REVIEW ARTICLE

Applied Immunohistochemistry in Differential Diagnosis of Female Genital System PEComas

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Pages: - / Published online: 01 February 2025

Cite this article: Campara E, Lazovic-Salcin E, Skopljak A, Tiric-Campara M. Applied Immunohistochemistry in Differential Diagnosis of Female Genital System PEComas – Review Article. Sar Med J. 2025; 2(1): Online ahead of print. doi 10.70119/0025-25

Original submission: 10 August 2024; **Revised submission:** 14 December 2024; **Accepted:** 28 December 2024

Abstract

PEComa (Perivascular epithelioid cell tumors) are a rare type of tumor composed of cells exhibiting characteristics of smooth muscle cells and melanocytes. They most commonly occur in the female genital system. This study is a narrative review based on the differential diagnosis of tumors in the female genital system, focusing on PEComa. The aim of the research is to analyze the immunohistochemical markers characteristic of PEComa in the female genital system and compare them with markers of tumors that may appear in the differential diagnosis. Specifically, the study examines epithelioid smooth muscle tumor (STUMP), malignant melanoma, alveolar soft part sarcoma (ASPS), poorly differentiated endometrial carcinoma (EC) and trophoblastic tumors of the placenta (PSTT). Comparison of immunohistochemical markers of PEComa with markers of other tumors revealed that: PEComas show overlap in positive staining with STUMP, but are distinguished by markers such as HMB45, PNL2, MiTF, and MelanA/MART1; PEComas share some melanocytic markers with malignant melanoma, but differ in the expression of myogenic markers and hormone receptors; compared to ASPS, PEComas share some positive staining but differ in marker expression and negative staining; they differ from EC by the expression of specific markers such as MiTF and PAX8; PSTT show specificity for markers of trophoblastic differentiation and implantation, while PEComas emphasize melanocytic and myogenic differentiation. The general conclusion is that an accurate diagnosis of PEComa in the female genital system can only be achieved through a multidisciplinary approach. Immunohistochemical evaluation serves as a helpful tool, but standard morphological staining remains the gold standard. Also, the advanced diagnostic techniques, particularly next-generation sequencing, hold promise for enhancing the understanding and management of mPEComas. By uncovering the genomic landscape and facilitating targeted therapies, these methodologies may lead to more effective treatment and improved outcomes.

Keywords: female genital system, epithelioid smooth muscle tumor, malignant melanoma, endometrial carcinoma, trophoblastic tumor.

INTRODUCTION

Perivascular Epithelioid Cell Tumor (PECOM) is a general term for soft tissue neoplasms found in visceral locations. They are most commonly located in the female genital system (1) which accounts for just over a quarter of all PEComa cases described in the literature, with the most common uterine location. The vulva, cervix, vagina, ovaries, and broad ligament are less frequently affected (2). Other locations include

the stomach, intestines, lungs, and urogenital system, though they are less frequently found in bones. Thus, most PEComas are described in women, with a female-to-male ratio in some case studies reaching up to 9:1, suggesting a possible hormonal role in the pathogenesis because of increased expression of ER and PR demonstrated in patients with uterine PEComas (3-4). Most PEComas are benign and do not have the potential for recurrence following complete surgical excision (5-6). However, a subset of these tumors is best classified as having uncertain malignancy due to the possibility of recurrences years after the initial diagnosis. Criteria for evaluating the malignancy of gynecological PEComa are proposed and are based on the presence of more than four tumor characteristics that include tumor size ≥5 cm, high-grade nuclear features, necrosis, vascular invasion, or mitotic activity ≥1/50 HPF (7). This rare epithelioid, mesenchymal tumor originates from perivascular epithelioid cells (PECs) (1). Tumor cell growth, regardless of the pattern, is closely associated with an emphasized vascular component. This perivascular tumor distribution has led to the hypothesis of a possible origin near blood vessels (8). The presence of thin, delicate blood vessels, which may have thickened walls, is characteristic, often found in the peripheral areas of the tumor tissue (8, 9). PEComas are often sporadic and in 10% associated with tuberous sclerosis complex (10). Recent studies have shown that sporadic and tuberous sclerosis complex-associated PEComa may respond to mTOR inhibitors underscoring the importance of recognizing this tumor (7). Immunohistochemically, they express both smooth muscle and melanocytic markers, but also show positivity for the myogenic, with variable staining intensity and distribution. They display negative reactions for S100 protein, AE1/AE3, and PAX8, which assists in the differential diagnosis of this tumors (11-12). PEComas have often been confused with smooth muscle tumors as they show overlapping in morphological and immunohistochemical features (7).

Differential Diagnosis

The diagnosis mainly relies on pathological approach and should be differentiated from some other tumors. The differential diagnosis of PEComa, based on morphological and immunohistochemical overlapping includes: Epithelioid Smooth Muscle Tumor (STUMP), Malignant Melanoma (MM), Alveolar Soft Part Sarcoma (ASPS), Poorly Differentiated Endometrial Carcinoma (EC), and Placental Trophoblastic Tumor (PSTT) (10).

PEComas are morphologically well circumscribed or infiltrative with growth patterns in sheets and nests (9, 13). Noncohesive epithelioid cells are with clear to eosinophilic granular cytoplasm. PEComas may have a component of spindled cells (usually minor). Variable cytologic atypia and mitotic index of tumor cells could be present, as well as melanoma-like nucleoli, intranuclear pseudoinclusions, multinucleated cells, Touton's giant cells and melanin pigment (14). Tumor is characterized by thin and delicate vessels but may also have thick walled (generally peripherally located). Radial distribution of tumor cells identified in less than 25% (8). Stromal hyalinization is common. Immunohistochemically, positive on melanocytic markers (HMB45, PNL2, MiTF, Melan A/MART1) and myogenic markers (SMA, Desmin, Caldesmon, Cathepsin K, Estrogen, Progesterone, TFE3 and negative on S100 (focally positive in 20%), AE1/AE3 (focally positive in 11%) and PAX 8 (12).

Epithelioid Smooth Muscle Tumor – STUMP – of the uterus are rare and their prognostic factors are not well established. They have been described under various names, including leiomyoblastoma, epithelioid leiomyoma, clear-cell leiomyoma, and plexiform tumor (15). Most smooth muscle tumors of the uterus can be classified as benign or malignant based on their macroscopic and microscopic characteristics (16). STUMP cells are round, polygonal and spindled shaped. Immunohistochemically, they show positive expression for desmin, H-caldesmon, SMA, ER, PR, and WT1. Immuno-

histochemical STUMP shows negative staining for p16 (which is negative or patchy in STUMP), p53, and CD10 (17). They are usually HMB-45 negative, without characteristic capillarity network of blood vessels. PEComa is supplied by rich blood vessels and the tumor cells surround the blood vessels which are often HMB-45 positive (18).

Malignant Melanoma – MM – genitourinary melanomas represent 0.5% of all malignant melanomas (19-21). Immunohistochemical staining shows that MM exhibits positive expression for melanocytic markers, including MelanA (MART1), HMB45, SOX10, and PRAME. Additionally, positive staining is observed for S100 and nerve growth factor receptor (NGFR). Negative expression is noted for p16 (22).

Alveolar Soft Part Sarcoma – ASPS – is a rare and distinctive sarcoma that typically occurs in young patients. ASPS is characterized by uniform, organoid nests of polygonal tumor cells separated by fibrovascular septa and delicate capillary vascular channels (23-24). These nests exhibit pronounced cellular discohesion, leading to the distinctive pseudoalveolar pattern from which the tumor derived its name. The organoid appearance can be completely lost, and the tumor may be composed of sheets of epithelioid cells (23-27). ASPS shows positive expression in immunohistochemical staining for NSE, S100, TFE, reticulin, desmin, myoglobin, and HHF53. Negative staining for ASPS is observed with GFAP (glial fibrillary acidic protein) and S100 (29).

Poorly Differentiated Endometrial Carcinoma – EC – is the most common gynecological malignancy. Among endometrial cancers this one is, by far, the most prevalent (30). EC typically presents with marked and diffuse cytological atypia and various architectural patterns such as papillary, glandular, or solid growth. Key characteristics defining EC are often absent. Almost every case harbors a TP53 mutation, which is associated with abnormal p53 immunohistochemical expression (31). The immunohistochemical profile of EC includes positive expression for: CK7, CK8/18, CK19, Vimentin, CEA, CA-125, ER, PR, PTEN, CD10, IFITM1, D1, and Cyclin. In poorly differentiated endometrial carcinomas, the immunohistochemical profile of the undifferentiated component shows negative expression for CK7, PAX8, ER, WT1, Claudin4, p16, MLH1, PMS2, MSH2, MSH6, wild-type p53, and loss of expression of SWI/SNF complex proteins (BRG1, INI1, or co-loss of ARID1A and ARID1B) (32).

Placental Trophoblastic Tumor – PSTT – accounts for 0.2–3% of all gestational trophoblastic neoplasms, with an estimated incidence of 1 in 100,000 pregnancies (33-34). It most commonly occurs in women of reproductive age and can follow a normal pregnancy, miscarriage, or gestational trophoblastic disease (35-37). PSTT is characterized by a neoplastic monomorphic population of trophoblastic cells resembling implantation, often appearing as sheets of polygonal, rounded, or occasionally spindled cells that significantly infiltrate the myometrium (38). Tumor cells represent a monomorphic population of large polygonal cells with irregular hyperchromatic nuclei (39). The immunohistochemical profile of PSTT shows positive expression for: HPL, Cytokeratin, MUC4, HLA-G, MEL-CAM (CD146), CD10, GATA3, PDL1, and Ki67. Negative expression is observed with staining for p63, HCG, as well as Inhibin and PLAP (40).

DISCUSSION

In research regarding PEComa, Liu CH et al. detailed 114 cases in their report and found that the melanocytic marker HMB-45 exhibited nearly universal expression, being positive in 113 out of 114 cases. Additionally, among the smooth-muscle markers, desmin was the most frequently expressed, showing positivity in 50 out of 85 cases, which accounts for approximately 58.9%. This suggests a strong association between HMB-45 expression and the conditions studied, while desmin also plays a significant

role, albeit to a lesser extent (41). Bennett et al. reported that HMB-45 and cathepsin K were strongly expressed in all PEComas, with 83% and 93% showing high intensity, respectively. Melan-A and MiTF were found in 77% and 79% of tumors with variable expression. All PEComas exhibited at least one smooth muscle marker, with smooth muscle actin (90%) being the most frequent, followed by desmin (76%) and h-caldesmon (75%). These results highlight the unique immunophenotype of PEComas and their consistent marker profiles (9).

In a recent meta-analysis, Travaglino et al. analyzed immunohistochemical patterns in gynecological STUMPs, classifying p53 as "abnormal" or "wild-type", p16 as "diffuse" or "focal/negative", and Ki-67 levels as ≥ 10% or < 10%. While p53 and p16 aid in risk assessment, they are not standalone prognostic markers (42). Additionally, studies by O'Neill et al. and Ünver NU et al. showed that CD10 negativity and H-Caldesmon positivity can help differentiate endometrial stromal nodules, whereas p16, p53, and Ki-67 are valuable for diagnosing STUMP (43-44). Additionally, several studies prove that PR and ER are commonly expressed in STUMP and leiomyoma but are less frequent in leiomyosarcoma. One study found that high PR and low p53 expression could effectively rule out leiomyosarcoma (44-45).

Comparing information about PEComas and Epithelioid tumors of smooth muscle origin of unknown malignant potential, there is an overlap in certain markers such as Desmin, ER, and PR when observing positive staining, while specific markers for PEComas, such as HMB45, PNL2, MiTF, and MelanA/MART1, are significantly different. Furthermore, when observing negative staining, there is a difference in negative staining between PE-

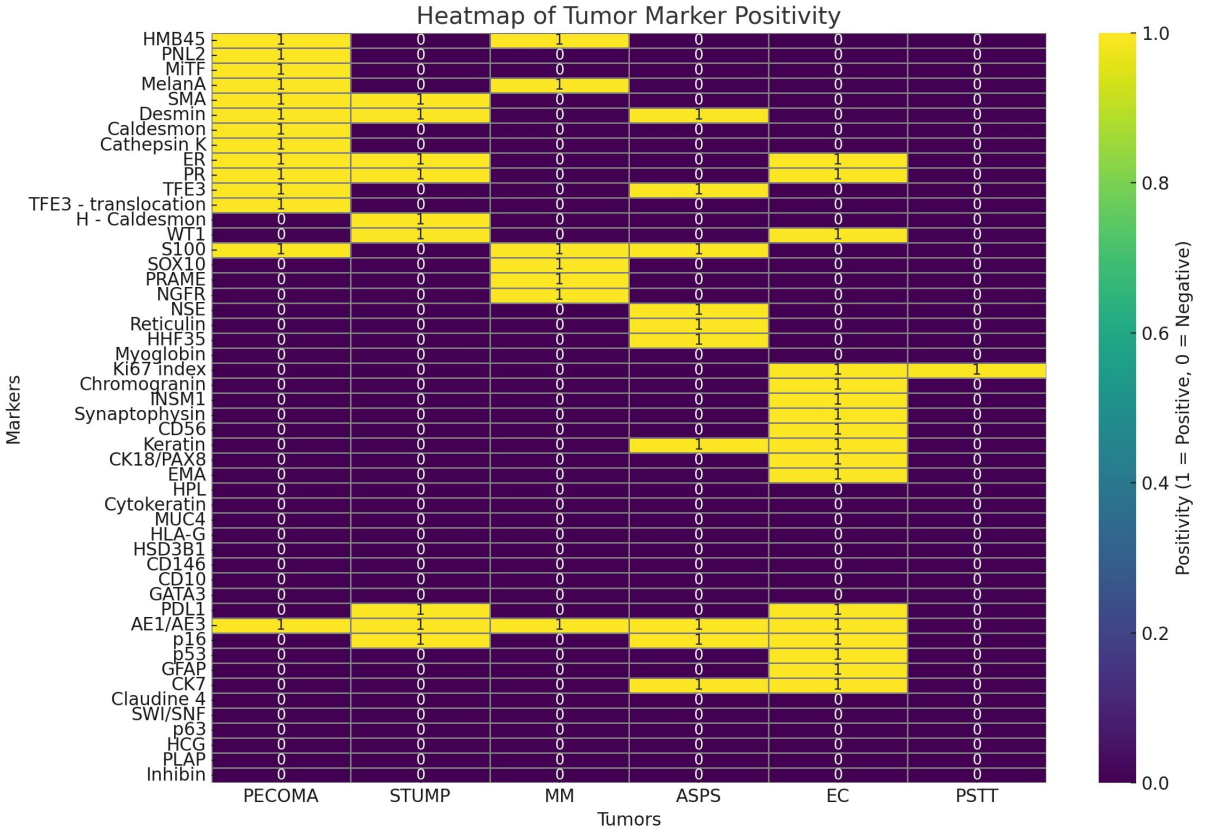

Table 1. The heatmap table lists the positive and negative staining patterns for all differential diagnoses of PEComas, showing the expression of each stain in: smooth muscle cell tumors of unknown malignant potential, malignant melanoma, alveolar soft part sarcoma, poorly differentiated endometrial carcinoma, and placental trophoblastic tumor. Positive staining is indicated by (1) and is colored in yellow. Negative staining is indicated by (0) and in color purple.

PECOMA - Perivascular epithelioid cell tumors; STUMP - study examines epithelioid smooth muscle tumor; MM - Malignant Melanoma; ASPS - Alveolar Soft Part Sarcoma; EC - Poorly Differentiated Endometrial Carcinoma; PSTT - Placental Trophoblastic Tumor.

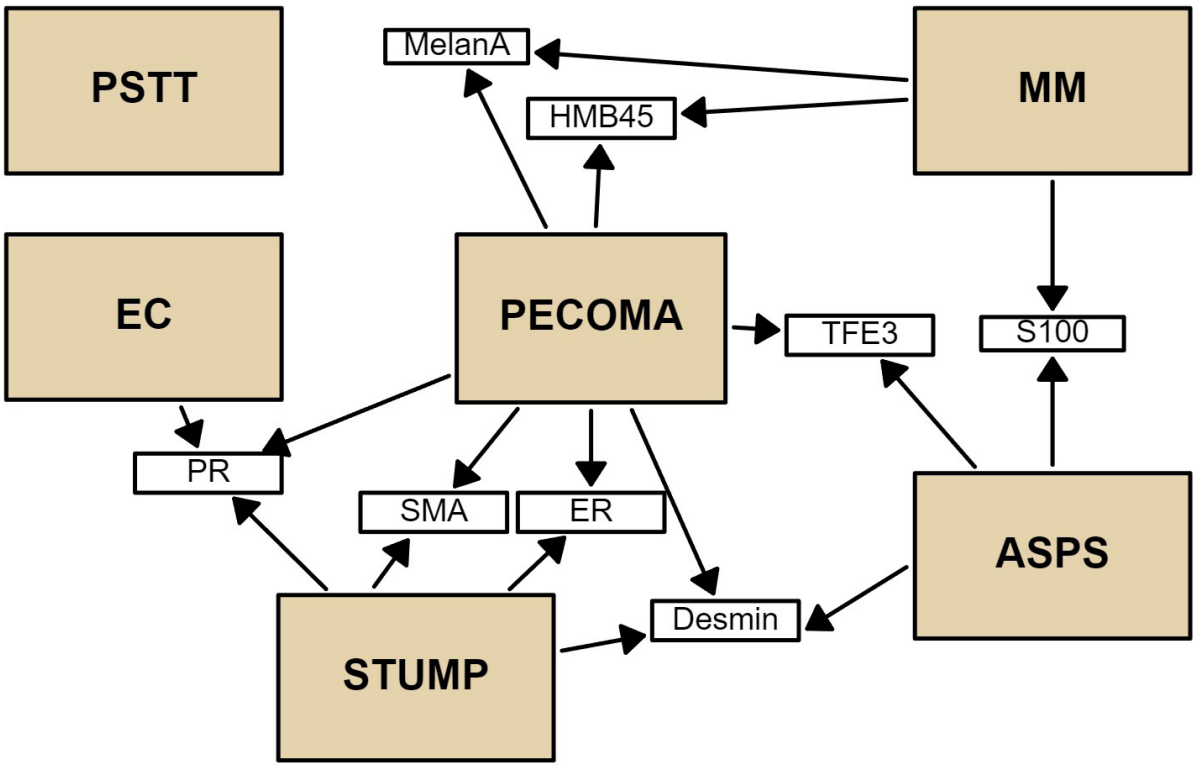

Figure 1. The diagram highlights the overlapping in immunohistochemical markers used to differentiate PEComa from other tumors – some demonstrate diagnostic challenges, while others help narrow the differential diagnosis.
PECOMA - Perivascular epithelioid cell tumors; STUMP - study examines epithelioid smooth muscle tumor; MM - Malignant Melanoma; ASPS - Alveolar Soft Part Sarcoma; EC - Poorly Differentiated Endometrial Carcinoma; PSTT - Placental Trophoblastic Tumor.

Comas and tumors of smooth muscle origin of unknown malignant potential. PEComas are negative for staining with S100, CK18/PAX8, AE1/AE3, while tumors of smooth muscle origin of unknown malignant potential are negative for staining with CD10, p16, p53. Additionally, specificities such as S100 and AE1/AE3, which can be focally positive in PEComas, further highlight the different characteristics of these two entities.

HMB-45 immunostaining revealed positive expression confined to MM and actively proliferating melanocytes, such as junctional nevus cells and cells in Spitz nevus, with no positivity in other skin components. This underscores HMB-45's high specificity for MM diagnosis (46). The results of the study conducted by Xia et al. show that S100 protein is highly sensitive for diagnosing melanoma (MM) and pigmented nevi, with positive rates of 96.8% and 100%, respectively, which is consistent with previous studies. However, S100 is also expressed in normal tissues, including glial cells, Schwann cells, muscle cells, and fibroblasts, which limits its specificity for MM and pigmented skin diseases. In one study, S100 expression was observed in hair follicle myoepithelial cells and some fibrocytes, indicating high sensitivity but low specificity in clinical practice (47-48). Regarding MITF, a higher copy number is associated with lower survival rates and poorer prognosis. However, MITF expression in various pigment diseases and MM has shown inconsistency across studies. It is not considered sensitive or specific for diagnosing desmoplastic and spindle cell melanomas, though it does have advantages in identifying these variants and metastatic melanomas (49-52).

The comparison between PEComas and Malignant Melanoma can be divided into several points based on the type of marker. Thus, we can observe that for melanocytic markers, PEComas show positive expression for staining with HMB45, PNL2, MiTF, MelanA/MART1, while malignant melanoma shows positive expression for HMB45, MelanA/MART1, and PRAME. Both entities share the expression of HMB45 and MelanA/MART1.

PRAME is specific to malignant melanoma, while PNL2 and MiTF are specific to PEComas. Myogenic markers showing immunohistochemical positive expression in PEComas include SMA, Desmin, Caldesmon, Cathepsin K, while malignant melanoma does not show specific myogenic markers with positive expression, leading to the conclusion that PEComas exhibit variable expression of myogenic markers, while malignant melanoma does not have specific markers in this context. Regarding hormonal receptors, PEComas show positive expression for ER, PR, and TFE3, while malignant melanoma does not have specific hormonal receptors, thus concluding that hormonal receptors are specific to PEComas, which may be important in differential diagnosis. Among other markers with positive staining, PEComas show focal positive expression for S100 in 20% of cases, while malignant melanoma shows strong positive expression for S100 staining, as well as SOX10, NGFR, and PRAME. Thus, PEComas and malignant melanoma have similarities in the expression of certain melanocytic markers but differ in the expression of myogenic markers and hormonal receptors. The highest sensitivity for visualizing invasive melanoma is shared between both tumors through S100, Sox10, and NGFR. Negative staining contributes to the differentiation between PEComas and malignant melanoma. While PEComas may show focal positivity for S100, specific negative staining such as CK18/PAX8 and AE1/AE3 can be helpful in distinguishing them from malignant melanoma, which is characterized by a complete loss of p16 expression.

ASPS are proven negative for epithelial markers like cytokeratins and epithelial membrane antigen, as well as for neuroendocrine markers such as chromogranin A and synaptophysin. They also lack specific melanocytic markers like HMB-45 and Melan-A. Non-specific markers, including neuron-specific enolase and vimentin, may be present in about 30–50% of cases. Interest in muscle-related protein expression in ASPS arises from the belief that it represents an unusual form of myogenic tumor. Antibodies to pan, smooth, and skeletal muscle actins have shown positivity in nearly 50% of cases, though actin expression is not specific for myogenic differentiation. Desmin is expressed in around 50% of ASPS cases but usually in only a small subset of neoplastic cells. It is important to recognize that desmin is not exclusive to myogenic tumors and can also be found in lesions such as melanoma, tenosynovial giant-cell tumor, Ewing's sarcoma, and angiomatoid "malignant" fibrous histiocytoma (28).

Comparing positive and negative markers between PEComas and Alveolar Soft Part Sarcoma, we conclude that in terms of positive staining, PEComas and alveolar soft part sarcoma share positivity for Desmin, but PEComas also show variable expression of other markers. Myogenic markers expressed by PEComas are SMA, Desmin, and Caldesmon, while alveolar soft part sarcomas emphasize Reticulin, Desmin, HHF53, and Myoglobin, which indicates overlaps in differential diagnosis, as both diagnoses show positive expression for desmin. In comparing hormonal receptors between PEComas and alveolar soft part sarcoma, only PEComas show expression for ER and PR, while alveolar soft part sarcoma does not. However, in some cases, TFE3 may be specific to both tumors under certain conditions. Comparing negative staining, we conclude that PEComas may show focal positivity for S100 and are negative for AE1/AE3, while alveolar soft part sarcoma is positive for S100, which may help in differential diagnosis. Additionally, alveolar soft part sarcoma shows negative expression for GFAP. Although PEComas and alveolar soft part sarcoma share some positive staining, differences in the expression of melanocytic, myogenic markers, hormonal receptors, and negative staining enable their differentiation in pathological analyses.

The extent of p16 expression helps distinguish between uterine serous and grade 3 endometrioid carcinomas. Serous carcinomas show p16 in 90–100% of cells, while grade 3

endometrioid tumors show 10–90%. A study found that serous carcinomas are typically ER/PR-negative, PTEN-positive, diffusely p16-positive, and show aberrant p53 staining. In contrast, grade 3 endometrioid tumors are often ER/PR-positive, PTEN-negative, focally p16-positive, and exhibit wild-type p53 (53). An immunohistochemical analysis of 180 cases (34 grade 3 endometrioid, 15 serous) showed p53, p16, and PTEN were more frequently expressed in serous tumors (69%, 90%, 100%) than in grade 3 endometrioid tumors (39%, 19%, 61%) (54). While WT1 is not routinely used for differential diagnosis, its diffuse expression suggests serous carcinoma (55). Han et al.'s study of 12 markers found that TFF3, ARID1A loss and beta-catenin were highly specific but had low sensitivity for endometrioid carcinoma. p53 (94%), p16 (80%), and IMP3 (63%) were strongly associated with serous carcinomas, compared to lower rates in grade 3 endometrioid tumors (26%, 11%, 11%) (56).

In differentiating PEComas and poorly differentiated endometrial carcinoma, PEComas show positive expression for melanocytic markers – HMB45, PNL2, MiTF, MelanA/MART1 – and myogenic markers – SMA, Desmin, Caldesmon, Cathepsin K, while poorly differentiated endometrial carcinoma shows positive expression for marker Ki67, which has an elevated index in this case, EMA, Keratin, PR, Chromogranin, INSM1, synaptophysin, and CD56. PEComas show negativity for S100, AE1/AE3, PAX8, while poorly differentiated endometrial carcinoma shows negativity for p53, p16, CK7, PAX8, ER, WT1, Claudin4, SWI/SNF complex, and mismatch repair deficiencies (MLH1, PMS2, MSH2, MSH6). PEComas are recognized by the expression of markers indicating melanocytic and myogenic differentiation, while poorly differentiated endometrial carcinoma shows specificity in the expression of markers associated with high proliferative index (Ki67), epithelial and neuroendocrine characteristics, which is crucial for establishing the correct diagnosis and for choosing treatment and prognosis for the patient.

Human placental lactogen (hPL) is typically highly expressed in histological sections and serum, with upregulation of β1-glycoprotein and CA-125 also common (57).

Comparing information on PEComas and Placental Trophoblastic Tumor, it can be concluded that PEComas show positive staining for markers related to melanocytic and myogenic differentiation, while placental trophoblastic tumors show specificity in the expression of markers related to trophoblastic differentiation and implantation – HPL, Cytokeratin, MUC4, HLA-G, HSD3B1, MEL-CAM, CD10, GATA3, PDL1. Also, PEComas are negative for S100, AE1/AE3, PAX8, while placental trophoblastic tumors are negative for p63, HCG (which is focally expressed in some cases), PLAP, and Inhibin (focally expressed). PEComas and placental trophoblastic tumors show different markers, reflecting different differentiation lines of these tumors. PEComas are characterized by the expression of melanocytic and myogenic differentiation markers, while placental trophoblastic tumor shows specificity for markers of trophoblastic differentiation and implantation.

PEComas, or perivascular epithelioid cell tumors, are a rare form of soft-tissue sarcoma characterized by their origin from perivascular epithelioid cells. Malignant PEComas (mPEComas) are particularly aggressive, often resulting in local and distant recurrences. In diagnosing and treating mPEComas, a significant advancement emerged from the AMPECT trial, which tested nab-sirolimus, an mTOR inhibitor, and demonstrated a response rate of 39% with a median progression-free survival of 8.9 months. In patients with TSC2 mutations, the response rate was even higher at 89% (58). In this issue, Akumalla et al. conduct a detailed analysis of the genomic landscape of malignant PEComas using next-generation sequencing (NGS). Their findings enhance our understanding of the pathogenesis of mPEComas and clarify why mTOR inhibitors are effective. Previous studies established that TSC1/2 gene inactivation is common in PEComas, leading to mTOR pathway activation. However, this study re-

veals that the genomic landscape of mPEComas is diverse, but they predominantly operate through the mTOR pathway (59).

Another study conducted by Groisberg et al. explores advanced gene inactivation mechanisms in PEComas, particularly loss of heterozygosity (LOH). It reveals that TSC1/2 is often bi-allelically knocked down via LOH, even in patients with "wild-type" TSC1/2, who still show mTOR pathway inactivation. Notably, FLCN mutations and unique TFE3 fusion partners also contribute to this pathway. While 31 cases were analyzed, only 20 could be explained, suggesting that unexplained mPEComas may still activate the mTOR pathway through alternative mechanisms. Future studies should adopt more comprehensive sequencing methods, like single-cell RNA sequencing. The findings stress the utility of next-generation sequencing (NGS) in understanding sarcoma subtypes and highlight the need for detailed genomic profiling beyond common mutations. Additionally, they advocate for targeted therapies focused on specific aberrations in ultra-rare tumors like mPEComas. Overall, the evolution of NGS demonstrates its increasing practicality in cancer research, signaling the importance of new technologies for future discoveries (60).

CONCLUSION

In comparison to smooth muscle tumors of unknown malignant potential, PEComas exhibit overlap in positive staining but are distinguished by specific markers such as HMB45, PNL2, MiTF, and MelanA/MART1. Relative to Malignant Melanoma, PEComas share some melanocytic markers, while differing in the expression of myogenic markers and hormonal receptors, which is crucial for differentiating these two entities. In comparison to Alveolar Soft Part Sarcoma, PEComas and this sarcoma share some positive staining (e.g., Desmin) but differ in the expression of markers and in negative staining, allowing for precise pathological diagnosis. Compared to poorly differentiated endometrial carcinoma, PEComas are distinguished by the expression of specific markers such as MiTF and by negative expression of CK18/PAX8, while endometrial carcinoma is characterized by positive expression of CK18/PAX8 and by the expression of markers associated with a high proliferative index and epithelial characteristics. Comparison with placental trophoblastic tumor highlights the diversity of markers reflecting different differentiation lines, with PEComas emphasizing melanocytic and myogenic differentiation, while placental trophoblastic tumor shows specificity for markers of trophoblastic differentiation and implantation.

After conducting the study, the general conclusion is that the definitive diagnosis of PEComa originating from the female genital system, can only be achieved through a multidisciplinary approach. Immunohistochemical evaluation of tumor cells is a good "helper", but for a definitive diagnosis, standard staining and morphological evaluation remain the "gold standard".

Also, the advanced diagnostic techniques, particularly next-generation sequencing, hold promise for enhancing the understanding and management of mPEComas in the future. By uncovering the complex genomic landscape and facilitating targeted therapies, these methodologies may lead to more effective treatment strategies and improved patient outcomes.

Acknowledgment: None.

Authors' Contributions: Conceptualization: Ema Campara, Edina Lazovic-Salcin, Amira Skopljak, Merita Tiric-Campara. Formal analysis Ema Campara, Edina Lazovic-Salcin, Amira Skopljak, Merita Tiric-Campara. Project administration: Ema Campara, Edina Lazovic-Salcin, Amira Skopljak, Merita Tiric-Campara. Visualization: Ema Campara, Edina Lazovic-Salcin, Amira Skopljak, Merita Tiric-Campara. Writing – original draft: Ema Campara, Edina Lazovic-Salcin, Amira Skopljak, Merita Tiric-Campara. Writing – review & editing: Ema Campara, Edina Lazovic-Salcin, Amira Skopljak, Merita Tiric-Campara.

Financial Support and Sponsorship: None.

Conflict of Interest: None.

REFERENCES

1. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol. 2005;29(11):1558-75. doi: 10.4081/rt.2012.e14
2. Agaimy A, Wünsch P. Perivascular epithelioid cell sarcoma (malignant PEComa) of the ileum. Pathol Res Pract. 2006;202(1):37-41. doi: 10.1016/j.prp.2005.10.008
3. Bonetti F, Martignoni G, Colato C, Manfrin E, Gambacorta M, Faleri M, et al. Abdominopelvic sarcoma of perivascular epithelioid cells: report of four cases in young women, one with tuberous sclerosis. Histopathology. 2007;50(5):563-8. doi: 10.1016/j.ejso.2007.04.005
4. Armah HB, Parwani AV. Malignant perivascular epithelioid cell tumor (PEComa) of the uterus with late renal and pulmonary metastases: a case report with review of the literature. J Cancer Res Ther. 2007;2(1):45. doi: 10.1186/1746-1596-2-45
5. Jeon IS, Lee SM. Multimodal treatment using surgery, radiotherapy, and chemotherapy in a patient with a perivascular epithelioid cell tumor of the uterus. J Pediatr Hematol Oncol. 2005;27(11):681-4. doi: 10.1097/01.mph.0000193475.06870.d5
6. Liu JL, Lin YM, Lin MC, Yeh KT, Hsu JC, Chin CJ. Perivascular epithelioid cell tumor (PEComa) of the uterus with aggressive behavior at presentation. Hematol Oncol Stem Cell Ther. 2009;2(4):426-30. doi: 10.1016/s1658-3876(09)50013-1
7. Schoolmeester JK, Howitt BE, Hirsch MS, Dal Cin P, Quade BJ, Nucci MR. Perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: clinicopathologic and immunohistochemical characterization of 16 cases. Am J Surg Pathol. 2014;38(2):176-88. doi: 10.1097/PAS.0000000000000133
8. Shibahara S, Takeda K, Yasumoto K, Udono T, Watanabe K, Saito H, et al. Microphthalmia-associated transcription factor (MITF): multiplicity in structure, function, and regulation. J Investig Dermatol Symp Proc. 2001;6(1):99-104. doi: 10.1046/j.0022-202x.2001.00010.x
9. Bennett JA, Braga AC, Pinto A, Van de Vijver K, Cornejo K, Pesci A, et al. Uterine PEComas: A Morphologic, Immunohistochemical, and Molecular Analysis of 32 Tumors. Am J Surg Pathol. 2018;42(10):1370-83. doi: 10.1097/PAS.0000000000001119
10. Wagner AJ, Ravi V, Riedel RF, Ganjoo K, Van Tine BA, Chugh R, et al. nab-Sirolimus for Patients With Malignant Perivascular Epithelioid Cell Tumors. J Clin Oncol. 2021;39(33):3660-70. doi: 10.1200/JCO.21.01728
11. Thway K, Fisher C. PEComa: morphology and genetics of a complex tumor family. J Clin Pathol. 2015;68(5):359-68. doi: 10.1016/j.anndiagpath.2015.06.003
12. Bradshaw MJ, Folpe AL, Croghan GA. Perivascular epithelioid cell neoplasm of the uterine cervix: an unusual tumor in an unusual location. Rare Tumors. 2010;2(4):e56. doi: 10.4081/rt.2010.e56
13. Fukunaga M. Perivascular epithelioid cell tumor of the uterus: report of four cases. Int J Gynecol Pathol. 2005;24(4):341-6.doi: 10.1097/01.pgp.0000168515.83557.89
14. Hornick JL, Fletcher CDM. PEComa: what do we know so far? Histopathology. 2006;48(1):75-82. doi:10.1111/j.1365-2559.2005.02316.x
15. Toledo G, Oliva E. Smooth muscle tumors of the uterus: a practical approach. Arch Pathol Lab Med. 2008;132(4):595-605. doi: 10.5858/2008-132-595-SMTOTU
16. Kurman RJ, Norris HJ. Mesenchymal tumors of the uterus, VI: epithelioid smooth muscle tumors including leiomyoblastoma and clear-cell leiomyoma: a clinical and pathologic analysis of 26 cases. Cancer. 1976;37(5):1853-65. doi: 10.1002/1097-0142(197604)37:4<1853::aid-cncr2820370433>3.0.co;2-e
17. Dall'Asta A, Gizzo S, Musarò A, Quaranta M, Noventa M, Migliavacca C, et al. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): pathology, follow-up and recurrence. Int J Clin Exp Pathol. 2014;7(11):8136-42.
18. Yang W, Li G, Wei-qiang Z. Multifocal PEComa (PEComatosis) of the female genital tract and pelvis: a case report and review of the literature. Diagn Pathol. 2012;7:15. doi: 10.1186/1746-1596-7-15
19. DePalo DK, Elleson KM, Carr MJ, Spiess PE, Zager JS. Genitourinary melanoma: An overview for the clinician. Asian J Urol. 2022;9(4):407-42. doi: 10.1016/j.ajur.2022.01.003
20. McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. Cancer. 2005;103(5):1000-7. doi: 10.1002/cncr.20866
21. Rambhia PH, Scott JF, Vyas R, Gerstenblith MR. Genitourinary melanoma. Urology. 2018;102:1692-7. doi: 10.1016/j.urology.2017.12.018
22. Urso C. Melanocytic Skin Tumors: Genetic Aberrations and Clinicopathological Classification. Dermatol Pract Concept. 2019;10(1):e2020005. doi: 10.5826/dpc.1001a05
23. Weiss SW, Goldblum JR, Folpe AL. Enzinger and Weiss's soft tissue tumors. 5th ed. Philadelphia: Elsevier Health Sciences; 2007.
24. McLaughlin CC, Harlan LC. Epidemiology of soft tissue sarcomas. Cancer Epidemiol Biomarkers Prev. 2008;17(3):723-31. doi: 10.1158/1055-9965.EPI-07-2544
25. Fanburg-Smith JC, Miettinen M, Folpe AL, Weiss SW, Childers ELB. Lingual alveolar soft part sarcoma: 14 cases with novel clinical and morphological observations. Am J Surg Pathol. 2005;29(4):511-9. doi: 10.1097/01.pas.0000153662.77529.87
26. Auerbach HE, Brooks JJ. Alveolar soft part sarcoma: a clinicopathologic and immunohistochemical study. Cancer. 1987;134(2):204-7. doi: 10.1002/cncr.2821340207
27. Sharon W. Alveolar soft part sarcoma. Urol Oncol. 2008;26(1):67-71. doi: 10.1016/S0002-9440(10)62545-X
28. Enzinger FM, Weiss SW. Soft Tissue Tumors. 3rd ed. St. Louis: Mosby; 1995.
29. Paoluzzi L, Maki RG. Diagnosis, Prognosis, and Treatment of Alveolar Soft-Part Sarcoma: A Review. JAMA Oncol. 2019;5(2):254-60. doi: 10.1001/jamaoncol.2018.4490
30. Kadar N, Malfetano JH, Homesley HD. Determinants of survival of surgically staged patients with endometrial carcinoma histologically confined to

the uterus: implications for therapy. Obstet Gynecol. 1992;80(5):812-6. doi 10.1097/00006250-199211000-00005
31. Sivridis E, Giatromanolaki A. Proliferative activity in postmenopausal endometrium: the lurking potential for giving rise to an endometrial adenocarcinoma. J Clin Pathol. 2007;60(5):575-9. doi: 10.1136/jclinpath-2007-020369
32. Tessier-Cloutier B, Kommoss FKF, Kolin DL, Němejcová K, Smith D, Pors J, et al. Dedifferentiated and Undifferentiated Ovarian Carcinoma: An Aggressive and Molecularly Distinct Ovarian Tumor Characterized by Frequent SWI/SNF Complex Inactivation. Mod Pathol. 2024;37(1):100374. doi: 10.1016/j.modpat.2023.100374.
33. Shih IM. Gestational trophoblastic neoplasia—pathogenesis and potential therapeutic targets. Lancet Oncol. 2005;15(6):652-5. doi: 10.1016/S1470-2045(14)70162-6
34. Stichelbout M, Devisme L, Franquet-Ansart H, Massardier J, Vinatier D, Renaud F, et al. SALL4 expression in gestational trophoblastic tumors: a useful tool to distinguish choriocarcinoma from placental site trophoblastic tumor and epithelioid trophoblastic tumor. Hum Pathol. 2014;54:121-6. doi: 10.1016/j.humpath.2016.03.012
35. Schneider D, Halperin R, Segal M, Bukovsky I. Placental-site trophoblastic tumor following metastatic gestational trophoblastic neoplasia. Gynecol Oncol. 1996;63(2):267-9. doi: 10.1006/gyno.1996.0318
36. Fisher RA, Paradinas FJ, Newlands ES, Boxer GM. Genetic evidence that placental site trophoblastic tumours can originate from a hydatidiform mole or a normal conceptus. Br J Cancer. 1992;65(3):355-8. doi: 10.1038/bjc.1992.72
37. Oldt RJ 3rd, Kurman RJ, Shih IM. Molecular genetic analysis of placental site trophoblastic tumors and epithelioid trophoblastic tumors confirms their trophoblastic origin. Am J Pathol. 2002;161(6):1989-94. doi: 10.1016/S0002-9440(10)62545-X
38. Zeng X, Liu X, Tian Q, Xue Y, An R. Placental site trophoblastic tumor: A case report and literature review. Intractable Rare Dis Res. 2015;4(3):147-51. doi: 10.5582/irdr.2015.01013
39. Horowitz NS, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: biology, natural history, and treatment modalities. Gynecol Oncol. 2017;144(3):455-63. doi:10.1016/j.ygyno.2017.01.024
40. Hancock BW, Tidy J. Placental site trophoblastic tumour and epithelioid trophoblastic tumour. Best Pract Res Clin Obstet Gynaecol. 2021;74:131-48. doi: 10.1016/j.bpobgyn.2020.10.004
41. Liu CH, Chao WT, Lin SC, Lau HY, Wu HH, Wang PH. Malignant perivascular epithelioid cell tumor in the female genital tract: preferred reporting items for systematic reviews and meta-analyses. Medicine (Baltimore). 2019;98(2):e14072.doi: 10.1097/MD.0000000000014072
42. Travaglino A, Raffone A, Gencarelli A, Neola D, Oliviero DA, Alfano R, et al. p53, p16, and Ki-67 as immunohistochemical prognostic markers in uterine smooth muscle tumors of uncertain malignant potential (STUMP). Pathol Res Pract. 2021;226:153592. doi: 10.1016/j.prp.2021.153592
43. O'Neill CJ, McBride HA, Connolly LE, McCluggage WG. Uterine leiomyosarcomas are characterized by high p16, p53, and MIB-1 expression compared with usual leiomyomas, leiomyoma variants, and smooth muscle tumors of uncertain malignant potential. Histopathology. 2007;50(7):851-8. doi: 10.1111/j.1365-2559.2007.02685.x
44. Ünver NU, Acikalin MF, Öner Ü, Ciftci E, Ozalp SS, Colak E. Differential expression of P16 and P21 in benign and malignant uterine smooth muscle tumors. Arch Gynecol Obstet. 2011;284(2):483-90. doi: 10.1007/s00404-010-1731-1
45. Mittal K, Demopoulos RI. MIB-1 (Ki-67), P53, estrogen receptor, and progesterone receptor expression in uterine smooth muscle tumors. Hum Pathol. 2001;32(9):984-7. doi: 10.1053/hupa.2001.27921
46. Gown AM, Vogel AM, Hoak D, Gough F, McNutt MA. Monoclonal antibodies specific for melanocytic tumors distinguish subpopulations of melanocytes. Am J Pathol. 1986;123:195–203. doi:: 10.1016/S0002-9440(10)63092-5
47. Xia J, Wang Y, Li F, Wang J, Mu Y, Mei X, Li X, et al. Expression of microphthalmia transcription factor, S100 protein, and HMB-45 in malignant melanoma and pigmented nevi. Biomed Rep. 2016;5(3):327-31.doi: 10.3892/br.2016.726
48. Cochran AJ, Holland GN, Wen DR, Herschman HR, Lee WR, Foos RY, et al. Detection of cytoplasmic S-100 protein in primary and metastatic intraocular melanomas. Invest Ophthalmol Vis Sci. 1983;24:1153–5. doi: 10.1167/iovs.24.8.1153
49. Granter SR, Weilbaecher KN, Quigley C, Fisher DE. Role for microphthalmia transcription factor in the diagnosis of metastatic malignant melanoma. Appl Immunohistochem Mol Morphol. 2002;10:47–51. DOI: 10.1097/00129039-200202000-00008
50. Miettinen M, Fernandez M, Franssila K, Gatalica Z, Lasota J, Sarlomo-Rikala M. Microphthalmia transcription factor in the immunohistochemical diagnosis of metastatic melanoma: comparison with four other melanoma markers. Am J Surg Pathol. 2001;25:205–11. doi: 10.1097/00000478-200102000-00006
51. Ugurel S, Houben R, Schrama D, Voigt H, Zapatka M, Schadendorf D, et al. Microphthalmia-associated transcription factor gene amplification in metastatic melanoma is a prognostic marker for patient survival but not a predictive marker for chemosensitivity and chemotherapy response. Clin Cancer Res. 2007;13:6344–50. doi: 10.1158/1078-0432.CCR-07-0739
52. King R, Googe PB, Weilbaecher KN, Mihm MC Jr, Fisher DE. Microphthalmia transcription factor expression in cutaneous benign, malignant melanocytic, and nonmelanocytic tumors. Am J Surg Pathol. 2001;25:51–7. doi: 10.1097/00000478-200101000-00006
53. Tashiro H, Blazes MS, Wu R, Cho KR, Bose S, Wang SI, et al. Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. Cancer Res. 1997;57(18):3935-40.
54. Alkushi A, Köbel M, Kalloger SE, Gilks CB. High-grade endometrial carcinoma: serous and grade 3 endometrioid carcinomas have different immunophenotypes and outcomes. Int J Gynecol Pathol. 2010;29(4):343-50. doi: 10.1097/PGP.0b013e3181cd6552.
55. Barcena C, Oliva E. WT1 expression in the female genital tract. Adv Anat Pathol. 2011;18:454–45. doi: 10.1097/PAP.0b013e31821e6a5c

56. Han G, Sidhu D, Duggan MA, et al. Reproducibility of histological cell type in high-grade endometrial carcinoma. Mod Pathol. 2013;26:1594–604. doi: 10.1038/modpathol.2013.133
57. Kim SJ. Placental site trophoblastic tumour. Best Pract Res Clin Obstet Gynaecol. 2003;17(6):969–84.doi: 10.1016/S1521-6934(03)00126-7
58. Wagner AJ, Ravi V, Riedel RF, Ganjoo KN, Van Tine BA, Chugh R, et al. Long-term follow-up for duration of response after weekly nab-sirolimus in patients with advanced malignant perivascular epithelioid cell tumors (PEComa): results from a registrational open-label phase II trial, AMPECT. J Clin Oncol. 2020. doi: 10.1200/JCO.19.03199
59. Akumalla S, Madison R, Lin DI, Schrock AB, Yakirevich E, Rosenzweig M,et al. Characterization of Clinical Cases of Malignant PEComa via Comprehensive Genomic Profiling of DNA and RNA. Oncology. 2020;98(12):905-12. doi: 10.1159/000510241
60. Groisberg R, Subbiah V. Sequencing PEComas: Viewing Unicorns through the Molecular Looking Glass. Oncology. 2021;99(1):62-4. doi:10.1159/000512034