Case Report

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Navigating Diagnostic Challenges in Uterine PEComa: A Case Report and Mini Review of the Literature

Stylianos Sergios Chatziioannou[1,2], Evangelia Mavromati[3], Artemis Stylianidou[3], Chrisostomos Sofoudis[2*]

[1]*European University of Cyprus, School of Medicine, Nicosia, Cyprus.*

[2]*1st Department of Obstetrics and Gynecology, Elena Venizelou, Maternity Hospital, Elena Venizelou, Athens, Greece.*

[3]*Department of Pathology, Elena Venizelou, Maternity Hospital, Elena Venizelou, Athens, Greece.*

Correspondence to: Chrisostomos Sofoudis, 1st Department of Obstetrics and Gynecology, Elena Venizelou, Maternity Hospital, Elena Venizelou, Athens, Greece.

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ABSTRACT

Perivascular epithelioid cell tumors (PEComas) represent rare mesenchymal neoplasms with dual myomelanocytic differentiation.

We report a case of a uterine PEComa in a female patient presenting with chronic abnormal vaginal bleeding initially attributed to leiomyoma. The patient underwent abdominal excision of the leiomyoma, and gross examination revealed a well-circumscribed, ovoid mass measuring 6.3 cm.

Histopathological evaluation showed a mesenchymal neoplasm with mild cytologic atypia, low mitotic activity (<1 per 50 high power fields), and no necrosis. Immunohistochemistry demonstrated positivity for smooth muscle markers (SMA, Desmin, Calponin, Caldesmon) and HMB-45, along with ER and PR, while Melan-A and other markers were negative. These findings support a diagnosis of uterine PEComa with uncertain malignant potential, as defined by Modified Specific Gynecologic Criteria and WHO 2020 guidelines.

A literature review was conducted to elucidate the clinical, radiological, and pathological characteristics of uterine PEComas. Although many uterine PEComas are benign, features such as tumor size exceeding 5 cm and infiltrative growth may indicate a risk for aggressive behavior. Surgical resection remains the primary treatment for localized disease, while emerging targeted therapies, including mTOR inhibitors, show promise for advanced cases.

This case highlights the diagnostic challenges of uterine PEComas, given their radiological resemblance to leiomyomas and other sarcomas, emphasizing the need for a multidisciplinary approach for accurate diagnosis and management.

Keywords:

Uterine PEComa, Mesenchymal neoplasm, Immunohistochemistry, mTOR inhibitors, Uncertain malignant potential.

Introduction

Perivascular epithelioid cell tumors (PEComas), a distinct category of mesenchymal tumors, have garnered significant attention in recent years due to their unique histological and immunophenotypic characteristics. Comprising a family of tumors that arise from perivascular epithelioid cells, PEComas are predominantly characterized by their co-expression of smooth muscle and melanocytic markers, notably HMB-45 and Melan-A [1]. The term “PEComa” was initially introduced in 1992, and over time, the World Health Organization (WHO) has classified these tumors under a broader umbrella of mesenchymal neoplasms [2]. This case report and literature review will focus on the presentations, clinical implications, and management strategies associated with PEComas of the uterus.

Uterine PEComas are recognized for their relative rarity, accounting for a small percentage of all gynecological tumors. The tumors predominantly affect women, particularly in their reproductive and perimenopausal years, with reported cases illustrating a peak incidence in those aged between 30 to 60 years [3]. Their occurrence is often sporadic, yet a notable subset has been linked to genetic syndromes such as Tuberous Sclerosis Complex (TSC), in which PEComas can present in conjunction with other tumors [4,5]. Epidemiological studies emphasize that while many cases of uterine PEComas are benign, malignancies are observed, particularly when tumor size exceeds 5 cm, characterized by increased cellular pleomorphism and high mitotic activity [6].

Histopathologically, uterine PEComas are distinctive. They typically display a proliferation of epithelioid cells with a varying appearance, often described as having a "cellular" or "spheriod" morphology. These tumors are classified based on histological patterns, including the presence of necrosis, atypical mitoses, and infiltrative growth characteristics, all of which can serve as prognostic indicators [7]. The immunohistochemical profile of PEComas is crucial for diagnostic differentiation from other tumors, such as uterine leiomyosarcomas, endometrial stromal sarcomas, and neuroendocrine tumors [8]. Notably, the expression patterns of markers such as SMA, desmin, and the aforementioned melanocytic markers elucidate their dual nature and can guide management strategies [9].

The clinical presentation of PEComas can vary, where some tumors are asymptomatic and found incidentally, while others may lead to significant symptoms due to mass effects or complications such as bleeding [10]. Surgical resection remains

the mainstay of treatment for localized tumors, with preoperative imaging studies playing a vital role in surgical planning. However, the management of malignant PEComas remains challenging, especially given their potential for metastasis, often evidenced by spread to the lungs or lymph nodes [11,12]. Recent advancements in targeted therapies, notably mTOR inhibitors, have shown promise in managing advanced cases of PEComa, reflecting a shift toward personalized treatment approaches [13].

The increasing awareness and understanding of PEComas underscore the need for a comprehensive review that encapsulates their clinical, pathological, and therapeutic aspects. This literature review seeks to analyze available research, elucidate gaps in knowledge, and provide a thorough contextual framework regarding uterine PEComas, thus contributing to improved diagnostics and management for affected individuals. The ensuing sections of this review will comprehensively dissect the existing literature, examining the nuances of clinical presentations, histopathological features, treatment approaches, and potential outcomes associated with uterine PEComas.

Case Report

A female patient (G0, P0) without previous medical history, presented to the hospital due to chronic abnormal vaginal bleeding from leiomyoma located in the uterine fundus. No medication could control the bleeding. Gonadorelin was not given as a medication.

Abdominal MRI depicted presence of intramural leiomyoma located at posterior uterine surface maximal diameter 8cm. Pap smear did not reveal any signs of malignancy.

The patient was scheduled for an abdominal leiomyoma excision (23/12/2024).

The specimen obtained was processed into paraffin blocks and sectioned for histological examination. The gross examination revealed an ovoid, well-circumscribed, whitish mass measuring 6.3 cm. On sectioning, the lesion exhibited a firm-elastic consistency, a predominantly whitish appearance with areas showing a subtle yellowish tint.

Microscopic analysis identified the lesion as a mesenchymal neoplasm of the uterus exhibiting morphological and immunophenotypical features consistent with myomelanocytic differentiation. These characteristics support the diagnosis of a perivascular epithelioid tumor (PEComa). The histological evaluation showed mild cytologic atypia without significant mitotic activity, quantified at less than 1 per 50 high power fields, and no areas of necrosis were observed. The tumor was well-

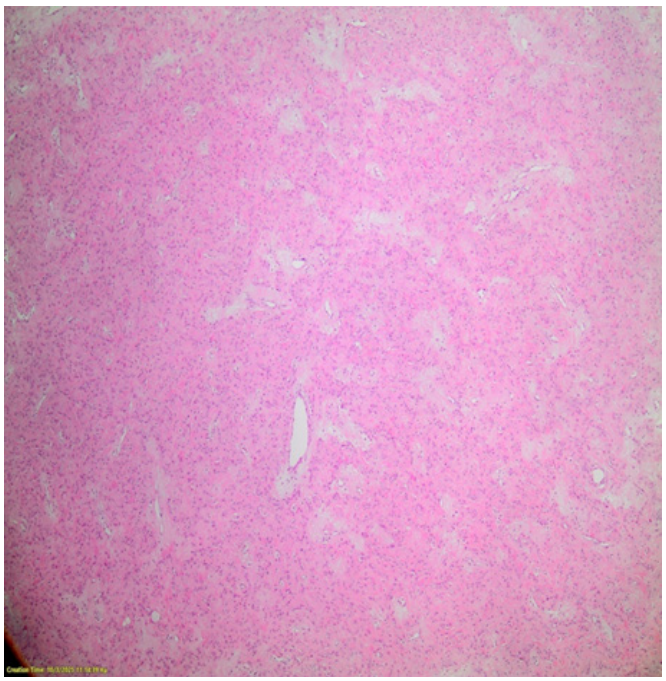

Figure 1: H&E X 40: Diffuse growth of epitheloid cells.

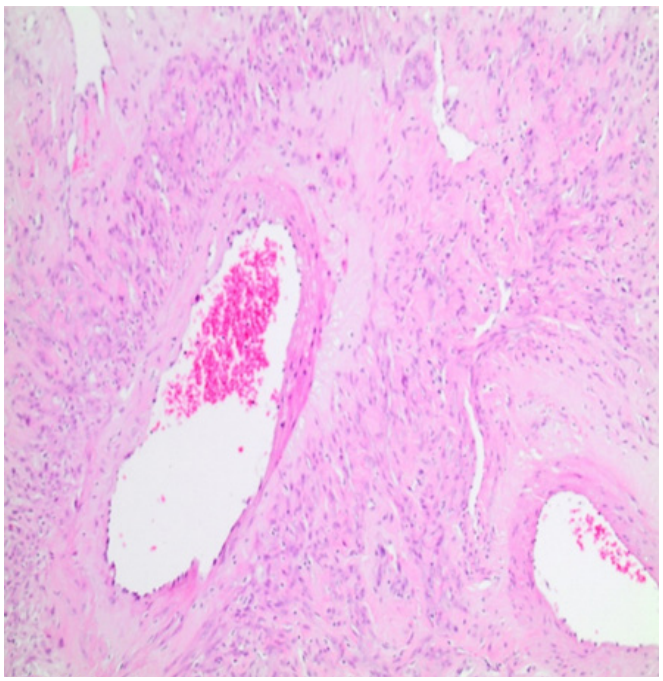

Figure 2: H&E X 100: Perivascular tumor growth.

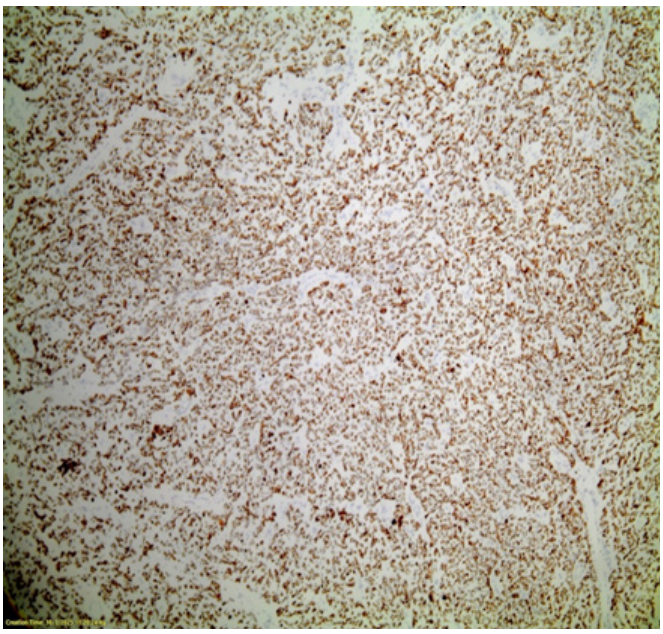

Figure 3: Desmin X 40: Positive Immunohistochemistry, myoid differentiation.

circumscribed, with its periphery occasionally demonstrating partially detached small strands of myometrium (Figure 1,2).

Immunohistochemical studies further supported the diagnosis. The neoplastic cells stained positive for SMA (smooth muscle actin), Desmin, Calponin, Caldesmon, HMB-45, ER, and PR, while they were negative for Melan-A, p16, CD10, CD117, CD34, Calretinin, EMA, ALK, and Pankeratin. Additionally, CD68 showed focal weak positivity and p53 exhibited a wild-type expression pattern (Figure 3-6).

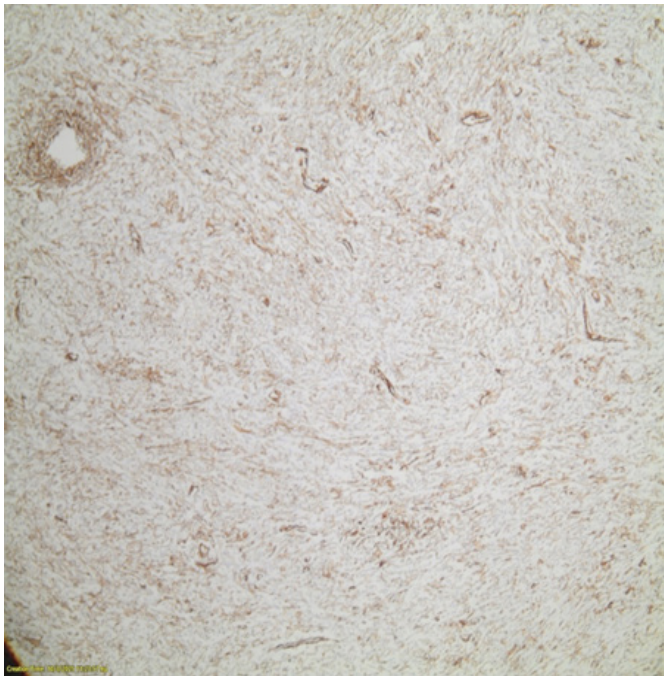

Figure 4: Caldesmon X 40: Positive Immunohistochemistry, myoid differentiation.

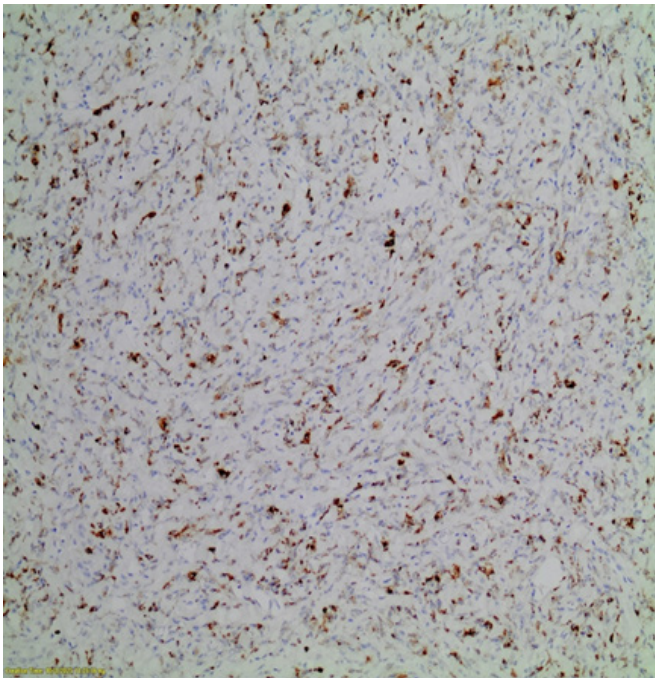

Figure 5: HMB-45 X 100: Positive Immunohistochemistry, melanocytic differentiation.

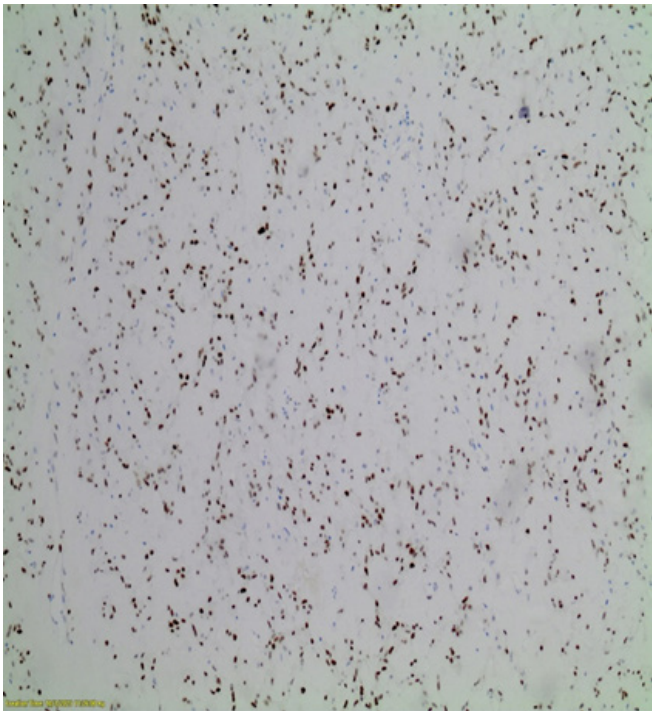

Figure 6: Estrogen receptors (ER) X 100: Positive Immunohistochemistry.

Based on the above findings, the final diagnosis is a Perivascular Epithelioid tumor (PEComa) of the uterus with uncertain biological behavior, as defined by the Modified Specific Gynecologic Criteria and WHO 2020 guidelines.

An imaging follow-up was recommended and thus an MRI of the Upper and Lower Abdomen (Examination Date: 25/02/2025) was performed using axial, coronal, and sagittal sequences, including T1- and T2-weighted images, opposite phase sequences, and fat suppression techniques. A dynamic study of the liver was also obtained before and after intravenous administration of a gadolinium-based contrast agent during arterial, portal venous, and venous phases. The study extended from the level of the hemidiaphragms to the region of the pubic symphysis. The clinical indication was the removal of a leiomyoma, with a comparative study available from 01/11/2024. The liver was described as normal in size and demonstrates homogeneous signal intensity on all sequences with uniform contrast enhancement, with two small cysts (each approximately 7 mm) identified in the left and right lobes. The intrahepatic and extrahepatic bile ducts are not dilated, and the gallbladder appears normal with no wall thickening, while the pericholecystic space is free. The spleen is within normal limits, with homogeneous signal and enhancement, and the pancreas appears normal in size and signal. Both adrenal glands and kidneys are normal in size and location, showing homogeneous cortex and uniform enhancement following contrast administration. The abdominal aorta is normal, and no lymphadenopathy is detected in the para-aortic region. The uterus, still in an anteverted position, is reported as normal in size with a normal myometrial structure, junctional zone, and endometrial cavity; the previously noted leiomyoma has been completely excised. The adnexa are unremarkable with the ovaries demonstrating normal size and follicles up to 13 mm. The urinary bladder wall is smooth, and the perivesical space

remains free. The radiological findings from both examinations corroborate the clinical and pathological assessment.

Literature Review

Uterine Perivascular Epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms characterized by their unique histopathological and immunohistochemical features. First described in the early 2000s, these tumors exhibit both smooth muscle and melanocytic markers, with the HMB-45 marker being most commonly associated with PEComas. Studies have shown that approximately 99% of PEComas express HMB-45, while around 80% demonstrate smooth muscle actin positivity [14,15]. The prevalence of these tumors is markedly higher in women, particularly during the fourth decade of life, with notable instances arising in the corpus of the uterus [1,16].

The imaging characteristics of uterine PEComas pose significant diagnostic challenges, as they often resemble conventional uterine myomas or sarcomas in imaging studies. Reports indicate that these tumors typically show heterogeneous echogenicity and prominent central vascularity on ultrasound, complicating their diagnosis prior to surgical intervention [10,16]. The frequent misdiagnosis highlights the need for greater awareness and understanding of the sonographic features indicative of PEComas, as differential diagnoses often include benign leiomyomas and other sarcomas, which can mislead clinical management [17,18].

From a pathological perspective, PEComas are distinctive and classified based on their malignant potential as benign, uncertain malignant potential (UMP), or malignant tumors. Risk factors contributing to malignancy include tumor size over 5 cm, infiltrative growth patterns, and high nuclear grade [19,20]. It has been estimated that approximately 50% of gynecological PEComas may carry uncertain malignant potential, necessitating careful case evaluation [21]. The histological hallmarks that define these tumors include epithelioid morphology, typically displaying clear to eosinophilic cytoplasm and central nuclei [15,21]. Management of uterine PEComas primarily revolves around surgical resection, which remains the gold standard, particularly for localized tumors. The literature consistently points to surgical excision as the most effective treatment approach, with studies indicating that complete resection offers a favorable prognosis, especially in non-aggressive cases [22,23]. In cases where malignancy is suspected or confirmed, adjuvant therapies may be considered.

While the clinical data surrounding PEComas are limited, evolving management strategies have incorporated the use of mTOR inhibitors, notably everolimus and sirolimus. Reports have demonstrated varying levels of response to these therapies, with some patients showing significant benefit even after experiencing resistance to conventional chemotherapy options [24]. Recent advances suggest that targeting the mTOR pathway could offer new avenues for treatment, especially for advanced or metastatic cases where standard chemotherapy proves ineffective [25].

Additionally, emerging treatments utilizing VEGFR inhibitors have shown promise in mitigating disease progression in select patients [26]. The comprehensive management of PEComas should involve a multidisciplinary team approach, adapting treatment modalities based on individual tumor genetics, histopathological characteristics, and patient health status [27]. Follow-up protocols emphasizing surveillance with imaging studies post-surgery are vital due to the risk of recurrence or metastasis, advocating for continued monitoring and tailored therapeutic interventions as needed [28].

Cases of PEComas with differing immunohistochemical profiles, including HMB-45 negativity, underscore the importance of comprehensive diagnostic approaches, emphasizing careful histological and immunohistochemical examination to accurately elucidate the nature of these tumors [17,29]. Reports have documented variable presentations of PEComas, ranging from benign to more aggressive forms, complicating their management and necessitating multidisciplinary collaboration among pathologists, oncologists, and surgeons [15,22].

Discussion

In analyzing uterine PEComas, it becomes evident that these neoplasms represent a complex interplay between benign and malignant behavior, influenced by histopathological characteristics and molecular profiles. The pathway to diagnosing PEComas has significant hurdles due to their imaging similarities with more common uterine pathologies, underscoring a need for heightened clinical awareness and education [1,20].

The high expression rates of specific markers such as HMB-45 necessitate careful consideration in diagnostic protocols to avoid misclassification with leiomyomas or sarcomas, which are frequently encountered in the differential diagnosis of tumors in the uterus [18,30]. Due to their overlapping clinical manifestations, a comprehensive immunohistochemical panel analysis remains crucial in effectively differentiating PEComas from other tumors. As reiterated in multiple studies, the current understanding of uterine PEComas continues to evolve, demanding a collaborative approach that encompasses improved imaging techniques and expanded histopathological evaluations [15,22].

Management of PEComas requires an individualized approach, as treatment strategies may differ based on perceived risk of malignancy, tumor size, and symptomatology. Surgical excision, being the cornerstone of treatment, offers a chance for cure, but the necessity of adjuvant therapies should not be overlooked in cases where malignancy is suspected or documented. Future studies exploring targeted therapies using mTOR inhibitors or similar biologic agents may reshape the therapeutic landscape for these tumors, particularly in cases with aggressive behavior [17,31].

Conclusion

In conclusion, the landscape of uterine PEComas remains fraught with challenges surrounding diagnosis, management, and prognosis. Although the literature has provided substantial insights and clarified some ambiguities surrounding these tumors, continuous research is essential to fully unravel the complexities of their clinical behavior. Enhanced understanding of their pathophysiology and a nuanced approach to treatment can pave the way for better clinical outcomes, reinforcing the imperative for ongoing collaboration and research in this intriguing area of gynecologic oncology.

Disclosure of Interest

All authors declare any financial interest with respect to this manuscript.

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