Acute and repeated haemoperitoneum: a challenging case of lymphangioleiomyomatosis with uterine PEComa

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SUMMARY

A 39-year-old woman presented in the emergency ward for abdominal pain and acute anemiation. Abdominal–thoracic CT scan showed haemoperitoneum, with a parauterine mass and a pathological pulmonary pattern suspicious for lymphangioleiomyomatosis (LAM), a systemic disease belonging to perivascular epithelioid cell tumours (PEComas). Gynaecological ultrasound showed a hypoechoic irregular solid mass of the uterine right wall. Ultrasonographic virtual organ computer-aided analysis showed the mass completely formed by arteriovenous vessels, and that allowed distinction from leiomyosarcoma. Repeated haemoperitoneum required uterine artery embolisation. Mass revascularisation occurred in the following 7 days. A laparotomic hysterectomy with removal of the uterus and right parametrium was performed in epidural analgesia. Histological features were consistent with the diagnosis of uterine PEComa of uncertain malignant features, in the presence of coexisting pulmonary LAM. In women with LAM, acute haemoperitoneum may indicate the presence of a uterine PEComa whose diagnosis can be challenging.

BACKGROUND

Lymphangioleiomyomatosis (LAM) is a rare disease that mostly affects fertile women. It is characterised by an abnormal proliferation of smooth muscle-like cells (LAM) in the lungs causing a cystic lung disease. It can occur in association with the tuberous sclerosis complex (TSC) (TSC–LAM) or without TSC (sporadic LAM) and is due to the mutation of TSC1 and TSC2 genes, strongly involved in the control of cell growth and proliferation.[1] In both cases, LAM is caused by mutations of the TSC1 or TSC2 genes, two tumour suppressor genes that encode, respectively, hamartin and tuberin, resulting in dysfunction of these two major regulatory proteins, leading to unchecked proliferation of LAM cells. Mutations of TSC have been demonstrated in both LAM and perivascular epithelioid cell tumour (PEComa), indicating the same origin of disease and progression. At present, LAM is included in a widely accepted group of tumours called 'perivascular epithelioid cell tumours' (PEComas).[1] The WHO defines PEComas as 'mesenchymal tumours composed of histologically and immunohistochemically distinctive perivascular epithelioid cells'.[2] PEComas can be defined as benign, at uncertain malignant potential and malignant in accordance with their size, mitotic rate, infiltrative growth pattern, vascular invasion, nuclear grade cellularity and areas of necrosis.[3] Clinical picture of genital lesions can be vaginal bleeding, abdominal pain, discomfort, compressive syndrome or palpable abdominal mass.[4 5] Diagnosis can be challenging, and surgery is the optimal treatment.[6] Herein, we present a case of a patient affected by pulmonary LAM presenting with repeated haemoperitoneum where preoperative ultrasound (US) was crucial to plan the diagnostic–therapeutic process of uterine PEComa.

CASE PRESENTATION

A 39-year-old Hispanic woman (gravida 0, para 1) with acute abdominal pain was evaluated at the emergency ward of a local public hospital. The personal and familiar clinical history of the patient was not contributive. The patient had regular menstrual cycles and was carrying a copper intrauterine device that was removed at admission. Abdominal and thoracic CT scan visualised haemoperitoneum, a right parauterine mass, suspicious for adnexal neoplasm and diffusely distributed small cystic lesions in the lung's parenchyma with a right apical–basal pneumothorax flap of 19 mm. Laboratory analysis showed acute anemisation with haemoglobin (Hb) values that further decreased from 9 g/dl to 7 g/dL in the following 24 hours. Two units of concentrated erythrocytes were transfused, and the patient was referred to the gynaecological academic unit of the San Martino Hospital of Genoa. At admission, clinical conditions were stable, and the patient was painless. Vital signs were normal: afebrile, blood pressure=120/70 mm Hg, heart rate (HR)=69 beats per minute (bpm) and oxygen saturation ($satO_2$)=99%.

INVESTIGATIONS

Laboratory tests performed showed low but stable Hb levels of 8.9 g/dL, low haematocrit (HCT) value of 26% and elevated d-dimer of 34 000 µg/L. Chest X-ray revealed complete pneumothorax reabsorption. CT scan confirmed the multicystic lung disease and haemoperitoneum (figure 1). Pneumologist identified these lesions as a suspicious LAM of the lung.

The association between LAM and TSC was investigated by a detailed history and physical examination. Genetic analysis was not performed, but when negative, this does not exclude the presence of TSC,

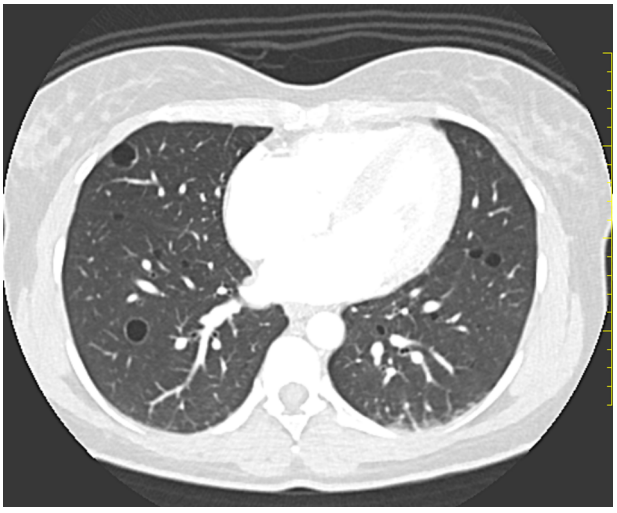
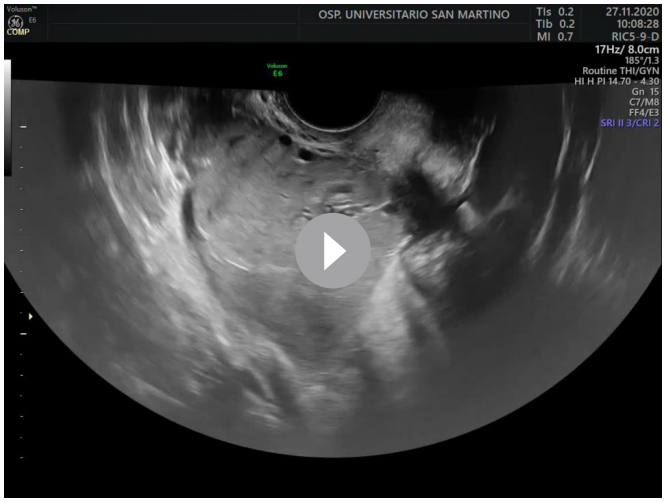


Figure 1 Chest CT demonstrates diffusely distributed small cystic lesions with reticular opacity.



Video 1 Transvaginal ultrasound video showing presence of a hypoechoic irregular solid mass rising from the right lateral wall of the whole myometrium.

whose diagnosis is based mainly on the concomitance of major and minor clinical features. Updated criteria for definite diagnosis of TSC reported two major features or one major feature with ≥2 minor features. A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet the criteria for a definite diagnosis.

In our patient, by physical examination, no signs of skin, dental, oral and ungual specific lesions were found.

Chest and abdominal CT scan did not detect lesions such as cardiac rhabdomyoma, multiple renal cysts, non-renal hamartomas and angiomyolipomas. The sole combination of LAM and PEComa did not meet the criteria to make a diagnosis of TSC.[7 8] Transabdominal and transvaginal US showed an irregular morphology of the uterus, with the presence of a hypoechoic irregular solid mass measuring 71×60×60 mm. The mass, rich of vessels, with a colour score of 4, at power Doppler (PD) analysis, was rising from the right lateral wall of the whole myometrium and extended in the right parametrium until the middle third of the cervix, below the entrance of the right uterine vessel (figure 2A,B) (videos 1 and 2). Three-dimensional (3D) PD US confirmed the abundance of arteriovenous vessels (figure 3) (video 3). The endometrium was unaffected, regular and with a uniform hyperechogenic echotexture that was consistent with the menstrual phase. Adnexa were not affected by the mass and were regular. Virtual organ computer-aided analysis (VOCAL) was used to perform semiquantification of the mass' blood flow, by using the Vascularisation Index (VI) function. VI measures the ratio of the number of colour voxels to the total number of voxels (%), and it is a representation of vascularity (ie, amount of blood vessels).[9] The calculated volume of the mass was 100.2 cm^3, with a VI of 96.1%, indicative of mass almost completely formed by vessels (figure 4). Transabdominal US scan showed haemoperitoneum and regular appearance of abdominal organs. At completion, an angio-CT, performed with iodinated contrast medium (Omnipaque 350), showed a parauterine mass affecting the whole myometrium, well vascularised by the right uterine artery.

Results of imaging techniques in conjunction with the evidence of a possible LAM in the lungs lead us to suspect a uterine PEComa.

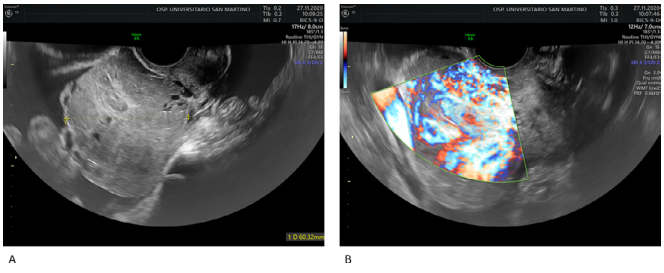
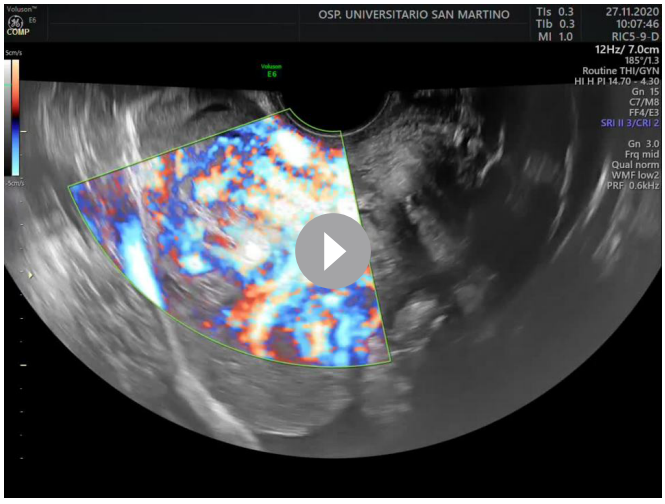


Figure 2 Transvaginal ultrasound showing (A) a hypoechoic irregular solid mass (71×60×60 mm) rising from the right lateral wall of the whole myometrium). (B) Power Doppler showing abundant vascularisation of the mass (colour score 4).

TREATMENT

Surgical removal of uterus and adjacent mass was proposed. Initially, the woman did not consent to the procedure to preserve her fertility.

Seven days after admission to our hospital, during the night, she complained about acute abdominal pain, sweating and vomiting, with a painful abdomen. Vital signs showed blood



Video 2 Transvaginal ultrasound video showing abundant vascularisation of the mass at power Doppler analysis (colour score 4).

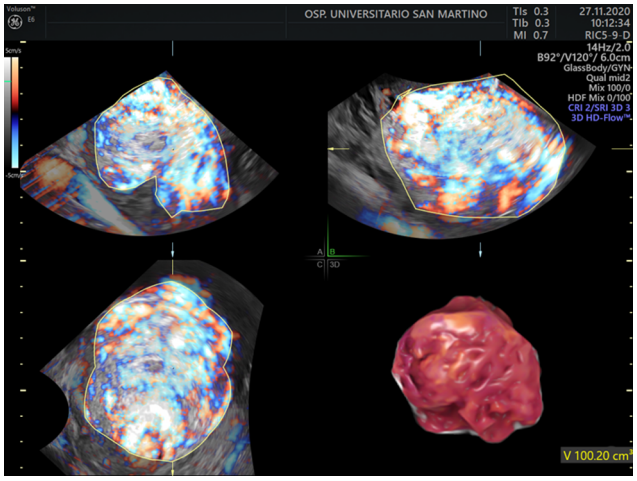


Figure 3 3D power Doppler image of the arteriovenous vessels inside the tumour. The mass appears almost completely consisting of vessels.

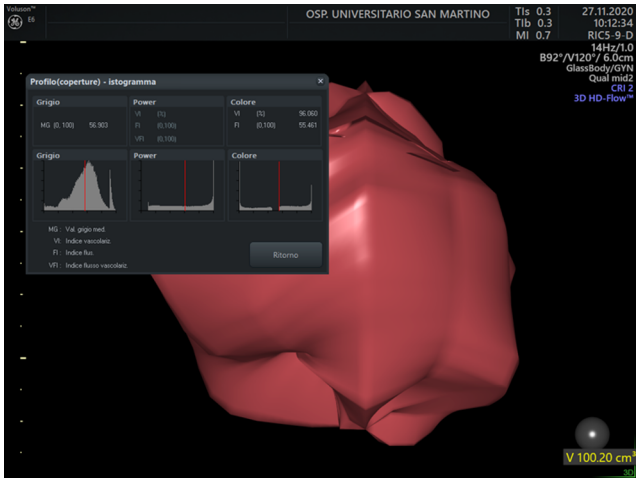


Figure 4 Virtual organ computer-aided analysis of the uterine mass. Volume=100.20 cm^3; Vascularisation Index=96.1%.

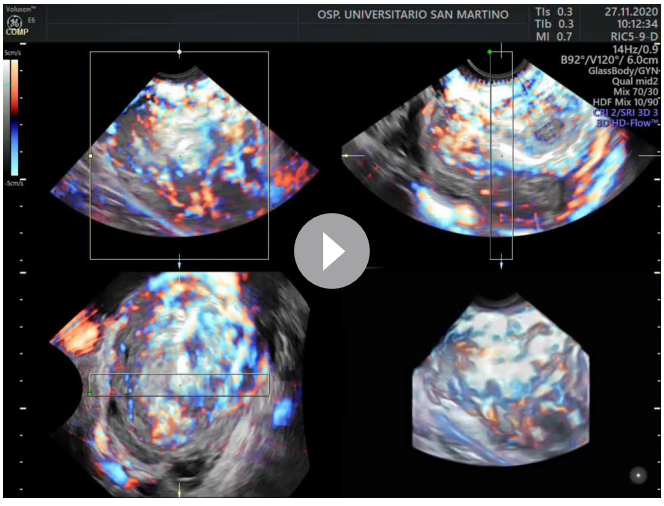
pressure of 100/70 mm Hg, HR of 115 bpm, 100% $satO_2$. At urgent blood count test, Hb value was 7 g/dL and HCT 21%. Transabdominal US showed abundant haemoperitoneum. Two concentrates blood cell units were urgently transfused. The patient was immediately transferred to the radiological unit where angiography and selective uterine artery embolisation (UAE) was performed until complete devascularisation of the mass was obtained (figure 5A,B).

The following day, a transvaginal and abdominal US confirmed abundant hypoechoic free fluid with free clots in the abdomen and the presence of the uterine mass with scarce vascularisation at PD (colour score 2). As the consequence of UAE, hyperechoic spots were present within the mass (figure 6).

Vital signs were adequate, and lab test showed anemisation but stable levels after the transfusion and UAE: Hb 8.3 g/dL and HCT 24%. The tenth day after embolisation, transvaginal US revealed an increase of uterine mass volume (93×57×79 mm) with resumption of blood flow (colour score 4).

Due to revascularisation and the real risk of another haemoperitoneum, a multidisciplinary team composed of anaesthetist, pneumologist, general surgeon, gynaecologist and pathologist convinced the woman to give her consent to the surgical removal of the uterus and the adjacent mass. The procedure was performed in epidural anaesthesia, to avoid rupture of pulmonary cysts induced by forced ventilation and pneumothorax. Total hysterectomy with bilateral salpingectomy was performed through a midline umbilicus–pubic laparotomy. On the right side, this required ureter isolation and parametrium excision. The surgical specimen was sent unfixed to the pathology department. Macroscopic examination revealed a uterus of 9×5×5 cm with the right parametrium occupied by a haemorrhagic mass of 8.5×4×3 cm involving the periuterine soft tissues and extensively infiltrating the myometrium (figure 7A,B).

The histopathological examination documented solid neoplasm consisting of large patches and cords of medium-sized epithelioid elements, with mild to moderate nuclear atypia. Mitotic count was <1/50 high power fields (HPF) (figure 7C). The neoplasm showed widespread areas of bleeding and extensive areas of necrosis (20% of the overall lesion evaluated) of uncertain interpretation given the previous embolisation procedure. In peripheral portions of the neoplasm, scattered thick-walled vascular structures were evident. The neoplasm revealed an infiltrative growth front towards the myometrium. Results of immunohistochemistry were as follows: estrogen receptore (ER): positive (60%; +), progesterone receptor (PGR): positive (40%; ++), CD10: positive (30%), HMB-45: positive (30%), smooth muscle actin (SMA): positive (40%), HHF35: positive (30%), h-caldesmon: positive (50%), β-catenin: positive (cytoplasmatic and membrane pattern), p53: negative (<1%), P16: spotty positive (nuclear and cytoplasmic pattern; 20%) and ki-67 (<5%).



Video 3 3D power Doppler video of the arteriovenous vessels inside the tumour.

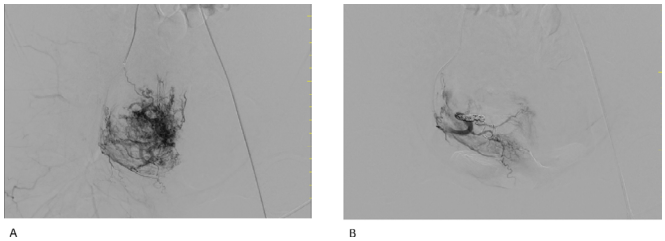


Figure 5 Angiography imaging showing the effect of the superselective uterine artery embolisation with microparticles on the tumour's vessels, (A) before and (B) after the procedure.

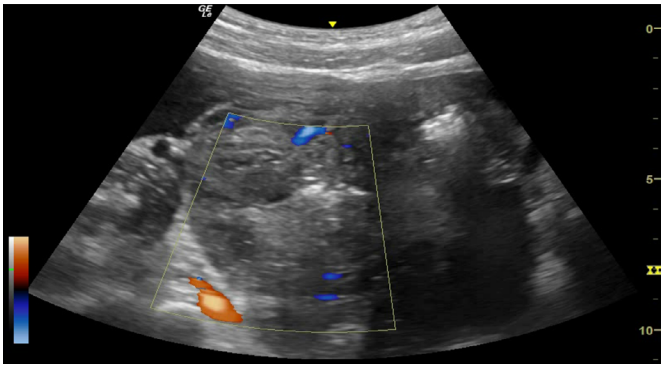


Figure 6 Transvaginal ultrasound performed the day after uterine artery embolisation showing the reduced vascularity of the mass (colour score 2) and hyperechoic spots.

Both morphology and immunophenotype appeared consistent with a PEComa with an uncertain malignant potential.

OUTCOME AND FOLLOW-UP

The postoperative course was uneventful with stable Hb levels of 11 g/dL. On the seventh day after surgery, the patient was discharged. After discharge, the patient started a gynaecological, pneumological and oncological follow-up every 4 months consisting in visit, US and annual thoracoabdominal CT. At the first follow-up visit, the patient was in good clinical conditions, with no sign of recurrence.

DISCUSSION

Herein, we report a case of uterine PEComa associated with sporadic pulmonary LAM in a 39- year-old woman. PEComas may affect the female genitourinary tract.[10] Varied clinical presentations of these tumours are reported, but they are typically discovered as incidental findings in the setting of chronic abdominal pain or vaginal bleeding.[10 11] In our case, it presented as an emergency case with acute abdominal pain and haemoperitoneum. Diagnosis of PEComas is often complicated because there is no clear description of their sonographic characteristics. PEComas were described either similar to fibroids,[12] ie, with

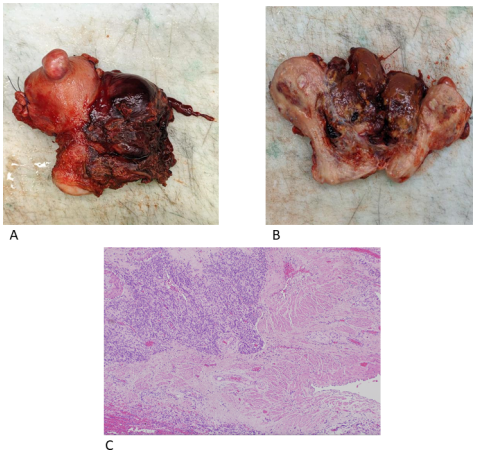


Figure 7 (A, B) Surgical specimen showing a haemorrhagic mass occupying the parametrium and infiltrating the right myometrium. (C) At microscopy (100×) after coloration with H&E, the neoplastic mass appears constituted by solid sheets of medium-sized epithelioid cells with scattered areas of necrosis haemorrhage infiltrating the uterine muscular wall.

well-defined margins, a heterogeneous echotexture, with no cystic areas and a significant vascularity at colour Doppler US, or similar to leiomyosarcoma with hyperechogenic aspect, no clear separation from the adjacent uterus and an extremely rich central vascular network.[13] In this specific case, the mass showed no clear separation from adjacent uterus, but the use of VOCAL analysis showed that the lesion was exclusively formed by vessels (VI=96%). This is different from leiomyosarcoma that is formed for more than 80% from solid tissue with an inhomogeneous echogenicity and with moderately to very well-vascularised irregular cystic areas.[14] The US features, particularly VOCAL analysis, in combination with the presence of pulmonary LAM, prompted us to consider PEComa as the first diagnostic hypothesis. To date, no optimal and unanimously accepted management strategy for gynaecological PEComas has been established, but complete surgical resection with a tumour-free margin is the standard of treatment.[6] The initial proposal of hysterectomy was refused. In the meantime, an acute exacerbation of the clinical situation with repeated haemoperitoneum forced us to proceed with emergent UAE. Treatment was momentarily satisfactory,but after 10 days, US investigation revealed mass revascularisation. Risk of a further life-threatening haemoperitoneum was very high. It was clearly documented that the mass was infiltrating the uterus and uterus sparing was not possible. After a multidisciplinary discussion, patient consent to uterus and mass removal was obtained. At histology, differential diagnosis was made with other uterine mesenchymal neoplasms such as epithelioid leiomyosarcoma or stromal sarcoma. Biological aggression markers such as p16 and p53, commonly expressed in leiomyosarcoma, were expressed at low levels, while coexpression of muscle and melanocytic markers such as h-caldesmon, SMA, HHF-35 and HMB-45 were consistent with a diagnosis of PEComa.[15] The neoplasm was voluminous and with infiltrative features, but atypia was mild and the mitosis counts low. Because of previous embolisation, the presence of neoplastic versus ischaemic necrosis was difficult to determine. Based on the clinical and histological characteristics, the uterine PEComa was established as uncertain potential of malignancy. Assay of serum vascular endothelial growth factor-D (VEGF-D) was not available, but compatible clinical history with LAM including young to middle-aged woman and specific characteristic of chest high resolution computerized tomography (HRCT) (multiple, bilateral, uniform, round, thin-walled cysts present in a diffuse distribution, often with normal-appearing intervening lung parenchyma) in conjunction with histopathological confirmation of pelvic mass is considered sufficient, also in some asymptomatic case to make the diagnosis of LAM.[7] In our patient, the absence of a positive personal and familial history and the absence of additional major clinical features such as hypomelanotic macule angiofibromas or fibrous cephalic plaque, ungual fibromas, shagreen patch and minor clinical features such as confetti skin lesions, dental enamel pits, and intraoral fibromas did not meet the criteria for LAM associated with TSC, and the case was classified as sporadic LAM.[8]

It has been reported that the uterus is the primary site of PEComas. PEComas and pulmonary LAM both express hormonal receptors and have a higher prevalence in women, and pulmonary LAM can recur after lungs transplantation.[16] Due to the presence of oestrogen and progesterone receptors, both LAM and PEComas can progress in pregnancy leading to complications such as pneumothorax, chylothorax, loss of lung function and uterine rupture.[17 18] Patients with severe LAM should be counselled to avoid pregnancy.[19] Sometimes, as in our case, patients with LAM are incidentally being diagnosed before

the development of respiratory symptoms.[7] In case of malignancy, metastatic diseases develop in 72% of cases over a median follow-up period of 11.5 months,[20] even before occurrence of respiratory symptoms. Accordingly, accurate follow-up of these cases is mandatory.

Learning points

- Uterine perivascular epithelioid cell tumours (PEComas) are composed of vessels that can extensively bleed and possibly induce an acute haemoperitoneum with rapid anemisation.
- The sonographic features of PEComas are not well defined, and differential diagnosis should be performed with uterine leiomyoma or leiomyosarcoma.
- This case suggested the difficulty of preoperative diagnosis of PEComa and treatment selection for a fertile woman.
- Artery embolisation may be useful to treat acute bleeding, but surgical removal of the lesion is necessary.
- Histological analysis is necessary to distinguish benign and malignant tumours and set the correct treatment and follow-up.

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REFERENCES

1 Hayashi T, Kumasaka T, Mitani K, *et al*. Prevalence of uterine and adnexal involvement in pulmonary lymphangioleiomyomatosis: a clinicopathologic study of 10 patients. *Am J Surg Pathol* 2011;35:1776–85.
2 Fletcher CDM, Unni KK, Mertens F. World Health organization classification of tumours pathology and genetics of tumours of soft tissue and bone 2002:221–2.
3 Folpe AL, Mentzel T, Lehr H-A, *et al*. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin. *Am J Surg Pathol* 2005;29:1558–75.
4 Matsui K, Tatsuguchi A, Valencia J, *et al*. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. *Hum Pathol* 2000;31:1242–8.
5 Leathersich S, Koay MHE, Khani A, *et al*. Isolated sporadic uterine lymphangioleiomyoma with unusual clinical and pathological features. *BMJ Case Rep* 2019;12:231683.
6 Liu C-H, Chao W-T, Lin S-C, *et al*. Malignant perivascular epithelioid cell tumor in the female genital tract: preferred reporting items for systematic reviews and meta-analyses. *Medicine* 2019;98:e14072.
7 Gupta N, Finlay GA, Kotloff RM, *et al*. Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. An official American thoracic Society/ Japanese respiratory Society clinical practice guideline. *Am J Respir Crit Care Med* 2017;196:1337–48.
8 Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational tuberous sclerosis complex consensus conference. *Pediatr Neurol* 2013;49:243–54.
9 Nieuwenhuis LL, Keizer AL, Stoelinga B, *et al*. Fibroid vascularisation assessed with three-dimensional power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective cohort study. *BJOG* 2018;125:577–84.
10 Musella A, De Felice F, Kyriacou AK, *et al*. Perivascular epithelioid cell neoplasm (PEComa) of the uterus: a systematic review. *Int J Surg* 2015;19:1–5.
11 Shan W, Shi Y, Zhu Q, *et al*. Five cases of uterine perivascular epithelioid cell tumors (PEComas) and review of literature. *Arch Gynecol Obstet* 2019;299:185–90.
12 Fontana E, Savelli L, Alletto A, *et al*. Uterine PEComa initially misdiagnosed as a leiomyoma: sonographic findings and review of the literature. *J Clin Ultrasound* 2021;49:492–7.
13 Socolov D, Scripcaru D, Ferariu D, *et al*. An unusual enhanced Doppler vascular profile of a rare uterine tumor: PEComa. *Eur J Gynaecol Oncol* 2016;37:741–3.
14 Ludovisi M, Moro F, Pasciuto T, *et al*. Imaging in gynecological disease (15): clinical and ultrasound characteristics of uterine sarcoma. *Ultrasound Obstet Gynecol* 2019;54:676–87.
15 Gadducci A, Zannoni GF. Perivascular epithelioid cell tumors (PEComa) of the female genital tract: a challenging question for Gynaecologic oncologist and pathologist. *Gynecol Oncol Rep* 2020;33:100603.
16 Prizant H, Sen A, Light A, *et al*. Uterine-specific loss of TSC2 leads to myometrial tumors in both the uterus and lungs. *Mol Endocrinol* 2013;27:1403–14.
17 Sullivan EJ. Lymphangioleiomyomatosis: a review. *Chest* 1998;114:1689–703.
18 Babayev E, Fay KE, Horowitz JM, E B, Kathryn E, *et al*. Perivascular epithelioid cell tumors (PEComa) in pregnancy with uterine rupture and ongoing abdominal gestation: a case report. *Case Rep Womens Health* 2020;25:e001:e00172.
19 Taveira-DaSilva AM, Moss J. Management of lymphangioleiomyomatosis. *F1000Prime Rep* 2014;6:116.
20 Tirumani SH, Shinagare AB, Hargreaves J, *et al*. Imaging features of primary and metastatic malignant perivascular epithelioid cell tumors. *AJR Am J Roentgenol* 2014;202:252–8.