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Case Report

Uterine Angiolipoleiomyoma. A Case Report and Systematic Literature Review

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Abstract

Uterine angiolipoleiomyomas are rare, benign mixed mesenchymal lesions. A manifestation in the gynecological region is quite uncommon, with few cases described in the literature so far. We present an interesting case of a 59-year-old woman diagnosed with uterine angiolipoleiomyoma, and the results of the conducted systematic review of the literature. The patient presented with a pelvic mass masquerading as a leiomyoma on the ultrasound and postmenopausal vaginal bleeding. At laparotomy, a large uterus was noticed and the histopathology set the diagnosis of angiolipoleiomyoma. Immunohistochemistry revealed negativity for Melan-A and HMB-45 melanoma-specific antibodies and positivity for Van Gieson and orcein histochemical stains.

We systematically reviewed the literature. The eligible articles were those written in English, excluding animal studies and studies reporting angiolipoleiomyomas in other regions beside the uterus. The present case is one of the 10 cases of uterine angiolipoleiomyoma reported in the literature. In 8 out of 11 (72.7%) cases, uterine angiolipoleiomyomas arose from the corpus of the uterus, while in 2 (18.1%) cases they were located at the cervix, and in one case (9%) angiolipoleiomyoma was located in the broad ligament. Concerning symptoms, four of the patients (36.4%) presented with abdominal and pelvic pain, two (18.1%) with postmenopausal vaginal bleeding, one with menometrorrhagia (9%), and one with uterine prolapse and cystocele (9%). Immunohistochemical staining of uterine angiolipoleiomyomas was positive for SMA in 4 patients (36.4%), positive for desmin in 3 cases (27.3%), positive for anti-S-100 protein antibody in 2 patients (18.1%), while in one case (9%) immunopositivity was observed for CD31. Only our case (9%) was also tested for CD34, Van Gieson and orcein, the first of these being negative and the other two positive (at the blood vessels in a specialized pattern). Three of the patients (27.3%) were also tested for HMB-45 and all three were immunonegative.

In order to establish the diagnosis of uterine angiolipoleiomyomas, ultrasonography and additional MRI may help the preoperative prediction of a benign mass. Immunohistochemistry will show strong positivity of alpha-smooth muscle actin and desmin. Complete abdominal hysterectomy is the preferable treatment.

Keywords

angiolipoleiomyoma, benign uterine tumours

INTRODUCTION

Angiolipoleiomyomas (ALLMs) are benign mesenchymal tumours, and their main histological characteristics include an admixture of blood vessels, smooth muscle tissue, and mature adipose tissue. Although few cases of ALLM in the female reproductive system have been described, the earliest one dates back to 1816 when Lobstein described the

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first case of a uterine fatty tumour. Distinction from other benign mixed mesenchymal uterine tumours containing fat tissue (ULT) relies on the evaluation of its characteristic immunohistochemical and histochemical features which distinguish it from angiomyolipomas (ALM), closely related tumours presumably originating from perivascular epithelial cells and are now categorized into the group of PEComas.[1]

We present a case of uterine angiolipoleiomyoma and a systematic review of the published literature and conclude that, although rare, angiolipoleiomyoma should be considered in the differential diagnosis of a pelvic mass.

CASE REPORT

A 59-year-old woman presented at our Gynecologic Department complaining about postmenopausal vaginal bleeding and pelvic discomfort for the last two months. Her medical history was unremarkable besides diabetes mellitus and hypertension. Her blood tests were normal besides a slight anemia and her physical examination revealed a solid lower abdomen tumour and a dilated exocervical from which a polypoid mass was projecting. Magnetic resonance imaging revealed the tumour as a lesion of inhomogeneous composition and inhomogeneous contrast enhancement, completely occupying the endometrial cavity ***(Fig. 1)****. Tumour markers, such as CA125, CEA, CA199 AFP, and HE4 were negative. She was admitted to our clinic in order to investigate the etiology of her symptoms, where she underwent a complication-free hysterectomy with bilateral salpingo-oophorectomy. At laparotomy, an enlarged uterus was recognized. The rest of the abdomen was examined for further lesions without any abnormal findings.*

Histopathological assay described a submucosal white tumour measuring 5.5 cm, from the lower part of which grew a flat, gray, 2.5 cm in diameter polypoidal structure. The tumour presented with abundant smooth muscle tissue and blood vessels with a thick wall and the absence of abnormal elastic tissue. The brisk presence of adipose tissue in the tumour raised suspicions for a diagnosis of angiolipoleiomyoma, so a further histochemical and immunohistochemical examination was performed. HMB-45 and Melan-A immunonegativity was observed, as well as Van Gieson and orcein stains positivity, visualizing the abnormal collagen and elastic fibers of the blood vessel wall ***(Fig. 2)****. The polypoid structure was diagnosed to be an endometrial polyp. The diagnosis of angiolipoleiomyoma was set and the patient received no further treatment.*

METHODS

We systematically reviewed the literature searching for the term 'uterine angiolipoleiomyoma' in PubMed, Scopus, and Google Scholar up to March 28, 2020. We also performed a snowball search in the references of studies that were relevant to our search.

Eligible articles for our review were articles written in English. Studies that were referred to animals were excluded. Moreover, studies reporting angiolipoleiomyomas in other regions beside the uterus were also excluded as well as abstracts from scientific papers, conferences, and editorials **(Fig. 3)**.

RESULTS

Nine articles are included to our review.[2-10] Adding the present case to the 11 cases of uterine ALLM reported in the literature **(Table 1)**, we found that the patients' median age was 51.5 years (range 26-67). In 9 out of 12 (75 %) cases, the uterine ALLMs arose from the corpus of the uterus, while in 2 (16.7%) cases they were located at the cervix and in one case (8.3%) ALLM was located in the broad ligament. The median size of the lesions was 7.5 cm (range 2-16) and in 4 of the cases (33.3%), the lesion was focal. Four of the patients (33.3%) presented with abdominal and pelvic pain, two (16.7%) with postmenopausal vaginal bleeding, one with menometrorrhagia (8.3%), and one with uterine prolapse and cystocele (8.3%). The histopathological diagnosis was angiolipoleiomyoma in 11 women (91.7%), while in one of them (8.3%), angiolipoleiomyoma was perplexed with leiomyoma with bizarre nuclei. So far, no aggressive pattern of behaviour or distant metastasis has been reported concerning ALLMs.

Immunohistochemical staining of uterine ALLMs was positive for SMA in 5 patients (41.7%), positive for desmin in 3 cases (25%), positive for anti-S-100 protein antibody in

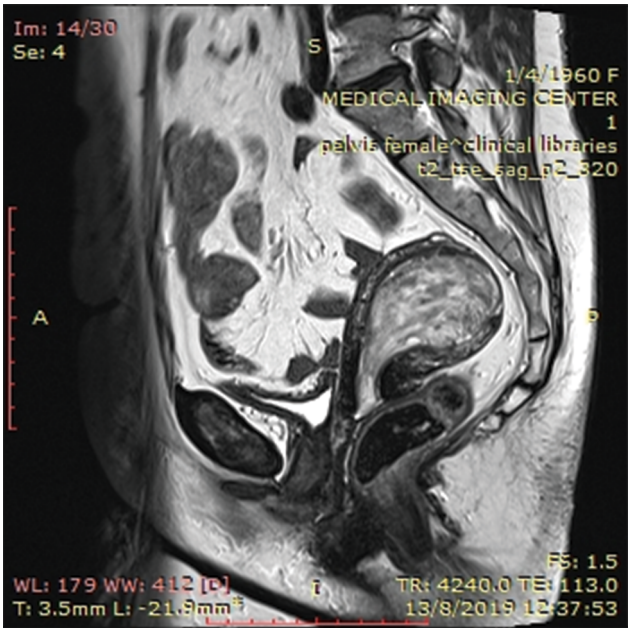

Figure 1. Magnetic resonance imaging revealed the tumour as a lesion of inhomogeneous composition and inhomogeneous contrast enhancement, completely occupying the endometrial cavity

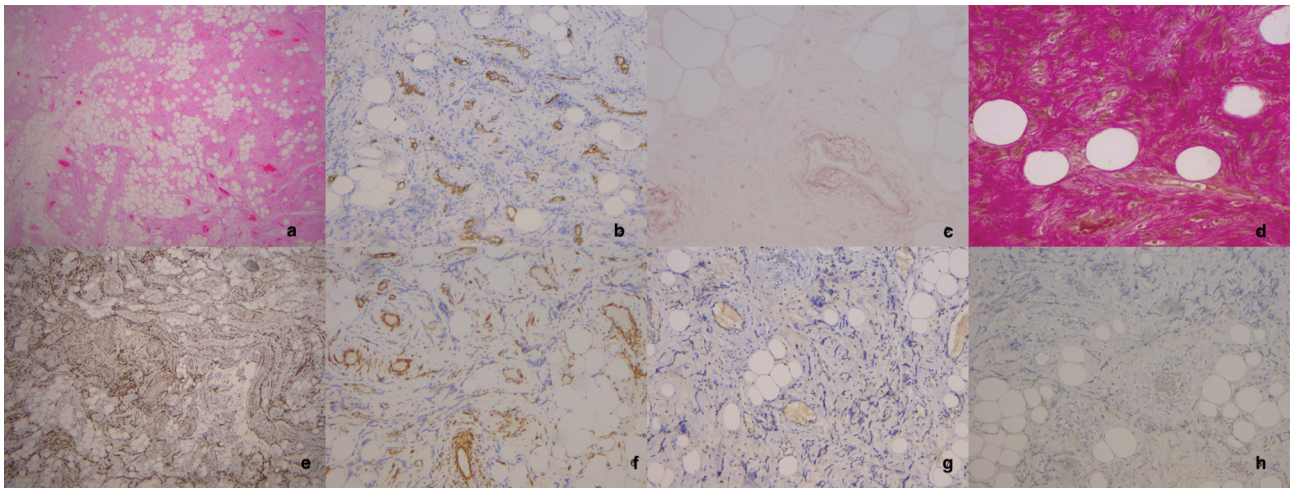

Figure 2. ALLM, although histologically similar to the renal angiomyolipoma, is not associated with tubular sclerosis and does not express melanocytic markers immunohistochemically (HMB-45 and Melan-A). The histological diagnosis is mostly morphological, while the differential diagnosis is based on immunohistochemistry: **a)** Microscopically we see an indeterminate mixture of smooth muscle tissue, mature adipose tissue and abundant, large, thick-walled, irregular vessels. **b)** CD34 paints all the vessels but is negative in smooth muscle tissue. It also differentiates from other spindle-shaped neoplasms in which it is positive. **c, d)** Orcein and Van Gieson stains are histochemical. The Van Gieson stain dyes collagen intensely reddish (also other elements of connective tissue and muscle, but fainter). Both dyes are used in our case to demonstrate the abnormal configuration of collagen within the vessel wall which is characteristic of ALLM. **e, f)** Smooth muscle tissue markers, desmin **(e)** more specific than SMA **(f)**, indicate the neoplastic muscle element. **g,h)** Melanocyte markers (positive in angiomyolipoma-negative here). Their negativity is compatible with the diagnosis of ALLM.

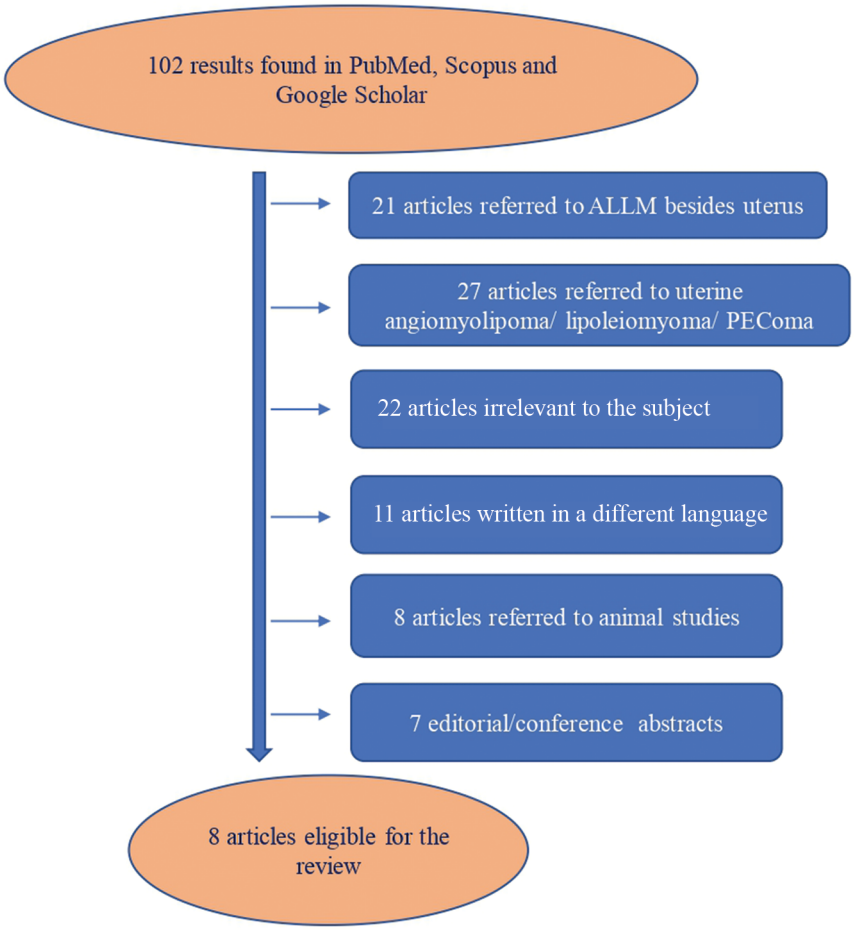

Figure 3. Diagram of excluded and included articles.

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Table 1. Patients' characteristics

Author	Year	Age	Location	Maximal diameter cm	Multiple	Symptom	Metastasis	Immunohistochemisty and histochemistry	Other pathology
Lo RV et al.[2]	1987	47	Corpus	5	NS	Menometrorrhagia	NS	NS	NS
Sienski M[3]	1989	52	Corpus	6	NS	NS	NS	NS	Endometrial hyperplasia
		52	Cervix	16	NS	NS	NS	NS	None
		57	Cervix	9	NS	NS	NS	NS	None
Shintaku M[4]	1996	67	Corpus	7	NS	Uterine prolapse, Cystocele	NS	Smooth muscle actin (+) desmin (+) anti-S-100 protein antibody (+)	None
Braun Hl et al[5]	2002	51	Corpus	2	No	Postmenopausal vaginal bleeding	No	NS	None
Ren RL et al.[6]	2003	40	Corpus	5	No	Low back and pelvic pain	No	Smooth muscle actin (+) desmin (+) HMB-45 (-)	Focal atypical leiomyoma
Bacanakgil BH et al.[7]	2015	44	Corpus	7,5	No	Lower abdominal pain	No	SMA, CD31 and S100 (+) HMB-45 and melan-a (-)	None
Shakarwal S et al.[8]	2017	28	Broad ligament	8	No	Lower abdominal pain and spotting	No	NS	None
Cendek BD et al.[9]	2018	59	Corpus	6		Lower abdominal pain	No	NS	None
Paryani NS et al.[10]	2020	26	Corpus	12	No	NS	No	Smooth muscle actin (+)	None
Present case	2021	59	Corpus	5,5	No	Postmenopausal vaginal bleeding	No	Smooth muscle actin (+) desmin (+) HMB-45 (-) CD34 (-) Van Gieson (+) orcein (+)	endometrial polyp adenomyosis

2 patients (16.7%), while in one case (8.3%) immunopositivity was observed for CD31. Only our case (8.3%) was tested for CD34, Van Gieson and orcein, the first of them being negative and the other two positive (at the blood vessels in a specialized pattern). Three of the patients (25%) were also tested for HMB-45 and all three were immunonegative. Moreover, two of the patients (16.7%), including our case, were tested for Melan-A and were both immunonegative. Regarding further pathology, endometrial hyperplasia was identified in one of the women (8.3%), another one (8.3%) was diagnosed with an atypical leiomyoma component (leiomyoma with bizarre nuclei according to WHO or symplastic) and our patient (8.3%) was diagnosed with a concurrent endometrial polyp and adenomyosis as well.

DISCUSSION

Uterine angiolipoleiomyomas are rare, benign mixed mesenchymal tumours, which are composed of vascular elements, smooth muscle, and mature adipose tissue. Interestingly, several nomenclatures have been given to such tumours, including angiolipoleiomyoma, lipoleiomyoma, hamartoma, lipoleiomyomatous tumour, benign mixed mesodermal tumour, and benign lipomatous lesion. This is possibly due to the fact that the World Health Organization's histological typing of female genital tract tumours does not officially list uterine AML.[11] More specifically, benign ULTs are distinguished by Sienski et al. in two major categories: lipoleiomyomas and angiolipoleiomyomas.[3]

Uterine ALLM is usually seen in both pre- and postmenopausal women and is typically asymptomatic. When symptomatic, the patient experiences symptoms comparable to those seen in leiomyomas such as abnormal uterine bleeding (menorrhagia/postmenopausal bleeding) and pelvic discomfort due to a palpable mass. From the few cases that have been reported in the literature, ALLM occurs most commonly in the uterine corpus and rarely in cervix and broad ligament. Our systematic review analysis revealed a mass ranging from 2 to 16 cm in size with mean size of 7.5 cm approximately, which is close to the mean size of 8.4 cm that was reported in the previously published literature[6] **(Table 1)**.

Various imaging modalities such as ultrasound CT scan and MRI can be used to diagnose ALLM. Ultrasound usually features a mass with high level of echogenicity without shadowing. ALLMs are most frequently revealed by ultrasound sonography as sharply marginated well-vascularized masses and sometimes appear as anechoic areas.[5] Increased echogenicity is a result of blood vessels with thick wall and bundles of smooth muscle cells. Magnetic resonance (MRI) as an additional screening method reveals a pelvic mass usually situated in the corpus of uterus, often rounded with high density in T2 (irregular hyperintensity) and low density in T1. However, these features are not specific.

Usually, these rare benign tumours are well defined with or without a pseudocapsule, but occasionally tumours demonstrate infiltrative growth. Macroscopically, these masses have a rubbery or firm consistency and show a gray-pink tan colour on cut surface. In microscopic sections, the mass consists of mature adipose tissue, smooth muscle tissue, and blood vessels (small/medium sized with thick walls). To confirm the diagnosis, the histopathological analysis should demonstrate all three elements. Abnormal blood vessels stain histochemically with Van Gieson and orcein dyes in a special manner. More specifically, the Van Gieson stain dyes collagen (and other connective tissue and muscle elements) intensely reddish, while both stains demonstrate a configuration of collagen within the vessel wall characteristic of ALLM.[4,11] However, the aforementioned histological findings are also present in angiomyolipomas, which, despite commonly occurring in the kidneys, have also been reported at various extrarenal sites, including the gynecological region. Angiomyolipomas, apart from comprising a distinguished histological category, originating probably from perivascular epithelial cells, are often associated with tuberous sclerosis and therefore the differential diagnosis among them and other mesenchymal uterine tumours is crucial.[1,11] Thus, in most of the cases, immunohistochemical staining is also warranted. Based on immunohistochemistry, ALLMs show strong positivity with antibodies against alpha-smooth muscle actin and desmin, demonstrating the neoplastic muscle element in the tumour. CD31 and CD34 are indicative of the blood vessels' element and positivity of CD34 also differentiates these specific tumours from other spindle-shaped neoplasms. Moreover, the adipose tissue is dyed with the antibody S-100. Last but not least, negativity of melanocyte markers is warranted to distinguish it from angiomyolipoma, since human ALLM lacks the melanoma black 45 immune reactive cells, and HMB45 (anti-melanoma antibody) is negative in ALLM and positive in angiomyolipoma.

To our knowledge, this is the first study in the English language systematically presenting the current evidence on uterine angiolipoleiomyomas. Nonetheless, there are several limitations that need to be addressed. These limitations are mainly inherent to the studies we included in the analysis. Firstly, the recruited studies are all reports of individual cases. Secondly, the number of the studies is quite small too, resulting in a small number of included patients, which further limits the cumulative interpretation of our findings. Further, larger and more high-quality studies are required in order to draw safe conclusions.

CONCLUSIONS

Uterine angiolipoleiomyomas are rare benign tumours that occur in women with a mean age of 55 years. In order to establish the diagnosis, the use of ultrasonography and additional MRI may help the preoperative prediction of a benign mass. Usually, the gross appearance shows a mass of muscle tissue with mean size of approximately 7.5 cm, situated in corpus, cervix or broad ligament of uterus. Immunohistochemistry will show strong positivity of

alpha-smooth muscle actin and desmin. Complete abdominal hysterectomy is the preferable treatment.

Author contributions

Ch.I. and G.V. – surgical and medical practices; V.P. – concept; A.F. – design; S.L. and K.K. – data collection or processing; L.K. and Ch.V. – analysis or interpretation; E.G. – literature search; V.P., E.G., S.L., and K.K. – writing.

Conflict of Interest

The authors report no conflict of interest.

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Ангиолиполеомиома матки. Отчёт о клиническом случае и систематический обзор литературы

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Резюме

Ангиолиполеомиомы матки — редкие доброкачественные смешанные мезенхимальные поражения. Проявление в гинекологической области встречается довольно редко, в литературе описано несколько случаев. Мы представляем интересный случай 59-летней женщины с диагнозом ангиолиполеомиома матки и результаты проведённого систематического обзора литературы. У пациентки выявлено новообразование в области таза, маскирующееся на УЗИ под лейомиому, и постменопаузальное вагинальное кровотечение. При лапаротомии была замечена большая матка, и гистопатология поставила диагноз ангиолиполеомиомы. Иммуногистохимия показала отрицательный результат на антитела, специфичные для меланомы Melan-A и HMB-45, и положительный результат на гистохимическую окраску по Ван Гизону и орсеину.

Мы систематически изучали литературу. Приемлемыми статьями были статьи, написанные на английском языке, за исключением исследований на животных и исследований, в которых сообщалось об ангиолиполеомиомах в других областях помимо матки. Настоящий случай является одним из 10 случаев ангиолиполеомиомы матки, описанных в литературе. В 8 из 11 (72.7%) случаев ангиолиполеомиомы матки возникали из тела матки, при этом в 2 (18.1%) случаях они располагались на шейке матки, в одном случае (9%) ангиолиполеомиомы располагались в широкой связке. Что касается симптомов, у четырёх пациенток (36.4%) были боли в животе и тазовой области, у двух (18.1%) – вагинальные кровотечения в постменопаузе, у одной – менометроррагия (9%) и у одной – пролапс матки и цистоцеле (9%). Иммуногистохимическое окрашивание ангиолиполеомиом матки было положительным на SMA у 4 пациенток (36.4%), положительным на десмин в 3 случаях (27.3%), положительным на антитела к белку S-100 у 2 пациенток (18.1%), в то время как в одном случае (9%) иммунопозитивность наблюдалась для CD31. Только в нашем случае (9%) также были проведены тесты на CD34, Ван Гизона и орсеин, причем первый из них был отрицательным, а два других положительными (в кровеносных сосудах по специальной схеме). Трое пациентов (27.3%) также были протестированы на HMB-45, и все трое были иммуноотрицательными.

Для установления диагноза ангиолиполеомиомы матки ультразвуковое исследование и дополнительная МРТ могут помочь в дооперационном прогнозировании доброкачественного образования. Иммуногистохимия покажет сильную положительную реакцию альфа-гладкомышечного актина и десмина. Полная абдоминальная гистерэктомия является предпочтительным методом лечения.

Ключевые слова

ангиолиполеомиома, доброкачественные опухоли матки