMA, vimentin, α-inhibin, CD10, CDX2, CK20, TTF-1, CK7	Recurrence at 3 months post-surgery with lung metastasis.
Liu et al. (11)	34-year-old female presenting with vaginal bleeding and a cervical mass.	Tumour exhibited infiltrative growth into the surrounding parenchyma and was composed of sheets, alveolar structures, or nests separated by thin fibrovascular septa. Prominent intratumoral haemorrhage, necrosis, and stromal calcification were observed.	**Positive:** TFE3, HMB45, Melan A **Negative:** Pan CK, SMA, S100, PAX8, PAX2	Tumour recurred two months post-surgery and was partially resected. Five months later, imaging suggested possible pelvic lymph node metastasis.
Argani et al. (12)	18-year-old female with a 5 cm renal mass containing a 2.6 cm calcified nodule.	Tumours demonstrated variable morphology, including spindle-shaped, clear, and eosinophilic cells with focal atypia.	**Positive:** SMA, Cathepsin K, TFE3 **Negative:** HMB45, Melan A, PAX8, EMA	Developed liver metastasis seven years after initial diagnosis.
Bouzid et al. (13)	9-year-old male with an orbital mass.	Tumour composed of large nests of epithelioid cells with abundant cytoplasm containing melanin pigment and round to oval nuclei showing mild cytologic atypia and low mitotic activity.	**Positive:** HMB45; Pangenomic RNA sequencing revealed an in-frame *NONO–TFE3* rearrangement **Negative:** Melan A, smooth muscle actin, desmin, S100	No recurrence after one year of follow-up.

SMA: Smooth muscle actin, **HPF:** High power field

thelioid cell tumors (PEComas) harboring *TFE3* gene rearrangements lack the *TSC2* alterations characteristic of conventional PEComas. These findings have critical implications for treatment, particularly for the effectiveness of targeted mTOR inhibitors, which may be minimized in *TFE3* rearranged PEComas. Therefore, identifying the rearranged variant of PEComa may help make important decisions for clinical management.

PEComas of the uterus are relatively rare, and accurate diagnosis can be challenging. The primary treatment for these tumors typically involves surgery, which may involve complete or partial removal of the uterus. In some cases, radiation therapy or chemotherapy may also be used alongside surgery to improve outcomes. If the PEComa is malignant, adjuvant therapy may be recommended to reduce the risk of recurrence and improve the patient's overall prognosis. The specific type of adjuvant therapy will depend on various factors such as the tumor's features and the patient's overall health. Given the uncommon nature of these tumors and their challenging diagnosis, close collaboration between the patient, healthcare provider, and pathologist is vital to ensure an accurate diagnosis and development of the best possible treatment plan.

mTOR inhibitors such as sirolimus, everolimus, and temsirolimus, have shown inconsistent responses in treating patients with malignant PEComas. Specifically, for malignant PEComas with *TFE* rearrangement, mTOR inhibitor therapy has demonstrated limited effectiveness, which highlights the need for alternative treatments. One approach is to target an alternative VEGF/VEGFR signaling pathway. One study investigated the use of aptanib in combination with mTOR inhibitor therapy, which may offer improved efficacy in treating malignant PEComas by targeting both the mTOR and VEGF pathways (9).

Conflict of Interest
Authors declare no conflict of interest

Authorship Contributions
Concept: **ACP,** Design: **ACP, SS (Sonal Sharma),** Data collection or processing: **ACP, GG, S (Swati),** Analysis or Interpretation: **ACP, S, SS,** Literature search: **ACP, GG,** Writing: **ACP, GG,** Approval: **All authors.**

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