TITLE: Perivascular epitheliod cell tumors: rare gynecological entities.

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ABSTRACT

Antecedents and objectives: Perivascular epitheliod cell tumor (PEComa) is a rare mesenchymal tumor composed of perivascular epitheliod cells (PEC). They are rare in the field of gynecology and have a heterogeneous clinical presentation, which makes them difficult for gynecologists to consider as a possible diagnostic option. We aim to contribute with our experience and review to ease clinical practice to others gynecologists.

Patients and methods: We contribute to literature with three gynecological cases; uterine, vaginal and retroperitoneal PEComas with different evolution and treatment.

Results: The uterine and vaginal PEComa, have only required surgical treatment, and are free of disease at 9 and 5 months respectively. The retroperitoneal PEComa has recurred at 72 months of follow-up in form of retroperitoneal mass and pulmonary lymphangioleomyomatosis, continues treatment with sirolimus with good tolerance and partial response.

Discussion and conclusion: Given the scarcity of cases, there are no clinical trials and the literature consists of case reports and mini reviews.

Some authors have categorized the PEComas based on prognostic factors, although it has not been possible to agree on a follow-up and treatment based on it. Most authors agree to perform surgical treatment. In case of recurrence or malignancy, the adjuvant treatment found in the literature is heterogeneous, with a lack of evidence regarding chemotherapy and radiotherapy. New therapies with inhibitory m-TOR open a hopeful therapeutic window.

F18-FDG PET/CT can help characterize these lesions showing intense or low uptake of FDG in malignant or benign PEComas respectively.

KEY WORDS: PEComa; Perivascular epithelioid cell tumor; mTOR inhibitor

INTRODUCTION

Perivascular epitheliod cell tumors (PEComa) are rare mesenchymal tumors composed of histologically and immuno-histochemically distinctive perivascular epithelioid cells (PEC). They are rare in the field of gynecology and have a heterogeneous clinical presentation, which makes them difficult for gynecologists to consider as a possible diagnostic option. We report three cases (uterine and vaginal PEComa in two menopausal patients and a retroperitoneal PEComa in a premenopausal patient) that led to differential diagnosis with other more common gynecological tumors.

In 2002 PEComas were classified by the WHO as tumors involving soft tissues (stomach, intestines, lungs, female reproductive organs and genitourinary organs). They are more frequent in women (ratio over 7:1) and are occasionally associated with the tuberous sclerosis complex (TSC)[1-3]. PEComa family tumors include angiomyolipoma (AML), clear cell "sugar" tumors of the lung (CCST), lymphangioleiomyomatosis (LAM), clear cell myomelanocytic tumors of the falciform ligament/ligamentum teres (CCMMT) and distinctive clear cell tumors which may be found at various other anatomic sites (pancreas, rectum, abdominal serosa, uterus, vulva, vagina, thigh and heart) [4]. The histological characteristics of these tumors are: co-expression of melanocytic and muscle markers (Smooth muscle actin, HMB45, Melan-A, S-100), epithelioid to spindle cellular shapes with ample clear to eosinophilic cytoplasm and arrangement around blood vessels [3].

Tumors involving the gynecologic tract account for just over 40% of the cases, and the uterus is the most commonly reported site. To our knowledge,

87 cases of uterine PEComa and 3 cases of vaginal location have been described to date [1-11].

Here we present our experience in gynecological PEComas and review the fundamental aspects of the literature on clinical and histological diagnoses as well as the main therapeutic options available and their outcomes.

MATERIALS AND METHODS

From January 2013 to December 2017, 3 women with gynecological PEComas were diagnosed at the Oncology Gynecology Unit of the Hospital Clinic in Barcelona. They had given their informed consent to store and dispose of the biological material that was obtained during their care process, as well as to use the clinical information for research purposes. We retrospectively reviewed clinical presentation, histopathologic and imaging features, treatment, follow-up and the last status from the clinical records.

RESULTS

Case 1: PEComa of the uterus

A 68-year-old Caucasian female, gravida-3 para-3, presented abdominal pain of a 1-year evolution and genital bleeding with loss of 5 kg of weight over 6 months. Clinical examination highlighted a pelvic mass of approximately 15 cm. A gynecological ultrasound showed a distorted uterus infiltrated by a large irregular heterogeneous solid tumor of 158x105x127mm in size and increased vascularization in the Doppler study (score 3/4). Abdominopelvic magnetic resonance imaging [MRI] showed a solid 18 cm uterine mass with necrotic areas inside with significantly restricted diffusion. The cervix seemed to have

secondary infiltration by the tumor (Fig 1a). Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT) showed a large hypermetabolic uterine mass suggestive of a primary tumor, extending to the cervix, with no signs of loco-regional or distant extension (Fig 1b). Upon suspicion of a possible malignant uterine-ovarian neoplasm, tumor markers were requested. CA-125 (20 U/ml), CA19-9 (7 U/ml), CEA (2 ng/ml), and HE4 (45.9 pmol/l) levels were within normal limits. The endometrial biopsy was negative for malignancy.

Hysterectomy and double salpingo-oophorectomy were performed by laparotomy, and the provisional perioperative diagnosis was compatible with uterine PEComa, without being able to rule out other malignancies such as uterine sarcoma/carcinosarcoma. The surgical team decided to complete the intervention by performing an omentectomy and pelvic nodal debulking due to intraoperative clinical suspicion of pelvic lymphadenopathies.

The definitive histological study showed a large multinodular mass, with areas of yellowish coloration, measuring 16 x 10 x 5 cm with epithelioid proliferation composed of polygonal cells of moderate to broad granular cytoplasm with clearing. These cells had rounded to slightly oval nuclei, with mild pleomorphism. There was an extensive vascular and capillary network and necrosis. The cells spread diffusely, forming asymmetrically separate strings of fibrous tracts. Less than 1 mitosis/10 CGA was observed. Immunohistochemical study revealed an extensive patchy positivity for HMB45 and CD10, with negativity for CK7, CK20, CK AE1-AE3, S-100, Melan-A, calretinin, inhibin A, CD99, CD68 and smooth muscle actin. The proliferative index evaluated by Ki-67 showed areas of up to 15 %. These findings were compatible with

malignant uterine PEComa with complete macroscopic surgery (size > 5 cm, infiltrative growth pattern, necrosis and vascular invasion). The omentum and the lymph nodes showed no evidence of metastasis. The patient did not receive adjuvant treatment and remained disease free 9 months after surgery.

Case 2. PEComa of the vagina

A 72-year-old woman, para 1, with obesity, diabetes and hypertension, was referred to our hospital for discomfort, vaginal pressure and difficulty in emptying the bladder. Clinical examination revealed a brownish vaginal tumor of 3 cm, with a solid multinodular appearance, pedunculated and inserted in the middle third of the lateral wall of the vagina. MRI showed a well-defined tumor in the middle third of the vagina and lateralized to the right, being iso-hyperintense in T1 and T2, without restricted diffusion, with a diameter of 24 x 21 x 33 mm and without extramural extension (Fig 2). Cyfra 21.1 (1.1 ng/ml), CEA (0.7 ng/ml) and SCC (0.7 ng/ml) levels were within normal limits. A biopsy was performed, obtaining a histological diagnosis of PEComa.

Wide local vaginal excision with free margins was performed. Hematoxylin and eosin examination showed a tumor with epithelioid cells with a clear cytoplasm and round nuclei without atypia. The cells presented diffuse arrangement, separated by fibrous tracts. The mitotic index was low, and necrosis or vascular invasion was absent. Immunohistochemical staining for HMB45 was positive in scant cells, and staining for desmin and smooth muscle actin was focally positive. Immunohistochemical staining for CK7, CK20, S-100 and Melan-A was negative.

The clinical and histological criteria were compatible with a benign PEComa (size 3 cm, no infiltrative growth pattern, no necrosis or vascular invasion). The patient was disease free at 5 months postoperatively.

Case 3. PEComa of the retroperitoneum

A 42-year-old, nulliparous woman presented for a second opinion because of a large retroperitoneal mass suspected of recurrence of PEComa. The patient referred a history of: bilateral ovarian cystectomy for endometriosis at 20 years of age, myomectomy and right cystectomy for endometriosis at age 26, and myomectomy and uterine adenomatoid tumor excision at 36 years of age.

At age 36 the patient was diagnosed with a 30 mm retroperitoneal lesion of cystic appearance. Resection by laparoscopy of the retroperitoneal lesion was performed with a diagnosis of PEComa. The paraffin block of the tissue from the previous biopsy was reanalyzed in our hospital, and the diagnosis of PEComa was confirmed based on the morphological and immunohistochemical profile. The most relevant findings were: proliferation of epithelioid perivascular cells arranged in the form of small fascicles around spaces delimited by endothelium, with abundant eosinophilic cytoplasm and a nucleus without pleomorphism. Mitotic activity was very low (Ki-67 of 1%). The immunohistochemical study showed that the tumor was intensely positive for smooth muscle actin and presented clear positivity for HMB45. The estrogen and progesterone receptors were positive (30% and 60%, respectively).

Over a 6-year follow-up the patient showed no evidence of recurrence. Thereafter, a control MRI showed a cystic multiloculated mass with a solid area

extending through the retroperitoneum (left para-aortic side) from approximately the renal area to the left inguinal region, suggestive of relapse of the basal disease, for which the patient requested a second opinion (Fig 3 b_{1-2}).

The ^{18}F-FDG PET/CT showed a multicystic retroperitoneal mass, with a metabolism similar to that of the adjacent tissues (SUVmax 1.9), suggesting recurrence of PEComa with low metabolic activity. No pathological deposits were identified in the remaining body sites studied (Fig 3 c). A chest scan was also performed showing multiple fine wall cystic images varying in size greater than 14 mm were observed in the lung parenchyma, being suggestive of lymphangioleomyomatosis (Fig 3a).

The Gynecological Tumor Committee of our hospital considered the final diagnosis of lymphangioleomyomatosis associated with a recurrent retroperitoneal PEComa and proposed surgical resection of the retroperitoneal lesion or biological treatment with immunosuppressive therapy. The patient decided to start treatment with biological therapy and received immunosuppressive treatment with 2 mg of sirolimus daily in an oncological reference center authorized for treatment and monitoring of therapy with mTOR inhibitors, with good tolerance. After 8 months of follow-up, the retroperitoneal lesions disappeared, and the lung lesions remained stable (Fig 3 d-e). The patient is undergoing surveillance and remains stable at 21 months of follow-up post relapse.

DISCUSSION

The PEComas family is a rare entity worldwide, although since the publication of the monographs recognizing this entity in 2002, the number of

cases reported has risen. Prior to the conceptual proposal of Bonetti to define PECs and group tumors with similarities and the classification of PEComas by Zamboni, no cases of PEComas had been reported in the literature [1,4].

Some clinical, radiological and immunohistochemical characteristics are shared by these tumors, although there is no pathognomonic pattern for PEComas. Cases associated with tuberous sclerosis are rarely reported, and none of our patients were diagnosed with this.

Initially, PEComas were considered to be benign tumors, but with the progressive description of cases a small subset of PEComas were reported to present local recurrences or distant metastases. Therefore, Folpe et al designed a classification based on several prognostic factors and categorized PEComas into three prognostic groups (benign, uncertain malignant potential or malignant tumors) according to the following six risk factors: 1) tumor size ≥ 5 cm, 2) infiltrative growth pattern, 3) high grade nuclear cellularity, 4) mitotic rate > 1/50 high power fields, 5) necrosis or 6) vascular invasion [5]. In some cases, there is no consensus regarding treatment, and it is not individualized according to prognostic factors. Surgical treatment is the standard procedure. There is no protocol of adjuvant treatment, and there is little information available regarding chemotherapy and radiotherapy in PEComa, with no successful results having been reported in advanced disease. Moreover, the evolution of these patients varies from case to case [2,5,11,12].

Regarding other adjuvant treatments, some recent results with the use of mTOR inhibitors seem to be promising in refractory cases or in those categorized as malignant. PEComas as well as LAM and AML show constitutive activation of the mTOR pathway (mammalian target of rapamycin complex 1)

derived from genetic alterations of the TSC1 or TSC2 locus [7]. Cases treated with mTOR inhibitors are scarce but encouraging. There are small series of cases or mini reviews in the literature reporting response rates of 50-100%, with most patients being treated with mTOR inhibitors after surgery. Some cases with contraindications for primary surgical treatment demonstrated a reduction of tumor size with the use of mTOR inhibitors, thereafter making surgery possible [7,13-16]. In case 3 of the present report, the recurrent retroperitoneal PEComa treated with sirolimus showed satisfactory response (stabilization of the pulmonary lesions and complete response at a retroperitoneal level).

Review of 25 cases in the literature after having ruled out those in which there was no follow-up or the treatment was prematurely discontinued, demonstrates the heterogeneity of the cases reported to date (tumors of different locations, some treated with chemotherapy before treatment with mTOR inhibitors, some receiving neoadjuvant treatment and some without previous surgery) (Table 1). In our evaluation, we defined complete response as radiological disappearance of the lesions, while partial response was considered as a decrease in lesion size and progression to worsening before 12 months. Therefore, response was achieved in 76.9% (20/26) of the cases, being complete in 30.8% (8/26) and partial in 46.1% (12/26), and 23.1% (6/26) of the cases showed progression [7,13,14,16-21].

Here, we presented three cases of PEComa with different clinicopathological features (Table 2 and figure 4). Most cases of PEComa require histopathological study following surgery in order to establish a definitive diagnosis. Epithelioid to spindle cellular shapes with ample clear to eosinophilic cytoplasm and arrangement around blood vessels are suggestive of PEComa in

the hematoxylin and eosin study. PEComas can co-express melanocytic and muscle immunohistochemical markers, but not all the tumors have to express the same marker. In our cases, vaginal and retroperitoneal PEComa were positive for smoot muscle actin, whereas the uterine PEComa was not, PEComas from all the patients were HMB45 positive and no tumor was positive for Melan-A and S-100.

In our report only the preoperative study of the case of vaginal PEComa was conclusive, given the possibility of histological study prior to surgery, but in the remaining two cases post-surgical study was required. Indeed, differential diagnosis with other malignancies may be necessary, requiring the need for an in depth immunohistochemical study. The perioperative diagnostic approach carried out in our center in the case of uterine PEComa is of note, taking into account the infrequent nature of this neoplasm and the need to perform an immunohistochemical study to achieve the diagnosis. The complexity of these unusual gynecological tumors justifies the referral of these patients to oncological reference centers.

Radiological studies and the clinical manifestations of PEComas are not very specific and their rarity makes a surgical approach necessary to clearly define this entity. Some cases in the literature have tried to define the radiological findings of PEComas, albeit unsuccessfully. Some authors have reported cases and have defended the role of ^{18}F-FDG-PET/CT in differentiating malignant and benign PEComas, with cases of malignant PEComas showing intense FDG uptake, and wide SUVmax ranges ranging from 3.2 to 72. However, most benign PEComas exhibited low or negative FDG uptake in ^{18}F-FDG-PET/CT images with a SUVmax less than 2 [15,22-25].

In the study of our third case, we observed a retroperitoneal lesion with low uptake, which may indicate a benign PEComa. However, the clinical behavior was similar to that of a malignant PEComa with a large retroperitoneal relapse and pulmonary lymphangiomyomatosis. Nonetheless, an ^{18}F-FDG-PET/CT study was not performed in the initial diagnosis, and therefore, the initial SUVmax was not known. In this case, the ^{18}F-FDG-PET/CT study was performed in the assessment of a relapsed retroperitoneal mass, and there are no reports regarding the value of ^{18}F-FDG-PET/CT in cases of recurrence.

CONCLUSION

In the field of gynecology, PEComas are rare tumors which are difficult to diagnose. These tumors may present with a benign and sometimes malignant behavior, leading to suspicion of malignant oncological entities such as sarcomas.

The three cases described in the present report included a vaginal PEComa and a uterus PEComa in two menopausal patients, who only required surgical treatment; and a recurrent retroperitoneal PEComa in a premenopausal patient, with a history of endometriosis, who continues treatment with sirolimus with partial response. The histological and immunohistochemical study was essential for the diagnosis in our patients.

The diagnosis of most cases is achieved by a postoperative histopathological study. Imaging tests are not conclusive, although morphometabolic studies such as ^{18}F-FDG-PET/CT can help to determine the diagnostic profile of a malignant or benign tumor. However, despite PEComas sharing histopathological criteria and possible prognostic factors, such as

surgery, there is no consensus regarding the use of adjuvant treatment, and the control and follow-up of these patients. Treatment with mTOR inhibitors should be considered as a therapeutic option in cases that are considered malignant, recurrent, or with initial contraindications for surgery or having poor prognostic factors.

Taking into account the lack of literature regarding the diagnosis and treatment of PEComas, further studies are needed in order to develop diagnostic and therapeutic protocols in these patients.

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AUTHOR CONTRIBUTIONS

IN, PF an AT selected the patients, reviewed the medical records, reviewed the literature and wrote the article. AS and JO analyzed the histopathology of the tumors. All the authors approved the final article.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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TABLES

Table 1. Reported cases of PEComas treated with m-TOR inhibitors and evolution

	Cases	Complete response	Partial response	Progression
Starbuck et al 2016	3	2	NA	1
Flechter et al 2016	1	NA	1	NA
Bunch and Sunde 2014	1	1	NA	NA
*Benson et al 2014	8	NA	6	2
Bergamo et al 2014	1	NA	1	NA
Gennatas et al 2012	1	NA	1	NA
Italiano et al 2010	2	1	NA	1
Wagner et al 2010	3	1	1	1
Nicolas et al 2018	1	NA	1	NA

*2 cases have been ruled out for not following the treatment; NA, not available

Table 2: Clinicopathologic caracteristics of the reported PEComa cases

	Uterine PEComa	Vaginal PEComa	Retroperitoneal PEComa
Age (Years)	68	72	37
Initial presentation	Abnormal uterine bleeding	Vaginal discomfort	Endometriosis follow-up
TSC	No	No	No
Tumor size (mm)	158	33	30
Histologic findings	Epithelioid proliferation of moderate to broad granular cytoplasm with clearing. Rounded nuclei to slightly oval with mild pleomorphism Extensive vascular and capillary network Cells spread forming asymmetrically separate strings by fibrous tracts. Necrosis and vascular invasion Less than 1 mitosis/10 CGA	Epithelioid cells with clear cytoplasm. Rounded nuclei without pleomorpihsm Extensive vascular and capillary network Cells with a diffuse arrangement separate strings by fibrous tracts Absence of necrosis or vascular invasion Less than 1 mitosis/10 CGA	Epithelioid perivascular cells with abundant eosinophilic cytoplasm Nucleus without pleomorphism Cells arranged in small fascicles around of spaces delimited by endothelium Absence of necrosis or vascular invasion
IHC profile	**Positivity**: HMB45 and CD10 **Negativity**: CK7, CK20, CK AE1-AE3, S100, Melan-A, calretinin, inhibin A, CD99, CD68 and smooth muscle actin **Ki 67**: 15 %	**Positivity**: HMB-45, desmin and smooth muscle actin **Negativity**:CK7, CK20, S-100 and Melan-A **Ki 67**: 5 %	**Positivity:** HMB-45 and smooth muscle actin. Estrogen receptors 30% and progesterone receptors 60% **Negativity**: Melan-A, S-100 **Ki-67**: 1%
Surgical treatment	Hysterectomy, double adnexectomy, omentectomy and pelvic lymphadenectomy	Vagina mass resection	Retroperitoneal cyst resection
Relapse	No	No	Lymphangioleomyomatosis and retroperitoneal relapse
Adjuvant treatment	No	No	mTOR inhibitor—sirolimus (ongoing)
Follow-up	ANED at 9 months	ANED at 5 months	AWD 93 months DFS 72 months

TSC, tuberous sclerosis complex; ANED, alive with no evidence of disease; AWD, alive with disease; DFS, disease free survival

LEGEND OF THE FIGURES

Figure 1. **Uterine PEComa:** a) Solid 18 cm uterine mass with necrotic areas.

b) Hypermetabolic uterine mass (SUVmax 22)

MRI, magnetic resonance imaging; PET, positron emission tomography

Figure 2. Vaginal PEComa: Isointense vaginal lesion in T1, with a diameter of 24 x 21 x 33 mm (white star).

MRI, magnetic resonance imaging

Figure 3. Retroperitoneal PEComa: a) Multiple fine wall cystic images in lung parenchyma of different sizes greater than 14 mm suggestive of lymphangioleomyomatosi. b and c) Cystic multiloculated mass with a solid area which extends through the retroperitoneum (left para-aortic side) from the renal area to the left inguinal region (white arrow) with low metabolic activity (SUVmax 1.9). d and e) After 8 months of sirolimus treatment, the lung lesions remained stable and the retroperitoneal lesions disappeared.

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Figure 4. Pathology and immunohistochemistry analysis of PEComas. Vaginal and retroperitoneal PEComa were positive for smoot muscle actin), whereas the

Uterine PEComa was not. PEComas from all the patients were HMB45 positive (Vaginal PEComa was patchy positive and the rest was strongly positive). No tumor was positive for Melan-A and S-100.

FIGURE 1

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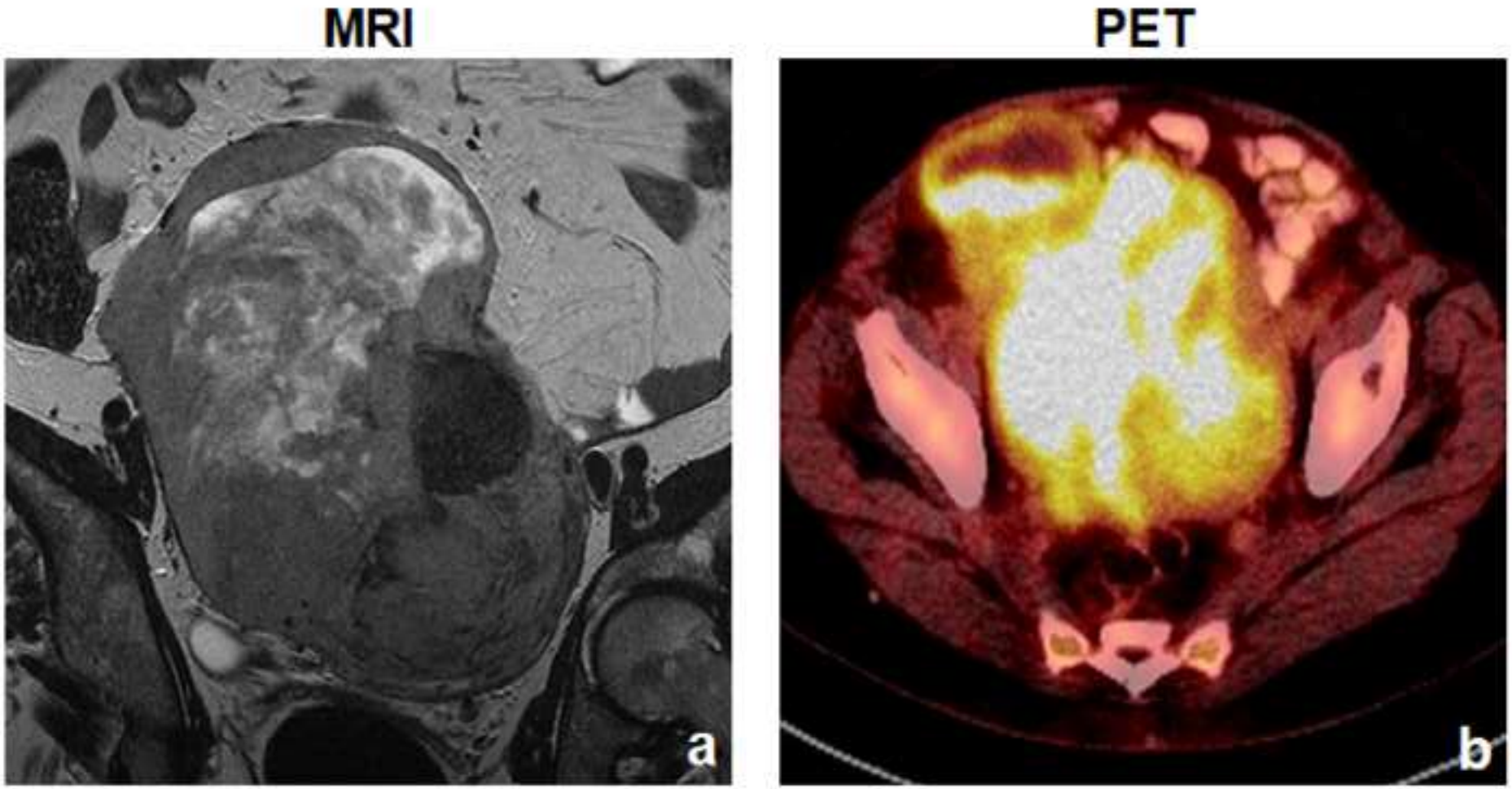

FIGURE 2

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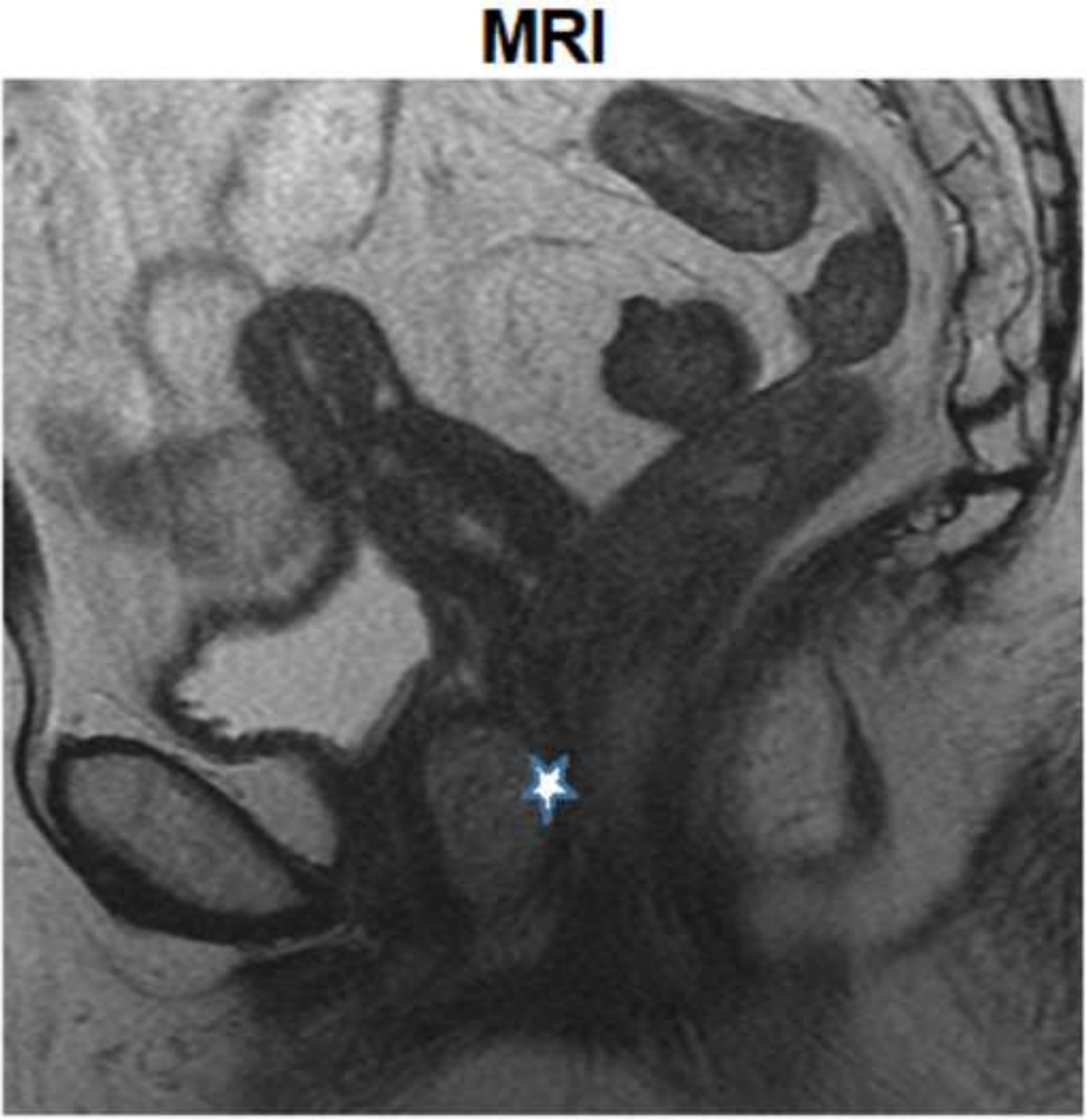

FIGURE 3

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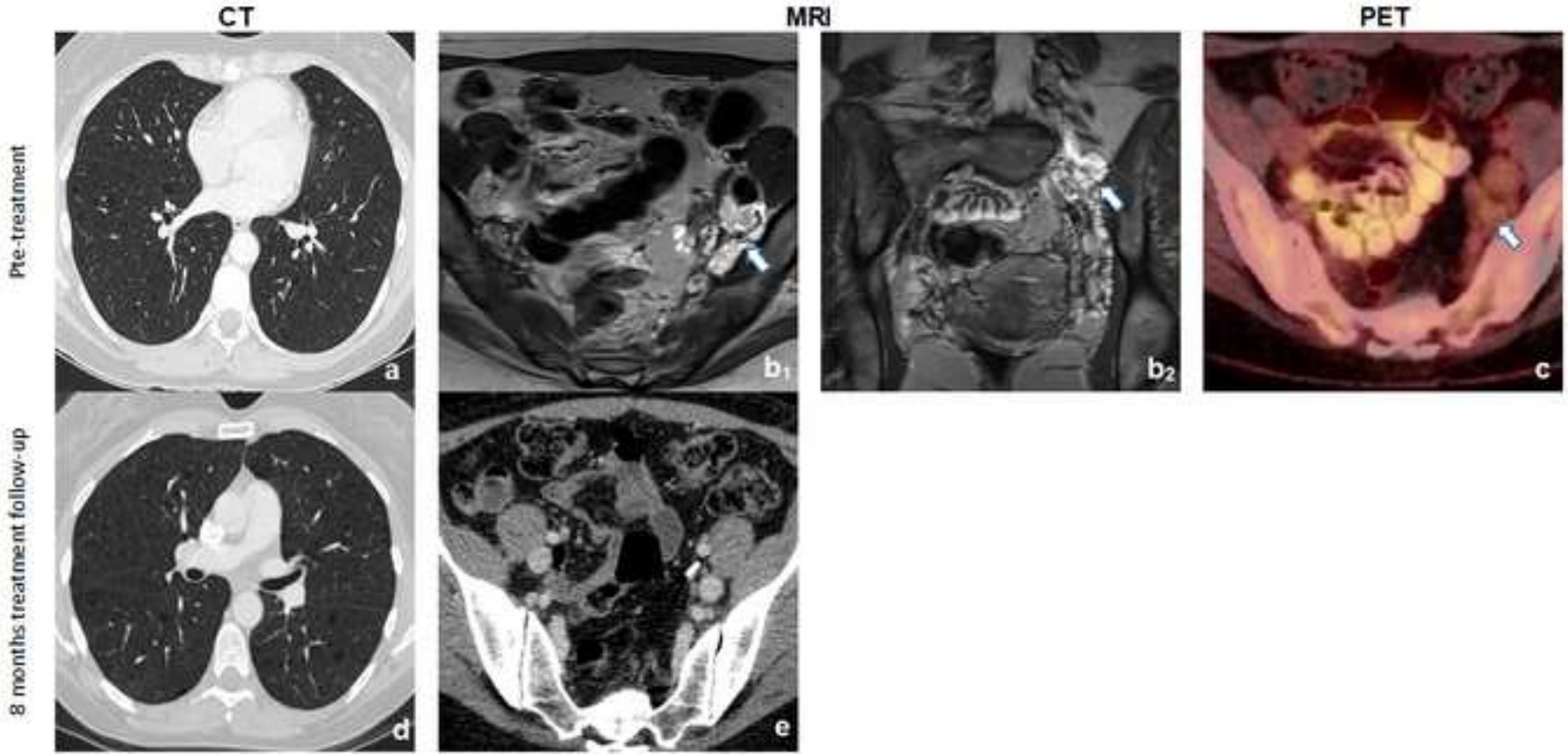

FIGURE 4

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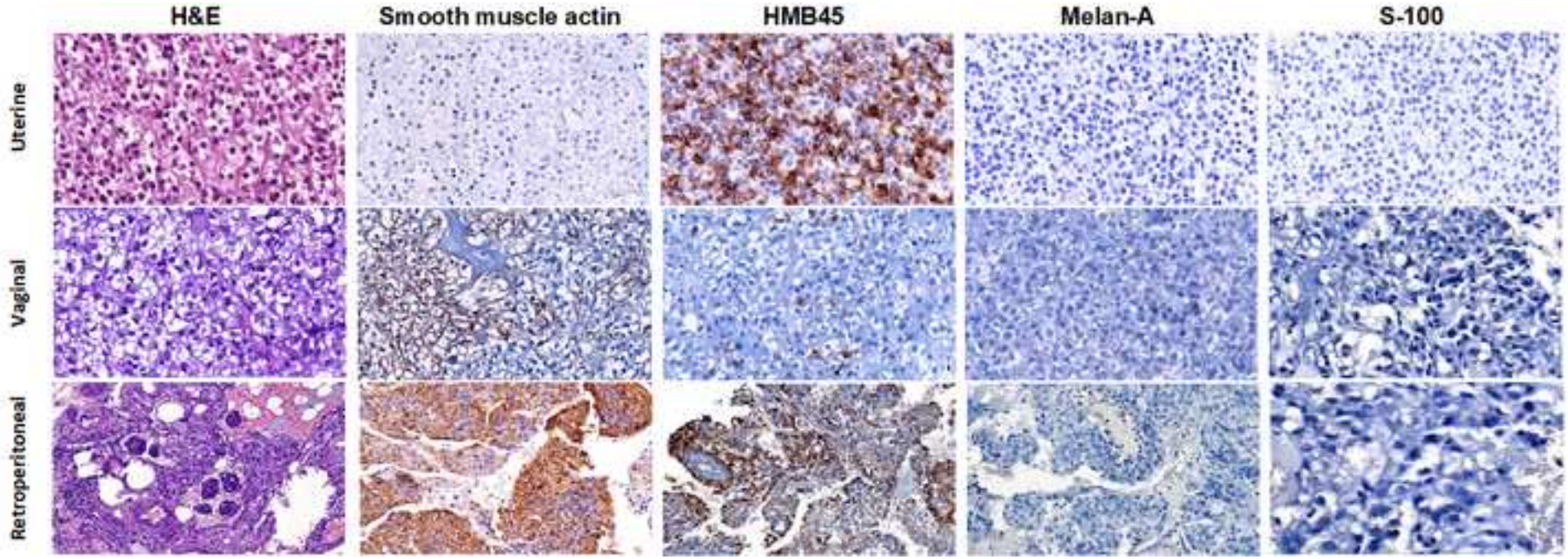

Otros archivos (vídeo, etc.)

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