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ORIGINAL ARTICLE

Clinico-pathological features of gynecological myopericytoma: a challenging diagnosis in an exceptional location

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Abstract

Myopericytomas (MPC) are rare mesenchymal tumors, originating from the perivascular myoid cells. They predominantly occur in the skin and superficial soft tissues of the extremities, while visceral involvement is rare. Histological features and clinical course are usually benign. To the best of our knowledge, MPC is still an uncharacterized tumor entity of the female internal genital tract. We describe three MPC cases involving the female internal genital tract: (1) a uterine wall MPC arising in a 49-year-old woman with progressive pelvic/abdominal pain; (2) a cervix MPC of a 49-year-old woman who presented with metrorrhagia, and (3) a MPC presenting as a simple ovarian cyst in a 26-year-old woman with pain located in the left iliac fossa. All patients were surgically treated, and recurrence occurred in two cases. The histological and immunohistochemical findings, supporting the diagnosis of MPC, are presented; in particular, one case showed characteristics pointing towards an uncertain biological behavior/low-grade malignancy. A literature search was conducted to identify previous reports of gynecological MPC and for possible alternative diagnoses. Leiomyoma, epithelioid leiomyoma, angioleiomyoma, perivascular epithelioid cell tumor, solitary fibrous tumor, and low-grade endometrial stromal sarcoma should be considered in the differential diagnosis. Awareness of possible occurrence of this rare neoplasm in the female genital tract is important to reach a correct diagnosis in the spectrum of mesenchymal tumors. Considering the risk of recurrence, we recommend careful evaluation of surgical margins and complete surgical removal whenever possible.

Keywords Myopericytoma · Differential diagnosis · Soft tissue tumor · Female genital tract · Gynecopathology · Gynecology

Introduction

Myopericytomas (MPCs) are rare mesenchymal soft-tissue tumors originating from the perivascular myoid cells, with morphological features similar to myofibromas, angioleiomyomas, and glomus tumors [1–3]. MPCs are usually benign masses arising in the skin of the extremities. Lower extremities are more frequently affected, followed by the upper extremities, head and neck region, and trunk [3]. Visceral organs (including heart, lung, kidney, and liver) and the central nervous system are rarely involved [4–8]. Although uncommon, malignant MPCs have also been reported [3, 9, 10]. In this paper, we describe three cases of MPC affecting the female internal genital tract, a neoplastic entity previously uncharacterized in this site.

Materials and methods

Cases were retrieved by searching the pathological and clinical medical records at the Pathology and Gynecology Units, Città della Salute e della Scienza University Hospital of Turin, Italy. Histological slides were reviewed by experienced gynecologic and soft tissue pathologists, and immunohistochemistry was performed (Supplementary Table 1). A literature search was conducted using PubMed, EMBASE, and Google Scholar. For this purpose, the keyword "myopericytoma"

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was used, together with one of the following terms: "female genital tract," "ovary," "fallopian tube," "salpinx," "uterus," "vulva," and "vagina." We did not find previous cases of MPC of the female genital tract, except for a case of a 20-year-old woman diagnosed with multiple MPCs, including one arising from the vulva [3].

Results

Clinical histories

Case 1: A 49-year-old woman presented with progressive pelvic and lower abdominal pain. Physical examination was negative. A pelvic ultrasound (US) examination and computerized tomography (CT) scan were performed revealing a septate, mixed fluid/solid cystic mass in the Douglas' pouch. The mass measured 14 × 12 × 9 cm and appeared highly vascularized. The preoperatory cancer antigen 125 (CA125) was 127.9 IU/ml. A laparotomic mass excision and a peritoneal washing were performed: the mass originated from the right side of the uterine wall and appeared firmly attached to the surrounding organs (right ovary and sigmoid colon). After 15 months of follow-up, the patient presented again with progressive abdominal pain. The CT scan revealed a pelvic mass, suggestive of tumor recurrence, with pelvic free-fluid. The lesion measured 7.5 × 13 × 16 cm and appeared attached to the surrounding tissues (small bowel, descending colon, and rectum-sigma). A month later, a laparotomic mass excision, together with radical hysterectomy, omentectomy, and peritoneal washing, was performed. The mass originated from the right uterine wall and was attached to the uterosacral ligament. The patient recovered completely and did not show signs of disease recurrence after a follow-up period of 30 months.

Case 2: A 49-year-old woman presented with metrorrhagia, in the absence of pelvic pain. Physical examination was negative. Pelvic US and magnetic resonance imaging (MRI) showed a pelvic mass with myxoid degeneration. The neoplastic markers carbohydrate antigen (CA) 19-9, CA125, and alpha-fetoprotein were negative. A laparotomic hysterectomy, combined with bilateral oophorectomy and peritoneal washing, was performed. The uterus appeared deformed due to the presence of a mass involving the cervix and extending to the lateral uterine wall. Large areas of colliquation were also noticed. The postoperative course was uneventful. After the surgery, the patient was discharged and no adjuvant treatments were provided. The patient is disease-free after a follow-up period of 86 months.

Case 3: A 26-year-old woman presented with pain localized to the left iliac fossa. The pelvic US examination showed an ovarian, non-vascularized, cystic lesion, on the left side. The neoplastic markers CA19-9, carcinoembryonic antigen (CEA), human epididymis protein (HE) 4, and CA125 were negative.

Laparoscopic excision of the pelvic lesion, without leaking, was performed. The wall of the lesion was incised, and drainage was carried out through an endobag. The intraoperative examination characterized the lesion as a cystic formation with multiple fine septa, weighing 67 g. These findings were suggestive of a simple ovarian cyst. The postoperative course was uneventful. After 17 months, the patient presented with another episode of acute pain localized to the left iliac fossa. Ultrasound imaging showed a new paraovarian, non-vascularized, and cystic lesion, 56 × 35 mm in size, on the left side. A laparoscopic excision was performed. At the last follow-up, after 11 months, the pelvic US examination did not show signs of recurrence.

Pathological findings

Case 1: The mass measured 15 × 12 × 10 cm and weighted 215 g. The solid component appeared partially gelatinous. Margin evaluation was not possible due to the fragmentation of the lesion during surgery. Histological examination showed a moderately cellular neoplasm characterized by plump, spindle cells growing around hemangiopericytoma-like blood vessels with a thin-walled branched structure (Fig. 1a). Concentric, prominent perivascular arrangement of tumor cells was also observed in some tumor areas (Fig. 1b). No cellular atypia or necrosis was present. Immunohistochemical analysis was positive for smooth muscle actin (SMA), estrogen receptor (ER), progesterone receptor (PgR), h-caldesmon, and calponin-1. Focal and weak desmin expression was observed. Blood vessels were lined by CD34-positive endothelial cells. The Ki-67 labelling index was less than 5%, and the mitotic count was 3/50 HPF. The peritoneal washing was negative for neoplastic cells. All these findings were suggestive of MPC with angioleiomyoma-like features (Fig. 1). The pathological findings of recurrence were consistent with the previously removed lesion.

Case 2: Macroscopically, the uterine mass was brown in color, approximately 8 cm in size, with a spongy consistency and sharp margins. Histological examination revealed round-oval cells arranged around numerous ectatic blood vessels (Fig. 2a). Some areas showed increased cellularity with staghorn-like blood vessels (Fig. 2b). In these areas, cytoplasm was scant and rare mitotic figures were observed with mild cellular pleomorphism. A focally infiltrative growth pattern was also observed. The neoplastic cells expressed SMA, h-caldesmon, calponin-1, ER, PgR, and desmin (focal). The CD31 and CD34 staining were identified only in the endothelial compartment. The peritoneal washing was negative for neoplastic cells. The Ki-67 labelling index was 5%, and the mitotic count was 4/50 HPF. Surgical margins were negative. Due to the presence of borderline characteristics between benign (low Ki-67 labelling and low mitotic count) and malignant (high cellularity and mild cellular pleomorphism) MPC, cytogenetic

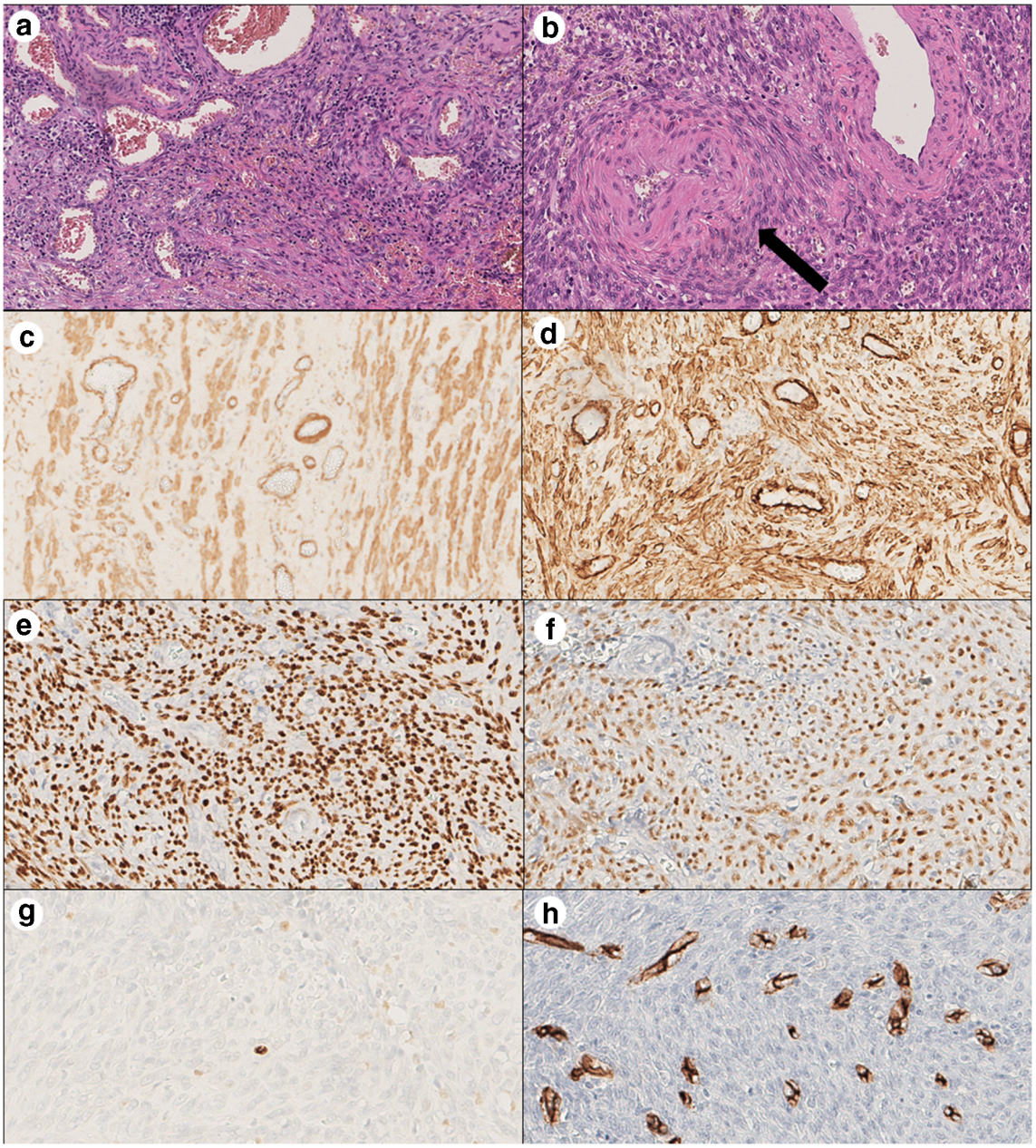

Fig. 1 Histological and immunohistochemical features of case 1. HE images (**a**, × 100; **b** × 200) showing neoplastic cells with spindle and glomoid morphology (**a**) arranged concentrically around blood vessels (arrow) with hemangiopericytoma-like features (**b**). Immunohistochemical findings were as follows: diffusely positive for smooth muscle actin (**c**, × 100) and h-caldesmon (**d**, × 100); ER and PgR were strongly and diffusely positive (**e**, **f**, × 100); proliferative index, assessed by Ki67 staining, was low (**g**, × 200); CD34 was negative in neoplastic cells (**h**, × 100). Final diagnosis was of MPC with glomoid/angioleiomyoma-like features

analysis of primary cultures of tumor cells was performed. The analysis revealed a partial trisomy of the long arm of chromosome 8 and partial monosomy of the distal short arm. Flow cytometric analysis of DNA did not detect the presence of aneuploidy populations. These findings were suggestive of MPC, with an uncertain biological behavior/low-grade malignancy (Fig. 2).

Case 3: Histological examination showed a neoplasm made of round cells with clear to slightly eosinophil cytoplasms (Fig. 3a) arranged around a rich vascular network (Fig. 3b). A variable hyalinized background stroma was present, while cellular atypia and necrosis were absent. The neoplastic cells expressed SMA, h-caldesmon, ER, and PgR. The Ki-67 labelling index was less than 1%, and the mitotic count was 4/50 HPF. These features were deemed compatible with a diagnosis of MPC with angioleiomyoma-like aspects and areas of pseudo-cystic involution. Surgical resection margins were not evaluable

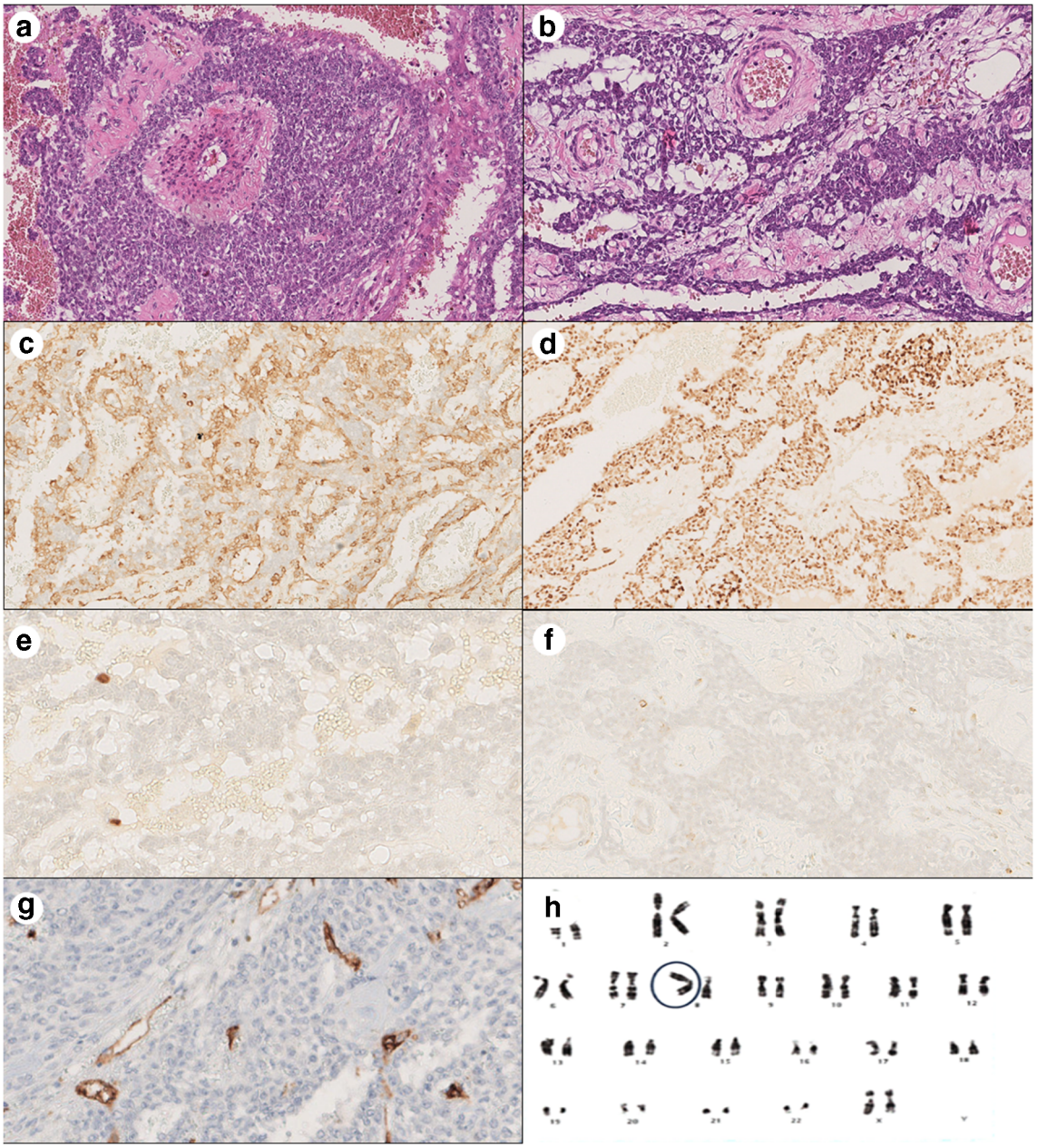

Fig. 2 Histological and immunohistochemical features of case 2. HE images (**a**, × 100; **b**, × 200) showing a higher cellularity compared with cases 1 and 3. Moderate nuclear pleomorphism was present with round-oval, scant cytoplasm. Immunohistochemical stainings were diffusely positive for smooth muscle actin (**c**, × 100) and ER (**d**, × 100); despite the higher cellularity, proliferative index (Ki67) was just slightly higher (**e**, × 200); desmin and CD34 (**f**, × 100 and **g**, × 200) were focal and negative in neoplastic cells, respectively. Partial trisomy of the long arm of chromosome 8 and partial monosomy of the distal short arm were observed. **h** Karyotype: 46,XX der(8) (qter àq21:.p23àqter). These findings were considered suggestive of MPC, with an uncertain biological behavior

(Fig. 3). Pathological features at recurrence overlapped with the initial diagnosis.

In all cases, CD10; p16; p53; p57Kip2; p63; epithelial markers, including pancytokeratin, 7, 18, and 20; neuroendocrine markers (as chromogranin A); HMB45; calretinin; S-100; EMA; and STAT6 were not detected. For this study, we also performed MED12 and HMGA2 for differential diagnosis with leiomyoma; both markers were negative.

Discussion

MPC is a rare tumor derived from myopericytes, and three main phenotypes have been described by Granter et al. [1]:

– Myofibromatosis-type perivascular myoma, characterized by a biphasic pattern (areas with bundles and sweeping fascicles of plump spindled cells mixed with areas of

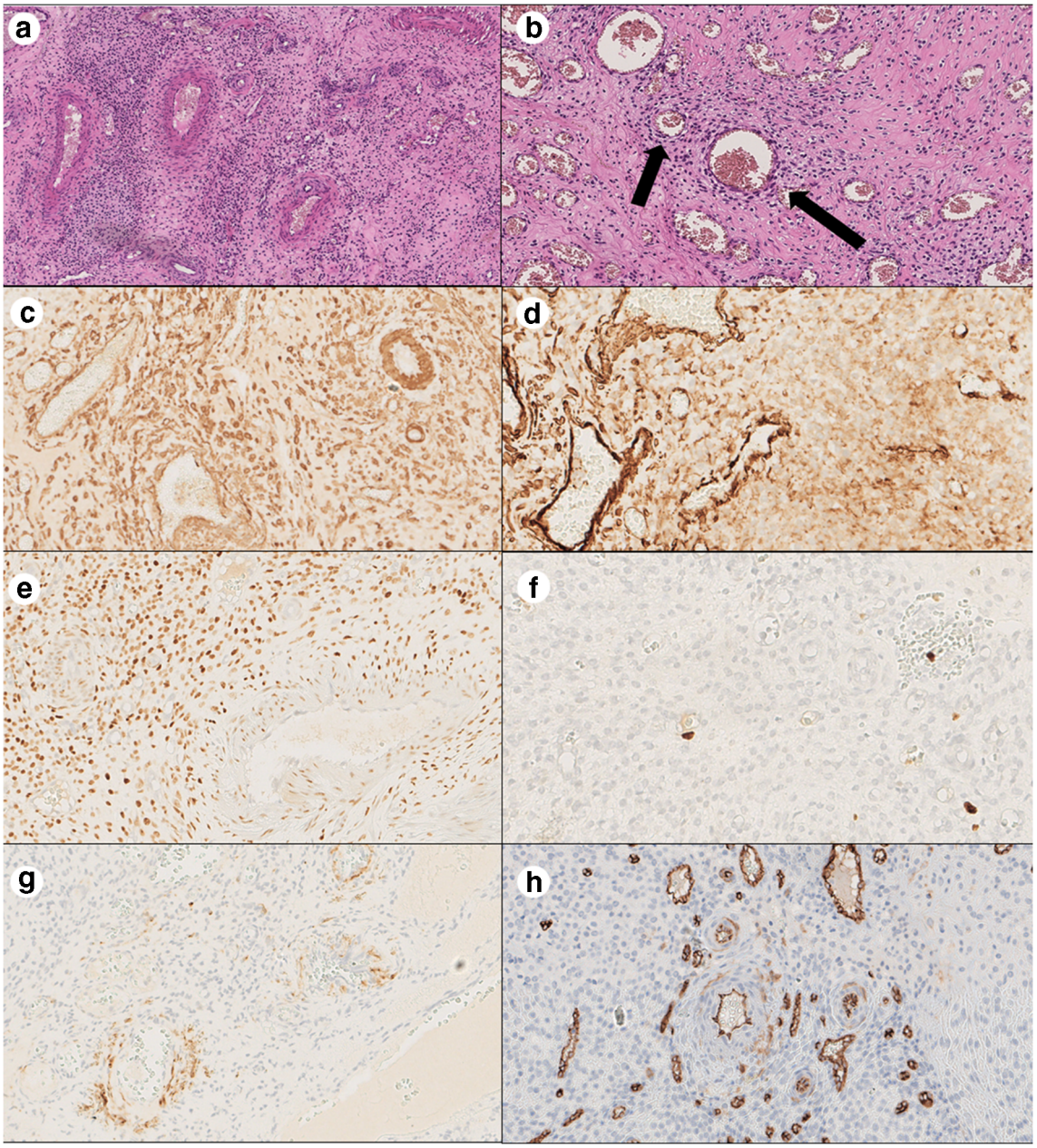

Fig. 3 Histological and immunohistochemical features of case 3. HE images (**a**, × 100; **b**, × 200) showing glomoid-like neoplastic cells arranged around blood vessels (arrow) with low/moderate cellularity. Cell membranes appeared well-defined and most cells harbored a clear to slightly eosinophilic cytoplasm. Immunohistochemical stainings showed diffuse positivity for smooth muscle actin (**c**, × 100) and h-caldesmon (**d**, × 100); diffuse with mild to strong intensity nuclear staining for ER (**e** × 100); low proliferation index (Ki-67) (**f**, × 200); desmin was focal in neoplastic cells (**g**, × 100) and CD34 was positive in endothelial cells only (**h**, × 100). Based upon these findings, a diagnosis of MPC with glomoid/angioleiomyoma-like features was made

small, round to spindled cells associated with branching vessels), hyalinized zones, and myoid nodules.

– Glomangiopericytoma-type perivascular myoma, characterized by uniform, round, or spindle cells around vascular spaces and branching, ectatic small-medium size vessels with variable wall thickness. Several tumors showed hyalinization with myxoid changes. This MPC type can mimic glomus tumors.
– Myopericytoma-type perivascular myoma, characterized by round to oval cells arranged circumferentially around vessels in a layered "onion-skin" pattern. Cell size is larger than myofibromatosis and glomangiopericytoma-type tumor cells. Hyalinization may be present and rarely (one case reported) can be extensive, involving over 50% of the tumor. Focal angioleiomyoma-like areas are characteristic.

Despite the description of these subtypes, it is important to note that morphological features can overlap. Moreover, considering this variability, immunohistochemistry is mandatory for diagnosis: MPC is usually SMA and h-caldesmon positive, while desmin expression is focal or negative [1, 3].

In the reported cases, both the clinical presentation and the macroscopic appearance of the tumor were heterogeneous, so it was not possible to identify a pathognomonic feature for these lesions. Interestingly, recurrence occurred in cases 1 and 3: in these cases, the same clinical and pathological findings were identified at recurrence supporting the hypothesis of an incomplete resection at first surgery compared with a true disease progression.

The second case showed some histological features suggestive of malignancy (high cellularity and mild cellular pleomorphism). However, other characteristics were compatible with a benign lesion (Ki-67, 5%; mitotic count, 4/50 HPF). We also found an aberration of chromosome 8 of undetermined significance, although abnormalities of chromosome 8 have been previously reported in a malignant MPC [10].

In all three cases, histology and immunohistochemical studies (Table 1) were suggestive of MPC with positive immunohistochemical staining for SMA and h-caldesmon, while CD34 was limited to the endothelial component. Desmin expression was focal. Moreover, all cases showed diffuse expression of ER and PgR, supporting the origin from the female genital tract. The presence of ER and PgR has been reported both in normal perivascular cells of endometrial stroma [11] and in a bladder MPC [4].

Based on pathological findings, leiomyoma, epithelioid leiomyoma (i.e., leiomyoblastoma), angioleiomyoma, perivascular epithelioid cell tumors (PEComa), solitary fibrous tumors (SFT), and low-grade endometrial stromal sarcoma (LGESS) should be included in the differential diagnosis.

Table 1 Immunohistochemical profiles of tumors

Markers	Case 1	Case 2	Case 3
SMA	+	+	+
Desmin	Focal	Focal	Focal
Caldesmon	+	+	+
ER	+	+	+
PgR	+	+	+
CD10	−	−	−
CD31	−	+	+
CD34	−	−	−
Calponin-1	+	+	+
Calretinin	−	−	−
p16	−	−	−
p53	−	−	−
p57Kip2	−	−	−
p63		−	−
Pancytokeratin	−	−	−
CK 7	−	−	−
CK 18	−	−	
CK 20	−	−	−
MED12	−	−	−
HMGA2	−	−	−
Chromogranin A	−	−	−
HMB45	−	−	−
S100	−	−	−
EMA	−	−	−
STAT6	−	−	−

CK, cytokeratin; *EMA*, epithelial membrane antigen; *HMB45*, human melanoma black; *SMA*, smooth muscle actin; *ER*, estrogen receptor; *PgR*, progesterone receptor; *STAT6*, signal transducer and activator of transcription 6

Leiomyoma, epithelioid leiomyoma, and angioleiomyoma

Leiomyoma is the most common benign tumor of the uterus; despite this, its features can lead to diagnostic difficulties, in particular with the rare epithelioid and angioleiomyoma variants.

Typical leiomyomas are made of uniform, spindle cells organized in fascicles and immersed in an abundant collagenous extracellular matrix. Tumor cells have oval nuclei and eosinophilic cytoplasm. Approximately 40–50% of cases show cytogenetic alterations involving chromosomes 6, 7, 12, and 14 [12, 13]. Epithelioid leiomyoma shows small nests or branching strands of small round cells recalling epithelioid features [14]. As regards cytogenetic abnormalities, trisomies 8, 12, 20, and X were noted [15]. Angioleiomyoma is characterized by partially fusiform cells with focal nuclear atypia and thick-walled blood vessels with a partially patent lumen. Areas of myxoid changes, hyalinization, and prominent vascular channels can be present [16, 17].

Angioleiomyoma and MPC can be easily mixed up due to the overlapping features, like the perivascular concentric growth pattern, which suggests a possible relation to either pericytes or glomus cells of these tumors [17]. Desmin and CD10 are usually positive in angioleiomyoma (although CD10 is usually negative in leiomyomas), but not in MPC; thus, they can help distinguish these two entities [17–20]. Nevertheless, an actin-positive and desmin-negative immunohistochemical profile can be present in about 15% of these tumors.

Gross features may also be helpful to achieve the correct diagnosis. Leiomyoma macroscopic examination commonly shows a solid, homogenous, round, and well-circumscribed lesion of various sizes. The cut surface is usually white whorled, sometimes with congested or hemorrhagic areas;

angioleiomyoma may show hemorrhagic multiloculated cysts [18, 19].

Leiomyomas may exhibit cytogenetic alterations not reported in MPC, except for the trisomy of chromosome 8 which has been reported in the epithelioid variant; in case 2, we found a partial trisomy of chromosome 8 which has been reported in a malignant MPC [10]. For this study, we also performed an immunohistochemistry analysis of MED12 and HMGA2 which are commonly expressed in leiomyoma but were negative in our cases [21, 22].

PEComa

Macroscopically most PEComas appear as a bulky nodular lesion, cut surface is pink to gray, and areas of necrosis or hemorrhage are frequently present [23, 24]. Histologically, it is comprised of medium-sized to large epithelioid cells with a trabecular, nested, and/or solid arrangement, and a typical tendency to aggregate around blood vessels. This tumor is characterized by the expression of SMA, desmin, and melanocytic markers like HMB45 and Melan-A, while cytokeratins and S100 protein are usually negative [23, 24].

Solitary fibrous tumor

The SFT appears as a well-circumscribed lesion with a yellow-tan cut surface.

SFT usually show bland, spindle cells with a patternless organization, and a hyalinized stroma in the background. It can also display cellular areas with prominent staghorn vessels (cellular variant), the histologic pattern known as "hemangiopericytoma." CD34 expression and *NAB2-STAT6* gene fusion on chromosome 12, with STAT6 overexpression, are common [25].

Low endometrial stromal sarcoma

LGESS macroscopic appearance is characterized by round soft and yellow nodules, sometimes with cystic degeneration and infarction. These nodules invade the surrounding myometrium [26].

LGESS shows sheets of bland, oval cells concentrically arranged around spiral arterioles, with a tendency to invade the vascular spaces. LGESS usually has a mitotic count < 3/10 HPF and shows diffuse CD10 positivity [27]. Nuclear atypia is mild, and necrosis is rare [17, 18].

Other sarcomas

Aggressive tumors like high-grade/undifferentiated endometrial stromal sarcoma and leiomyosarcoma have not been taken into consideration for the differential diagnosis due to the lack of frank characteristics of malignancy (high mitotic activity, marked cellular atypia, vascular invasion, and necrosis) [26, 28–30, 31].

Conclusions

Several case reports described MPC in soft tissues as well as visceral organs, suggesting its ubiquitous nature. To our knowledge, this is the first report characterizing a case series of MPC involving the female internal genital tract, although it is possible that some cases had been previously reported as angioleiomyomas.

Based on our findings, a careful pathological examination is warranted if MPC is suspected and macroscopic, histological, and immunohistochemical features should all be taken into consideration. If possible, complete surgical resection and margins evaluation are advised considering the possibility of local recurrence.

We hope that this report will increase the awareness about the possible occurrence of MPC in the female genital tract. Further studies, possibly supported by larger series, are needed to better understand the behavior of this tumor in this peculiar anatomical site.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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