***Case report***

**An Elusive Diagnosis: Malignant PEComa of the Uterus Mimicking Uterine Fibroids – A Rare Case Report.**

**Abstract**

**Aim:**

To present a rare case of malignant uterine perivascular epithelioid cell tumor (PEComa), highlighting diagnostic challenges and management strategies.

**Case Presentation:**

A 55-year-old woman presented with abnormal uterine bleeding (AUB) and ultrasound findings suggestive of uterine fibroids. Despite medical therapy, her symptoms persisted, needing surgical intervention. A total abdominal hysterectomy with bilateral salpingo-oophorectomy revealed a uterine tumor with histopathological features characteristic of PEComa. Immunohistochemistry confirmed markers consistent with malignant PEComa, including HMB45 positivity. Based on the WHO and Folpe’s criteria, the tumor was classified as malignant. The disease was confined to the uterus, with clear surgical margins. She was placed under active surveillance and showed no evidence of recurrence at follow-up.

**Discussion:**

Malignant uterine PEComa is an exceptionally rare neoplasm, often presenting with nonspecific symptoms mimicking common uterine tumors. Diagnosis relies on histopathology and immunohistochemical markers. Surgery remains the cornerstone of treatment, as PEComas are resistant to chemoradiation. Disease confined to the uterus with clear margins is associated with a favorable prognosis. While the role of adjuvant therapy remains unclear in early-stage disease, but mTOR inhibitors show promising results in advanced or recurrent cases. Active surveillance is recommended due to its highly variable clinical courses.

**Conclusion:**

This case underscores the importance of considering rare entities when standard treatments fail. Early surgical intervention and comprehensive histopathological and immunohistochemical evaluation are critical for accurate diagnosis and management.

*Keywords: Malignant uterine PEComa; Perivascular epithelioid cell tumour; HMB45; Folpe’s Criteria; mTORs inhibitors.*

**INTRODUCTION**

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms characterized by the presence of distinctive perivascular epithelioid cells. These tumors comprise a spectrum of entities, including angiomyolipomas, lymphangio-leiomyomatosis, and clear cell sugar tumours.[1,2] Malignant Uterine PEComa represents an even smaller subset of these tumors, with fewer than 100 reported cases, accounting for a fraction of uterine mesenchymal neoplasms.[3]

The epidemiology of PEComas remains poorly understood. These tumors have been reported across a wide age range, with a predilection for adult women, particularly during the reproductive and perimenopausal years.[4] While PEComas occur sporadically, some cases are associated with tuberous sclerosis complex (TSC), resulting from mutations in the TSC1 or TSC2 genes. [2,3]

Malignant uterine PEComas often present diagnostic challenges due to their non-specific clinical presentation and overlapping histological features with other mesenchymal tumours.Their malignant potential is highly variable, with some cases demonstrating indolent behavior and others exhibiting aggressive clinical courses characterized by metastasis and recurrence.[5]

WHO classification recognizes PEComas as a distinct tumour entity, with malignancy determined by histhopathological features.[5] Immunohistochemical staining is crucial for diagnosis with PEComas typically expressing melanocytic markers and smooth muscle markers. [1,3]

This case report highlights a rare instance of malignant PEComa of the uterus, detailing the clinical presentation, pathological findings, and treatment approach, hopefully contributing to the knowledge of this rare entity.

**CASE PRESENTATION**

A 55-year-woman, para 5 (last childbirth 15 years ago), presented with abnormal uterine bleeding (AUB) since December 2022. On clinical examination, the uterus was enlarged to the size of a 12-week pregnancy. A pelvic ultrasound revealed multiple heterogenous uterine masses, with the largest being a 6x4cm posterior intramural fibroid with submucosal component. Endometrial sampling was performed which was reported as simple hyperplasia. The patient was treated with progestogen therapy for six months, after which a repeat sampling revealed normal results. Initially, her AUB improved with continuous progestogen therapy and cyclical tranexamic acid, but her symptoms worsened over time, becoming prolonged and heavier.

In December 2023, the patient was admitted for symptomatic anaemia (haemoglobin level of 8.0 g/Dl), requiring blood transfusion. Examination revealed increasing uterine size, now consistent with a 14-week pregnancy. The endometrial thickness (ET) was measured at 9.1mm, and a repeat sampling was inconclusive due to a fragmented atypical sample. Counselling for surgical intervention was conducted during multiple follow-up visits but declined. In July 2024, the patient finally consented to surgery owing to persistent symptoms. The uterus was still 14-weeks size pre-operatively. Pelvic ultrasound revealed a distorted endometrial cavity and an increased posterior fibroid size, now measuring 8 x 6 cm with both ovaries appearing normal.

A red heart with a piece of paper

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Figure 1a Figure 1b

**Figure 1a Posterior view of the uterus showing multiple subserosal fibroids and the subserosal component of the uterine PEComa (black arrow). Figure 1b is cut section view of anterior uterus showing submucosal component of uterine PEComa**

The patient underwent a total abdominal hysterectomy with bilateral salphingo-oophorectomy (TAHBSO). Intraoperatively, multiple uterine fibroids were observed, including a few small anterior and fundal fibroids and a large posterior intramural fibroid with a submucosal and subserosal component measuring up to 8cm. (Figure 1a and 1b). The rest of the endometrium appeared normal, omentum was unremarkable with no evidence of enlarged pelvic lymph nodes.

Histopathological evaluation (HPE) revealed a large posterior submucosal tumour measuring 77 x 64 x 55mm. The tumour was composed of solid sheets of medium size epitheloid cells with clear to eosinophilic cytoplasm, arranged around a delicate vascular network. Focal perivascular cuffing by tumour cells were notable features. Atypia was mild in some areas and moderate in others with focal high grade nuclear atypia and multinucleated cells. No necrosis, lymphovascular space invasion (LVSI), or significant mitotic activity (>1/50mm2) was identified. Margins were free from tumour.

Immunohistochemical (IHC) analysis showed the tumour cells diffusely expressed TFE3, ER, PR, with focal positivity for CD56, SMA, WT1. There was focal, moderate positivity for HMB45. The tumour was negative for CD10, Melan A, S100, Caldesmon, and pancytokeratin. The Ki 67 was low, <18%. Based on the Modified Gynecological-Specific Criteria outlined in the WHO Classification, the tumour was classified as malignant PEComa.[5] Features supporting malignancy included tumour size more than 5cm, focal infiltrative edges, and focal high grade cytological features with marked atypia and multinucleated cells.

The tumour was staged as FIGO Stage I, with the disease confined to the uterus. The patient was under active surveillance following surgery. CT imaging performed at three months postoperatively showed no evidence of local recurrence, regional or distant metastasis. At her five-month follow-up, she remained asymptomatic and well. A PET scan is scheduled at the six-month mark to ensure comprehensive evaluation and continued surveillance.

**CASE DISCUSSION**

Malignant PEComa is exceedingly rare, with only a limited number of cases reported in the literature. These tumours can arise in various anatomical sites, including the lungs, kidneys, liver, and soft tissues, but uterine involvement is particularly uncommon.[1] Malignant uterine PEComa presents a diagnostic and therapeutic challenge due to its rarity and the overlap of clinical features with more common uterine tumours, such as leiomyomas and endometrial stromal sarcoma.[7] In this case, the patient presented with AUB and pelvic scan findings that were consistent with clinical diagnosis of benign leiomyoma. This is a common scenario as PEComas often present with non-specific gynaecological symptoms such as AUB, pelvic pain, or palpable pelvic mass.[1] The patient was treated conservatively with hormonal therapy initially, but her symptoms persisted, prompting eventual surgical intervention.

The appearance of this tumour is similar to the typical description of PEComas in the literature. It appeared as a well circumscribed mass, with a solid or fleshy appearance.[6] Histopathological and immunohistochemical evaluation were pivotal in diagnosing malignant PEComa. This tumour exhibited the typical histological features of PEComas, including epithelioid cells with clear to eosinophilic cytoplasm associated with delicate vascular network and notable feature of focal perivascular cuffing by tumour. PEComas typically express melanocytic markers such as Human Melanoma Black 45 (HMB45) and Melanoma Antigen (Melan-A) and smooth muscle markers, such as Smooth Muscle Actin (SMA), Desmin, and Caldesmon. The expression of HMB-45 is found to be always positive in PEComas, while the positive rate of Melan-A is 80%, SMA is ranging 50-80%. TFE is always positive too. Interestingly, S100 and cytokeratins are always negative. [1,3,8,9]. Similarly in this case, the diagnosis was confirmed with the tumour demonstrating diffuse positivity to TFE3, Desmin, ER, PR, and moderate positivity for HMB45, SMA, WT1, with S100 and Pancytokeratin negative.

The 2020 WHO classification categorizes PEComa into benign, uncertain malignant potential, and malignant. In this case, histological features favoring malignancy included tumour size more than 5cm, infiltrative pattern, and high-grade cytologic features although necrosis, high mitotic activity (>1/50 HPF) or LVSI were absent. Similarly, this tumour fulfilled the criteria (≥2 worrisome criteria) for malignancy under Folpe’s classification.[8] Three out of 5 worrisome criteria were present in this tumour (*size ≥5 cm*, *infiltrative growth pattern, marked atypia*, mitotic rate >1/50 HPF, LVSI).

Management strategies of malignant uterine PEComa are not well-established. Various treatment plans have been adopted, however treatment primarily involves surgical resection as PEComa is relatively resistant to chemoradiation therapy, similar to other uterine sarcomas.[2,10] Surgery with the aim of achieving tumour free margin in disease confined to uterus, and optimal debulking in cases of advanced disease, is associated with reduced risk of recurrence and increased disease free survival.[2,10,11]. TAHBSO (with ovarian preservation in selected cases) is often curative, which was performed in this patient, although the initial intention was for symptomatic uterine fibroids. Gratefully, the resection margin was clear.

Literature reviews showed mixed results in the utilisation of adjuvant therapy such as chemotherapy, radiotherapy, or combination thereof due to absence of established guidelines with treatment decisions often guided by case reports or small case series. Recently, adjuvant therapy with mammalian target of rapamycin (mTOR) inhibitors (everolimus or sirolimus) showed promising results in treating advanced or recurrent disease. This is related to the tumour’s association with the mTOR pathway. There is no consensus on the role of adjuvant therapy in localized disease, particularly in the absence of high-risk features such as necrosis, significant mitotic activity, or positive LVSI as observed in this case. [7,11-13] These suggest a relatively less aggressive malignant behaviour. Nevertheless, continuous efforts to develop criteria for postoperative adjuvant therapy is needed, aiming to maximize the treatment outcomes.[14]

Surveillance is crucial in the postoperative period as malignant uterine PEComas have an unpredictable clinical course with the potential for late recurrences. Long-term follow-up with periodic imaging is recommended as recurrences can occur years after the initial treatment, up to 36 months. [7,8,11,14]. Generally, a disease confined to uterus with negative tumour margin coupled with low proliferative index suggests a good overall prognosis in this patient.

**CONCLUSION**

Malignant uterine PEComas pose a diagnostic challenge and are a dilemma in management strategies, attributed to its rarity and lack of reported cases. The eventual diagnosis of malignant PEComa in this case highlights the importance of maintaining a high index of suspicion for rare entities, particularly when standard therapy fails to control symptoms. This is to avoid delays in diagnosis and treatment. Comprehensive histopathological and Immunohistochemical evaluation is essential for an accurate diagnosis. Early surgical intervention with careful postoperative surveillance is most crucial in the treatment of malignant uterine PEComas. Adjuvant therapy is controversial but use of mTOR inhibitors can be considered. The continued reporting of such cases will help to improve the knowledge of their clinical behaviours, guide therapeutic strategies, and optimize patient outcomes.

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