Case report

Isolated sporadic uterine lymphangioleiomyoma with unusual clinical and pathological features

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Accepted 26 September 2019

SUMMARY

We report a unique uterine neoplasm, favoured to represent an isolated extrapulmonary lymphangioleiomyoma with unusual pathological features, in a postmenopausal woman without tuberous sclerosis complex. The large neoplasm consisted of smooth muscle fascicles and cystic spaces lined by lymphatic cells, which were negative for the melanocytic staining that is characteristically positive in lymphangioleiomyomatosis (LAM). There are fewer than 30 cases of uterine LAM reported, none of which have demonstrated this morphology or these immunohistochemical findings. The origin of LAM cells in the more typical pulmonary LAM remains unclear; the unusual features in this case may represent a distinct pathological entity or a rare variant of typical extrapulmonary LAM, and may contribute to determining the cellular origin of these rare tumours. Conversely, this may represent a case of 'prepulmonary' LAM, providing supporting evidence for a possible gynaecological origin of these tumours in the broader affected (almost exclusively female) population.

BACKGROUND

Lymphangioleiomyomatosis (LAM) is a rare multi-system disorder that usually affects women of reproductive age, being estimated to affect approximately 1 in 1 million people in the USA and Europe.¹ Although the aetiology is not well understood, the strongest association is with tuberous sclerosis complex (TSC-LAM); up to 40% of women with TSC will develop LAM, however men with TSC do not develop LAM.² Cases not associated with TSC are referred to as sporadic LAM. Both TSC-LAM and sporadic LAM are almost universally associated with cystic pulmonary lesions, which can result in progressive respiratory failure and death. LAM is now recognised as being part of the perivascular epithelioid cell neoplasm (PEComa) family, which also includes angiomyolipomata and clear cell 'sugar' tumours of the lung as well as a variety of unusual visceral, intra-abdominal and soft tissue/bone tumours.^{3,4} There is a strong association between angioleiomyomata and LAM and the TSC, although this link is less strong for other members of the PEComa family.³

TSC-LAM and sporadic LAM are both thought to result from mutations that inactivate the TSC-1 and TSC-2 tumour suppressor genes, which together control mTOR (the mammalian target of

rapamycin, a cell cycle regulator);⁵ however, the underlying pathogenesis and the origin of the cells which form these tumours remain elusive.⁶

Extrapulmonary LAM is a rare finding. Patients most commonly present with lymphatic tumours or angiomyolipomata, usually renal, although LAM lesions have been reported in the retroperitoneum, mesentery, liver and biliary tract, adrenal gland, ureters, ovaries and lymph nodes.

Here we describe an atypical case of an isolated uterine lymphangioleiomyoma in a postmenopausal woman in the absence of pulmonary disease with unusual pathology; the first such case of which we are aware.

CASE PRESENTATION

A 67-year-old postmenopausal woman presented with an incidental finding of an uterine mass detected during CT imaging for hip arthropathy. She had previously been aware of an abdominal mass but had never undergone investigation and had no vaginal bleeding, abdominopelvic pain, urinary symptoms or bowel symptoms.

During her reproductive years she had regular menses with no abnormal bleeding. She was gravida 3 para 3, having had one vaginal birth and two caesarean sections. She went through menopause aged 49 and never had any postmenopausal bleeding. She had never taken menopausal hormone therapy. Cervical screening was negative, as were regular screening mammograms. Her medical history was unremarkable; in particular, she had no history of respiratory disease. Her family history included only breast cancer in her mother at the age of 96.

A large, smooth, mobile, non-tender pelvic mass was felt on abdominal and pelvic examination. The uterine fundus was felt 6 cm cephalad to the umbilicus. Abdominal examination was otherwise unremarkable, as was speculum examination. Cardiorespiratory and general examinations were normal.

INVESTIGATIONS

Ultrasound revealed a mixed cystic and solid structure measuring 195×100×180 mm, favoured to represent a uterine tumour. The ovaries were not visualised and no lymphadenopathy was seen.

MRI (figure 1) detailed a multicystic mass within the uterus measuring 170×100×150 mm with a solid central component. Fat planes were preserved

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To cite: Leathersich S, Koay MHE, Khani A, et al. *BMJ Case Rep* 2019;**12**:e231683. doi:10.1136/bcr-2019-231683

Figure 1 T2 MRI, sagittal and axial planes, showing a multicystic uterine mass with a central solid component.

and both ovaries appeared normal. There was no free fluid, lymphadenopathy or renal abnormalities. The radiological impression was of myxoid cystic degeneration of a leiomyoma; however, sarcoma could not be excluded.

Full blood picture, inflammatory markers, renal function and liver function were all normal. Tumour markers were normal except for a slightly elevated Human Epididymis Protein 4 (HE4) of 74 pm (normal range (NR) <70), giving a Risk of Ovarian Malignancy Algorithm (ROMA) score of 20.4% (NR <25.3%). Cancer antigen (CA) 125 was 21 kU/L (NR <35), alpha-fetoprotein (AFP): 1 kU/L (NR <11), CA 19-9: 12 kU/L (NR <37) and carcinoembryonic antigen (CEA): 2 µg/L (NR <5).

DIFFERENTIAL DIAGNOSIS

Given the clinical and imaging findings, our primary diagnosis was myxoid degeneration of a leiomyoma. As the patient was uncertain of the duration of the mass, we could not exclude a more sinister and rapidly developing cause such as leiomyosarcoma. An inherited tumour disorder was considered unlikely given the lack of other lesions on imaging along with presentation in the seventh decade with no previous health problems and an unremarkable family history. Imaging clearly delineated the endometrial cavity, making endometrial pathology less likely, and the absence of other abdominopelvic lesions made a metastatic process unlikely. Clinical and MRI features were not consistent with adenomyosis or an infectious cause such as tuberculosis.

TREATMENT

Surgical management was recommended to prevent mass effects and confirm the diagnosis. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus was grossly enlarged by a smooth, steel-grey, cystic mass with a degenerating appearance, suspicious for leiomyosarcoma or myxoid degeneration. The procedure was uncomplicated with en bloc removal of the specimen; no other intra-abdominal lesions were identified, washings were taken for cytology and an omental biopsy was taken. Anaesthetic management and post-operative recovery were unremarkable, and she was discharged home on the second postoperative day.

OUTCOME AND FOLLOW-UP

Pathology

Histopathology revealed a solitary neoplasm, 175 × 129 mm with numerous prominent dilated cystic spaces, which was completely circumscribed by normal myometrium (*figure 2*). The neoplasm was composed of intersecting fascicles of smooth muscle fibres

Figure 2 Gross examination revealed a single, well-circumscribed, multicystic neoplasm.

separated by cystic spaces (*figure 3*). The smooth muscle cells were cytologically bland, spindle-shaped and demonstrated positive desmin, actin, estrogen receptor (ER) and progesterone receptor (PR) staining. They did not show a 'spinning off' pattern from blood vessels. The cystic spaces were lined by a single layer of flattened cells that showed positive staining with ERG (erythroblast transformation-specific (ETS)-related gene), CD31 and D2-40, confirming lymphatic origin (*figure 4*). The cells were negative for calretinin, MiTF (microphthalmia-associated transcription factor), Melan A and HMB-45 (Human Melanoma Black 45) (*figure 5*). Although larger than 5 cm, there was no high grade atypia, necrosis or lymphovascular space invasion and the mitotic count was less than 1/50 high power fields. The remainder of the specimen was unremarkable with no further lesions.

This appearance was unique. A leiomyoma with prominent dilated lymphatic spaces was considered, especially given the negative melanocytic markers, but as both the smooth muscle fascicles and lymphatic spaces appeared to be integral to the tumour (and literature search for uterine leiomyoma with prominent dilated lymphatic spaces did not yield any reports), it was thought best reported as a lymphangioliomyoma. A comment was made that this did not resemble classic lymphangioliomyoma (on morphology or on immunohistochemistry) but that other/extruterine LAM and tuberous sclerosis should be still be excluded. Peritoneal cytology and omental histopathology were normal.

Clinical outcome

Postoperative chest X-ray was normal. Biphase abdominopelvic CT imaging revealed no abnormality other than a 16 mm

Figure 3 H&E staining: low power demonstrates multiple cystic spaces within smooth muscle. High power shows well-developed fascicles of smooth muscle between the cystic spaces.

Figure 4 D2-40 staining (brown) revealed a single layer of flattened lymphatic cells lining the cystic spaces.

hypodense lesion in the liver, consistent with a haemangioma. Eighteen months postoperatively the patient remains clinically well.

DISCUSSION

To our knowledge, fewer than 30 cases of uterine LAM (and roughly 100 cases of uterine PEComa⁷) have been reported in the global literature, and the variable presentation and extensive symptomatic and radiological crossover with far more common pathologies such as leiomyomata or leiomyosarcoma make preoperative diagnosis challenging. Most PEComa of the gynaecological tract are sporadic and not associated with TSC;⁴ however, cases of uterine LAM/PEComa which are associated with pulmonary LAM support the hypothesis presented by Prizant *et al* that LAM lesions may in fact originate in the uterus and gynaecological tract.⁸ This would help to explain why LAM

tumours can recur in lung transplants despite the supposedly abnormal tissue being entirely removed, why they share histological features with benign leiomyomata and finally why those affected are almost exclusively female. This would also explain the very high prevalence of microscopic uterine LAM lesions on histopathological examination of uteri from women with pulmonary LAM but without clinically evident uterine tumours.⁹

It is noteworthy that our patient's tumour was very unusual in terms of pathology. Macroscopically, the presence of one large solitary lesion contrasts with the more common pattern of multiple small (and sometimes microscopic) foci on the uterus (and sometimes adnexae). Microscopically, thin delicate cleft-like spaces, a prominent intrinsic vasculature, epithelioid cells, cells showing cytoplasmic clearing, perivascular distribution of lesional cells, small whorls and trabeculae were not seen. Rather, the smooth muscle cells showed spindle morphology, being arranged in well-developed fascicles.

Hayashi *et al* studied 10 cases of uterine LAM, some of which were TSC-associated and the others sporadic.⁹ In comparison to sporadic LAM, the uterine LAM associated with TSC demonstrated less clear macroscopic margins, a tongue-like growth pattern, less frequent slit-like lymphatic spaces and more prominent HMB-45 positive cells. The morphological features seen more commonly in the TSC-associated cases were not present in our case, in keeping with the lack of other extrauterine lesions and TSC.

Uterine PEComa can, in a minority of cases, show weak, patchy or even negative HMB-45 staining.⁷ In our case, the HMB-45 was negative. The tumour was also negative for the melanocytic markers Melan A and MiTF. Our case differs from other reported HMB-45 negative cases. Rabban *et al* reported a series of 26 cases in which LAM was incidentally detected in pelvic/para-aortic lymph nodes of women undergoing staging for gynaecological or bladder malignancies.¹⁰ One case was HMB-45 negative. This case showed classical LAM morphology and the tumour cells were also positive for MiTF. It is not clear whether this particular case was associated with TSC or pulmonary LAM, but of the 26 cases only two had TSC and none had pulmonary LAM.

Figure 5 Although scattered non-tumoural cells show weak staining for HMB-45, this was considered non-specific and the tumour cells were HMB-45 negative.

Learning points

- ▶ New or growing uterine masses in postmenopausal women should raise suspicions for a neoplastic process.
- ▶ Although most commonly associated with pulmonary manifestations in premenopausal women, uterine lymphangioleiomyomata should be considered as a rare cause of uterine masses.
- ▶ Women with lymphangioleiomyomata should be investigated with thoracic and abdominopelvic imaging, with particular attention to excluding pulmonary cystic lesions and renal angiomyolipomas.
- ▶ Lymphangioleiomyomata usually occur in the context of tuberous sclerosis or sporadic lymphangioleiomyomatosis (LAM); however, as this case demonstrates they may occur as isolated lesions and should be considered as a rare mimic of leiomyosarcoma, even among women without tuberous sclerosis complex.
- ▶ This unique tumour has not previously been described and raises into question the possible heterogeneity of disease processes leading to LAM, as well as the cellular origin of these tumours.

Bennet *et al* reported a series of 32 uterine PEComa. One showed a spindled smooth muscle-like component juxtaposed with an epithelioid component. The spindled component was HMB-45, Melan A and MiTF negative. There is one further report of HMB-45 negative LAM in a female patient, who was diagnosed with localised retroperitoneal disease not involving the uterus.¹¹ There was no pulmonary involvement reported in that case. The immunohistochemistry of our case differs from that of Jaiswal *et al* with regard to estrogen and progesterone receptors, staining for which was positive in our case; the expression of these is variable in other reported cases of LAM, though often seen in spindle cells as demonstrated in our case.

In conclusion, we present an atypical case of isolated extrapulmonary LAM affecting the uterus in a postmenopausal woman, with unusual pathological findings. The origin of LAM cells in pulmonary and extrapulmonary LAM remains unknown; however, the gold standard for immunohistochemical diagnosis of pulmonary LAM is considered the HMB-45 positivity.⁶ Therefore, this constellation of unusual features may represent a distinct pathological entity or a rare variant of typical extrapulmonary LAM, and may contribute to determining the cellular origin of these rare tumours. Conversely, this may represent a case of 'prepulmonary' LAM, providing supporting evidence for a possible gynaecological origin of these tumours in the broader affected population.

Contributors SL conceived and drafted the original version under the supervision of SMB. MHEK and AK reported the pathological findings and contributed to the final manuscript. The final version was reviewed and edited by all the authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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