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SPECIAL SECTION: DISTINGUISHED PAPERS FROM JSAR

MR findings of uterine PEComa in patients with tuberous sclerosis: report of two cases

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Abstract
Tuberous sclerosis complex (TSC), a rare autosomal dominant neurocutaneous disorder, is characterized by the presence of benign congenital tumors in multiple organs. Neoplasms with perivascular epithelioid cell differentiation (PEComas), including angiomyolipoma (AML) and lymphangioleiomyomatosis (LAM), can occur in association with TSC. This report describes two cases of uterine PEComas presenting characteristic MR imaging features reflecting pathological findings. From MR images, both cases showed single or multiple large, irregularly shaped or lobulated hemorrhagic lesions within the myometrium. They differed from typical adenomyotic cysts in their large size and irregular margins. Histopathologic analysis revealed that the hemorrhage was caused by adenomyosis and tumor cells that proliferated in surrounding stroma of the hemorrhagic lesions, compatible with PEComas. Microscopic observation revealed an infiltrative growth pattern of PEComas, with small nodules formed. The tumor lesions, however, were difficult to detect on MR images. The myometrium showed normal appearance on both T1-weighted and T2-weighted images in both cases. We speculate that PEComas may infiltrate extensively into the myometrium even when the myometrium shows almost normal radiologic appearance.

Keywords LAM · MRI · PEComa · TSC

Case reports

Tuberous sclerosis complex (TSC), a rare autosomal dominant neurocutaneous disorder, is characterized by the presence of benign congenital tumors in multiple organs. Cardiac rhabdomyoma, renal angiomyolipoma (AML), neurologic involvement encompassing cortical or subependymal tubers and white matter abnormalities, and pulmonary and/or retroperitoneal lymphangioleiomyomatosis (LAM) are the common imaging findings [1]. Though the uterus is not an uncommon site of neoplasm with perivascular epithelioid cell differentiation (PEComa) involvement [2], a few reports describe uterine lesions in TSC [3–7]. We herein report two cases of the uterine lesions in TSC patients that presented characteristic imaging findings with radiologic–pathologic correlation.

Case 1

A 33-year-old nulliparous woman with intermittent abnormal vaginal bleeding from her twenties referred to our institution because of elevated tumor markers: CA125 449.3 U/ml (normal range ≤ 35.0 U/ml) and CA19-9 47 U/ml (normal range ≤ 37.0 U/ml). She was diagnosed as having uterine adenomyosis and right ovarian endometriotic cyst based on clinical examinations by gynecologist, ultrasonography (US), and magnetic resonance (MR) imaging findings. At

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that moment, MR images showed multiple large and irregularly shaped hemorrhagic cavities within the uterine myometrium (Fig. 1a, b) and a right adnexal hemorrhagic cyst with clots. Computed tomography (CT) showed bilateral renal AML, multiple lung nodules suggestive of multifocal micronodular pneumocyte hyperplasia (MMPH), and sclerosis within vertebra in addition to the pelvic lesions. Brain MR examination showed cortical or subependymal tubers and white matter abnormalities. All of these features were consistent with TSC, but no family history was evident. Nine months after her first visit, the tumor markers were elevated compared with earlier data. Enlargement of the right ovarian lesion was observed while using US imaging. Pelvic MR study was reexamined for more detailed evaluation. The uterine appearance was unchanged, but a solid enhanced lesion was observed in the right ovarian endometriotic cyst.

Abdominal total hysterectomy (ATH), right salpingo-oophorectomy (RSO), and left salpingectomy (LS) were performed under the suspicion of a malignant right ovarian tumor associated with endometriotic cyst. The intraoperative findings revealed severe adhesion among the uterus, right ovarian tumor, and left salpinx. The uterus was soft and hemorrhagic. The right ovarian tumor was enlarged as large as the neonatal head size at operation and $13.5 \times 9.5 \times 0.7$ cm after fixation. Histologic analyses revealed that the endometrial glands with stroma were scattered in the myometrium, compatible with adenomyosis. In addition, spindle cells with clear cytoplasm, which were immunoreactive with human melanin black-45 (HMB-45), grew and infiltrated the myometrium (Fig. 1c). Histological and immunohistochemical findings were consistent with LAM. Multiple smaller nodules composed of uniform epithelioid cells with clear cytoplasm and round nuclei that partially expressed HMB-45 were also observed and also diagnosed as PEComa (Fig. 1d–f). The right ovarian tumor was proven to be an endometriotic

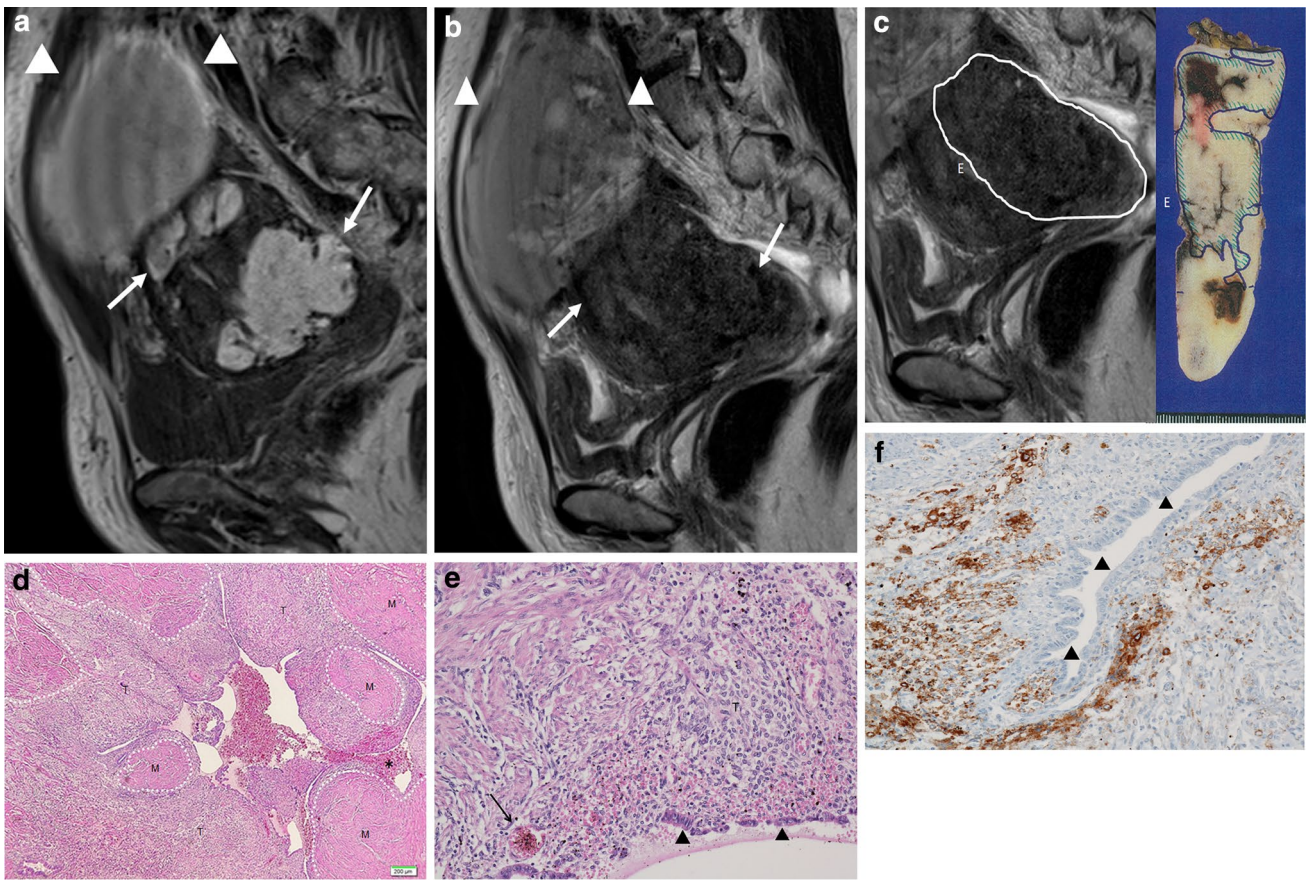

Fig. 1 Case 1: A 33-year-old woman with history of tuberous sclerosis complex (TSC). Sagittal T1-weighted image (**a**) and T2-weighted image (**b**) show multiple irregularly shaped hemorrhagic lesions in the myometrium (white arrows). Endometriotic cyst is observed cephalad to the uterus (arrowheads). **c** White line on T2-WI corresponds to the uterine specimen. The area drawn by blue on the specimen suggested microscopic tumor cell infiltration; *E*, endometrium (**d**) H-E stain: Histopathological image of the hemorrhagic lesion caused by adenomyosis. Hemorrhage infiltrating into the surrounding tumor lesion is observed (asterisk). **e** H-E staining: Spindle cells with clear cytoplasm are visible next to the endometrial cells (arrowhead). Hemosiderin deposits are also observed (arrow). **f** By immunochemical staining, tumor cells are positive for HMB-45: *M*, myometrium; *T*, tumor cells

cyst with no malignancy. Solid enhanced lesion on MR imaging was not clarified.

Case 2

A 44-year-old nulliparous woman was scheduled for a surgical procedure for ovarian endometriotic cysts because of recurrent abdominal pain and enlargement of the cysts despite of hormonal therapy over 6 years.

Contrast-enhanced CT at her late thirties revealed one unilocular and lobulated-multilocular cystic lesions, observed respectively within the posterior and right sides of the myometrium (Fig. 2a). The left adnexa were accompanied by unilocular cystic lesion. Uterine adenomyotic cysts and left ovarian endometriotic cyst were suspected at that time. She was also under follow-up of TSC lesions in the brain, lung, bone, and kidneys. Four years later, MR imaging showed enlarged hemorrhagic cysts both within the uterine myometrium and at the left adnexa (Fig. 2b, c).

Intraoperative findings revealed strong adhesion in the pelvic space and a left paratubal cyst was observed with bilateral normal ovaries. A ruptured hemorrhagic cyst was observed at the uterine fundus, and its hemorrhagic cavity penetrated into the endometrial cavity. Massive hemorrhagic ascites (1500 ml) accumulated in the peritoneal cavity.

Histologically, the uterus showed adenomyosis. The wall of the ruptured hemorrhagic cyst in the uterine fundus consisted of endometrial cells. Spindle cells of a tumor infiltrated diffusely along almost the entire myometrium, with cervical involvement as well, resulting in little normal myometrium left. The same type of cells (spindle cells) also infiltrated the endometrium and adnexa. Immunochemical staining showed that the tumor cells were positive for α-smooth muscle actin (SMA), h-caldesmon, Melan-A, and

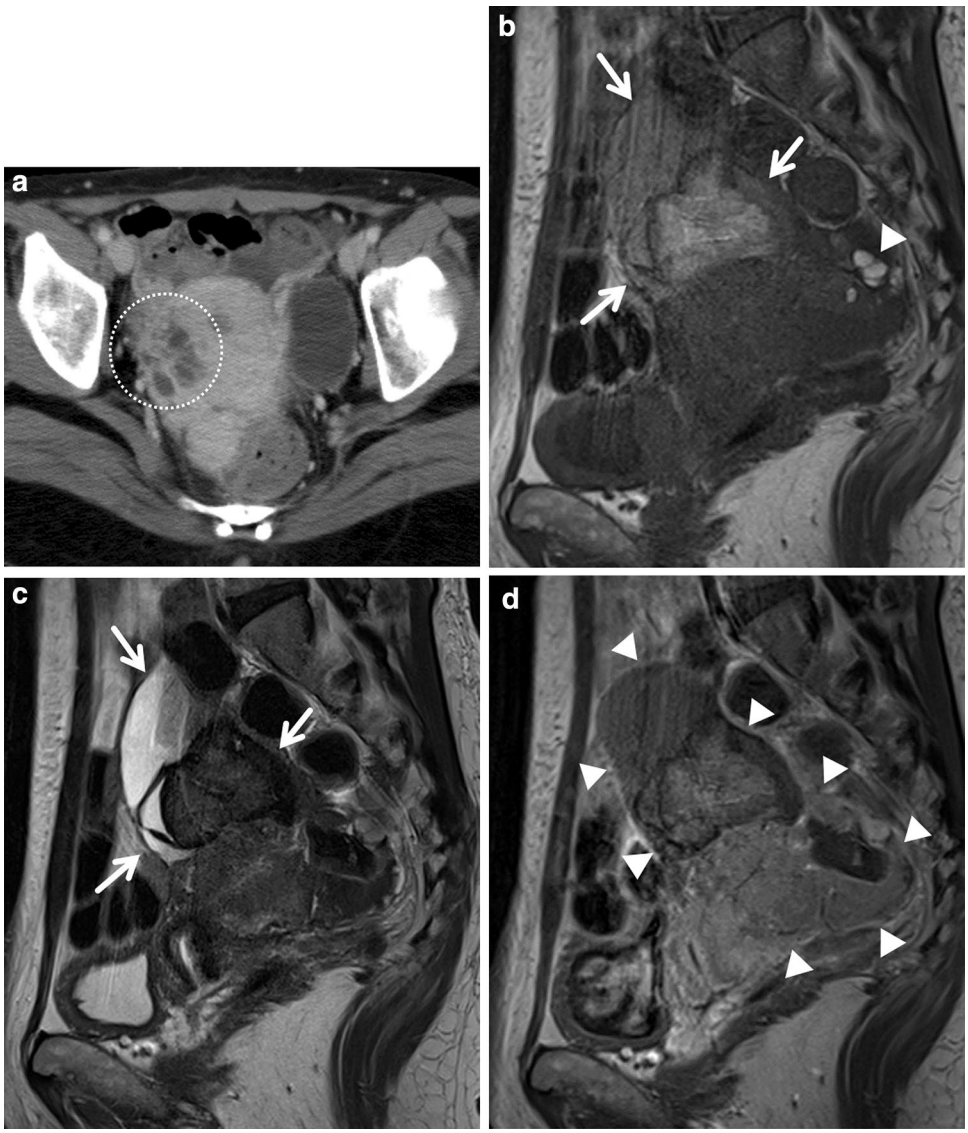

Fig. 2 Case 2: A 44-year-old woman with history of TSC. Axial contrast-enhanced CT in her late thirties shows a lobulated-multilocular cystic lesion on the right side of the myometrium (**a**). Four years after CT (Fig. 2a), sagittal T1-weighted image (**b**) and T2-weighted image (**c**) show a large hemorrhagic cyst (arrows) adjacent to the uterine anterior wall. The uterine contour is distorted considerably, as shown by arrowheads on sagittal contrast-enhanced T1-weighted image (**d**). Small hemorrhagic lesions, suggestive of adenomyosis, are also apparent in the myometrium [arrowhead (**b**)]

HMB-45. Based on these findings, the tumor was diagnosed as PEComa with component of LAM.

Discussion

We revealed two cases of uterine lesions in TSC that presented characteristic imaging findings. On CT and MR images, both cases showed single or multiple irregularly shaped hemorrhagic spaces within the myometrium or subserosa. Adenomyotic cysts were initially suspected from the imaging findings. However, they differed from typical imaging findings of adenomyosis in that the hemorrhagic lesions were large and had irregular margins [8].

Hayashi et al. reported that uterine lesions of LAM in TSC patients (TSC-LAM) have different histologic features from those in non-TSC (sporadic-LAM) [3]. In the sporadic-LAM, the uterine LAM lesions tend to make macroscopically well-circumscribed masses. They are often misdiagnosed as leiomyomas on imaging [3, 5]. By contrast, TSC-LAM lesions of four cases do not macroscopically show apparent nodules in the uterus and are microscopically infiltrative, with a more tongue-like growth pattern [3, 6]. In the case by Froio et al., the tumor was macroscopically poorly demarcated and unencapsulated accompanying TSC and extensive infiltration of adenomyosis [7]. Kim et al. reported radiologic findings of uterine LAM lesions with TSC [6]. Although adenomyosis was not described in that case, our cases showed similar imaging findings: multiple irregularly shaped hemorrhagic cavities without solid portions in the myometrium.

In the present study, the walls of the hemorrhagic lesions consisted of endometrial cells. They were diagnosed pathologically as adenomyotic cyst. PEComas showed an infiltrative growth pattern intermixed with normal myometrial cells in the surrounding stroma of the hemorrhagic lesions similar to the three cases presented by Hayashi et al. [3]. Therefore, little normal myometrium was left in case 2. From MR imaging, the uterine myometrium was found to be "normally" low in signal intensity on T2-weighted and T1-weighted images in both cases. However, considering these pathological results, tumor cells infiltrated into the "radiologically normal myometrium." In other words, it is speculated that hemorrhagic cavities were not in the normal myometrium but within the tumor. Therefore, because the tumor lesions were softer than the normal myometrium, we suspect that adenomyotic cysts were able to enlarge easily and that large hemorrhagic cavities with irregular margins were formed. We have experienced two other cases of clinically suspected uterine PEComas with TSC patients, not shown in this article. Their appearance was very similar, with irregular-shaped hemorrhagic cavities within the low signal myometrium on T2WI. Also, an irregular or jagged endometrial margin was observed in these two cases. In one case, the patient presented with recurrent hematometra and infection, which we suspect is related with an infiltrative PEComa, with consequent loss of myometrial contraction strength and, thus, promote large hemorrhagic cavities which may disrupt into the endometrial cavity.

In conclusion, this report describes two cases of uterine PEComas in TSC patients, which present with distinct and characteristic MR imaging findings. The findings were single or multiple, large, irregularly shaped, or lobulated hemorrhagic cysts within the myometrium. From the results of the clinical course and radiological and pathological findings, it might be speculated that PEComas infiltrate extensively into the normal myometrium in TSC patients even when the uterus shows an almost normal radiologic appearance.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were conducted in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent A statement of informed consent was not applicable because the manuscript includes no patient data.

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