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Clinical characteristics and treatment outcomes of angioleiomyoma of the female genital tract: a retrospective cohort study

Sili He¹ and Jianfa Jiang^{1*}

Abstract

Background Angioleiomyoma, a benign tumour composed of smooth muscle cells and thick-walled vessels, is expected to be very rare in the female genital tract. This study aimed to describe the clinicopathological features and treatment outcomes of angioleiomyoma in the female genital tract.

Methods We retrospectively reviewed 89 women with angioleiomyoma in the genital tract who were treated at Third Xiangya Hospital of Central South University between July 2008 and October 2023. Symptom remission rate was the primary outcome of the study.

Results Angioleiomyomas accounted for 0.6% of leiomyomas of the female genital tract. The average age of the 89 women was 41.8 ± 8.7 years. Seventy women (78.7%) had a history of uterine surgery, of whom two patients had removed uterine angioleiomyoma by laparoscopic myomectomy. The angioleiomyomas of 61 (68.5%) women were located in the uterine corpus, 17 (19.1%) in the broad ligament, 10 (11.2%) in the cervix and only 1 (1.1%) in the vagina. Abnormal uterine bleeding was the main clinical manifestation of angioleiomyomas located in the uterine corpus or cervix, whereas the main clinical manifestation of angioleiomyomas in the broad ligaments was pelvic mass. Of the 89 women, 59 underwent surgery to preserve the uterus, and 30 underwent total hysterectomy or subtotal hysterectomy. The intraoperative blood loss was more than 500 ml (700–4,500 ml) in six women. The symptom remission rate was 100% after surgery. Among the 59 women with preserved uterus, 8 showed multiple uterine leiomyomas during follow-up, but it was difficult to determine whether they were angioleiomyomas. Angioleiomyomas recurred in one woman who underwent total hysterectomy.

Conclusion Angioleiomyoma is rare in the female reproductive tract, and patients may present with diverse symptoms, which are related to the location of the tumour. Hysterectomy and myomectomy are both effective treatment methods, but the risk of intraoperative bleeding should be recognised for multiple lesions and those with large diameters. Relapse may occur in some patients.

Keywords Angioleiomyoma, Female genital tract, Treatment, Hysterectomy, Prognosis

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Background

Angioleiomyoma is an exceptionally uncommon subtype of leiomyoma composed of smooth muscle cells and thick-walled vascular vessels [1]. It belongs to the pericytic (perivascular) tumour group according to the 2020 World Health Organization Classification of Soft Tissue Tumors [2]. The aetiology of angioleiomyoma remains unknown, but a few studies have found clonal karyotypic alterations in such patients [3].

Angioleiomyoma shows a wide anatomical distribution, occurring most frequently in the subcutaneous tissue of the lower extremities but also in the head, neck and trunk. They have been rarely reported in uterine corpus [4, 5], cervix [6, 7] broad ligament [8] and ovary [9, 10], usually occurring in middle-aged women. Patients commonly present with abnormal uterine bleeding (AUB) and a lower abdominal mass [11], and there have been case reports of spontaneous rupture of uterine angioleiomyomas causing massive haemorrhage [12] or with disseminated intravascular coagulation [13]. Various imaging modalities, including ultrasound, computed tomography and nuclear magnetic resonance imaging (MRI), have been employed to detect angioleiomyoma, but it is difficult to be detected by preoperative investigations because these lesions usually present as intramural or subserosal nodules. The sonographic picture in most cases was indistinguishable from that of a conventional leiomyoma. The computed tomography and MRI appearance of angioleiomyomas is also nonspecific [14]. Pathologic confirmation is the only conclusive diagnosis.

The definitive treatment is complete removal of the angioleiomyoma through either total hysterectomy or angiomyomectomy. In the majority of cases, surgical management of uterine angioleiomyoma involved hysterectomy with or without salpingo-oophorectomy. Angiomyomectomy was rather rare, and its decision depended upon the patient's desire to maintain fertility. No recurrence was reported in any case [1, 4, 7]. However, most of the existing studies about angioleiomyoma of the female genital tract are case reports, without large-sample studies. Therefore, there is a lack of overall assessment of the clinical pathological characteristics and surgical treatment of uterine angioleiomyoma. The treatment outcomes between total hysterectomy and angiomyomectomy with preservation of the uterus have not yet been studied. Large-sample studies will help summarize the clinical characteristics and treatment protocols of angioleiomyomas of the female genital tract, as well as assess the prognosis.

The present article reports our experience of angioleiomyoma of the female genital tract. To our knowledge, we present the largest cohort study ever published on this topic. In this study, we retrospectively analyzed the clinicopathological features and treatment outcomes of

angioleiomyoma in the female genital tract confirmed by pathology in our hospital.

Materials and methods

Patient selection

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the ethics committee and institutional review board of Third Xiangya Hospital of Central South University. This retrospective cohort study was conducted in the gynaecology department of Third Xiangya Hospital of Central South University from July 2008 to October 2023. Patients were identified using the hospital's electronic medical record analytical database. Informed consent for participation was obtained from all subjects. The inclusion criteria comprised women (1) with a diagnosis of angioleiomyoma confirmed by pathological examination, (2) a lesion located in the uterine corpus, cervix, broad ligament or other female reproductive tract organs (3) with complete clinicopathological and follow-up data. The follow-up lasted through December 2023. Exclusion criteria included (1) angioleiomyoma with adipose tissue components; (2) combined with malignant tumor of reproductive tract; (3) follow-up data were not available.

Data on demographic characteristics, treatment, clinicopathological parameters and follow-up were collected for each subject. They included age, parturition, menopausal status, previous history of uterine surgery, symptoms, location, tumour size, pathology and primary treatment. Patients were followed up by physical examination and ultrasound at 1 month after surgery, at 3 months and yearly thereafter. Symptom remission rate was the primary outcome of the study. The follow-up period lasted until January 2024. Follow-up information, including improvement of symptoms and recurrence, was obtained from medical records or by telephone.

Morphological evaluation and immunohistochemistry

Two pathologists confirmed the morphological features of angioleiomyoma. Immunohistochemical staining for smooth muscle actin (SMA), desmin, h-Caldesmon, CD10, CD34, Human Melanoma Black (HMB) 45, Melan-A and Ki67 was performed using an automated platform (Ventana BenchMark XT, Roche, Mannheim, Germany).

Statistical analysis

Descriptive statistics were computed using SPSS Statistics version 24 (IBM Corp.). The normally distributed continuous data are presented as mean \pm standard deviation and the non-normally distributed continuous data as median and range. Categorical variables are expressed as number and percentage. *P* values < 0.05 was considered statistically significant.

Results

From July 2008 through October 2023, we observed 97 cases of angioleiomyoma in the female genital tract. During this period, a total of 15,043 cases of female reproductive tract leiomyomas underwent surgical treatment in our hospital, so angioleiomyoma accounted for 0.6%. Of the 97 patients with angioleiomyoma in the genital tract, 8 were lost to follow-up, so a total of 89 patients were included in the study.

Clinical characteristics

Table 1 shows the patients' clinical characteristics. Their average age was 41.8 ± 8.7 years (range: 19–69 years), and most patients (94.4%) were premenopausal. Seventy women (78.7%) had a history of uterine surgery, among whom two patients had previously removed uterine angioleiomyoma by laparoscopic myomectomy in other hospitals, with recurrence within 6 months after surgery. A CA-125 test was completed in 78 patients, including 14 patients with >35 U/ml, and 53 patients underwent a

Table 1 The demographic and clinical characteristics of patients with angioleiomyoma of the female genital tract

Characteristics	Values
Age (years)	41.8 ± 8.7
Gravidity	3 (0, 7)
Parturition	
Yes	74 (83.1)
No	15 (16.9)
Menopausal status	
Premenopausal	84 (94.4)
Menopausal	5 (5.6)
Previous uterine surgery	
Induced abortion	56 (62.9)
Caesarean section	20 (22.5)
Myomectomy	8 (11.2)
Angioleiomyomectomy	2 (2.2)
Hysteroscopic myomectomy	2 (2.2)
Loop electrosurgical excisional procedure	1 (1.1)
Diagnostic curettage	1 (1.1)
Anemia	
Yes	44 (49.4)
No	45 (50.6)
Ca125 (U/ml)	17.1 (4.2, 448.8)
LDH (U/L)	179.5 (131, 248)
Location	
Uterine corpus (intramural, and subserosal)	32 (36.0)
Uterine corpus (submucosal)	29 (32.6)
Broad ligament	17 (19.1)
Cervix	10 (11.2)
Vagina	1 (1.1)
Number of angioleiomyoma	
Single	69 (77.5)
Multiple	20 (22.5)

Values are given as n (%) unless otherwise stated

lactate dehydrogenase (LDH) test, all of which were in the normal range. There were 44 patients with anaemia, including 5 with severe anaemia. None of the patients showed angioleiomyoma on a preoperative ultrasound or MRI.

We classified the location of the angioleiomyomas in the reproductive tract. Patients with multiple angioleiomyomas in different locations were classified according to the location of the main lesion. The angioleiomyomas of 61 (68.5%) women were located in the uterine corpus, 17 (19.1%) in the broad ligament, 10 (11.2%) in the cervix and only 1 (1.1%) in the vagina. Of the cases in the cervix, 7 were located in the cervical canal. Most patients with angioleiomyoma had single tumours, but 22.5% had multiple tumours.

As the symptoms and treatment methods of uterine leiomyomas are closely related to their location and because angioleiomyoma is a special type of leiomyoma, the patients' clinical manifestations and treatment methods were statistically analysed by location (Table 2). AUB was the main clinical manifestations of angioleiomyomas located in the uterine body or cervix. Among them, one patient with cervical angioleiomyoma presented with haemorrhagic shock caused by sudden vaginal haemorrhage; her haemoglobin was only 24 g/l at admission. The main clinical manifestation of angioleiomyomas in the broad ligaments was pelvic mass, and the median largest angioleiomyoma in diameter was 101.5 (43, 242) mm. Among 17 patients with broad ligament angioleiomyoma, 3 were suspected to have ovarian malignant tumour before the operation. A few patients had abdominal pain, abdominal distension, postmenopausal vaginal bleeding and haemorrhagia sub coitu as the main clinical manifestation.

Of the 89 patients, 59 underwent surgery to preserve the uterus and 30 underwent total or subtotal hysterectomy. Most (96.6%) submucosal angioleiomyomas and cervical angioleiomyomas were treated with hysteroscopic myomectomy.

Some patients with angioleiomyomas in the broad ligament or uterine corpus face the risk of massive haemorrhage during surgery. Table 3 lists the clinical data of 6 patients with angioleiomyoma whose intraoperative bleeding exceeded 500 ml (range: 700~4,500 ml). All these patients had multiple angioleiomyomas, and the maximum diameter of the tumours was large (129–400 mm). All 6 patients received blood transfusion therapy.

Pathological characteristics

All the cases had the morphological features of angioleiomyoma, comprising interlacing fascicles of monotonous spindled smooth muscle cells surrounding abundant thick-walled blood vessels. Representative pathologic

Table 2 Clinical features and treatment of angiomyolipomas in different locations of female genital tract

Data	Uterine corpus (intramural, subserosal) n = 32	Uterine corpus (submucosal) n = 29	Broad ligament n = 17	Cervix n = 10	Vagina n = 1
Symptoms					
Pelvic mass	10 (31.2)	-	13 (76.4)	8 (80.0)	-
Abnormal uterine bleeding	17 (53.1)	24 (82.8)	1 (5.9)	-	-
Abdominal pain	3 (9.4)	3 (10.3)	-	-	-
Postmenopausal bleeding	-	1 (3.45)	1 (5.9)	1 (10.0)	1 (100)
Abdominal distension	2 (6.3)	-	2 (11.8)	1 (10.0)	-
Haemorrhagia sub coitus	-	1 (3.45)	-	-	-
Massive vaginal bleeding	-	-	-	-	-
The largest angiomyoma in diameter (mm)	82.5 (23, 400)	32 (9, 85)	101.5 (43, 242)	38.5 (8,85)	86
Surgical approach					
Total abdominal hysterectomy	6 (18.8)	-	5 (29.4)	1 (10.0)	-
Subtotal abdominal hysterectomy	1 (3.1)	-	-	2 (20.0)	-
Laparoscopic hysterectomy	8 (25.0)	1 (3.4)	5 (29.4)	-	-
Laparoscopic subtotal hysterectomy	1 (3.1)	-	-	1 (10.0)	-
Laparotomy myomectomy	2 (6.2)	-	1 (5.9)	6 (60.0)	-
Laparoscopic myomectomy	14 (43.8)	-	6 (35.3)	-	1 (100)
Hysteroscopic myomectomy	-	28 (96.6)	-	-	-
Transvaginal myomectomy	-	-	-	-	-
Intraoperative blood loss (ml)	100 (10, 2500)	10 (5, 150)	100 (10, 4500)	20 (5, 150)	30

Values are given as n (%) unless otherwise stated

Table 3 The clinical characteristics of patients with intraoperative blood loss more than 500 ml

Date	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	50	51	51	38	40	37
Symptoms	Abdominal distension	Abdominal distension	Pelvic mass	Abdominal pain	Abdominal distension	Pelvic mass
Preoperative hemoglobin (g/l)	93	117	94	102	109	85
Location	Broad ligament	Broad ligament	Uterine corpus	Uterine corpus	Uterine corpus	Uterine corpus
Number of angiomyoma	Multiple	Multiple	Multiple	Multiple	Multiple	Multiple
The largest angiomyoma in diameter (mm)	242	143	203	400	129	147
Surgical approach	TAH	TAH	TAH	LM	TAH	LTH
Intraoperative blood loss (ml)	4500	800	2500	700	2500	700
Intraoperative blood transfusion	Yes	Yes	Yes	Yes	Yes	Yes

TAH: Total abdominal hysterectomy; LTH: Laparoscopic total hysterectomy; LM: Laparotomy myomectomy

images are provided in Fig. 1. No malignant features, such as pleomorphism, mitosis, hyperchromatic nuclei or necrosis, were found in any tumours. Lipogenesis was observed in 3 patients. Immunohistochemistry was performed in 28 patients, all of whose angiomyomas were positivity for SMA, desmin and h-Caldesmon and negative for HMB-45 and Melan-A. CD10 was focally weakly positive in 10 patients and negative in the rest. The endothelial cells express positivity for CD34. Ki67 index was 10% in 6 patients and lower than 10% in other patients. Representative immunohistochemistry images are provided in Fig. 2.

Follow-up results

The median follow-up time for all patients was 64 months, ranging from 2 to 185 months. The symptom remission rate was 100% after surgery. A patient with uterine angiomyoma who underwent laparotomy and bilateral salpingo-oophorectomy died of cerebrovascular accident 5 years after surgery without recurrence. All the remaining patients survived.

Among the 59 patients with preserved uterus, 10 showed multiple uterine leiomyomas during follow-up. As the leiomyomas' diameters in all patients were less than 4 cm and there were no obvious symptoms, no further surgical treatment was performed. However, because uterine leiomyomas and angiomyomas may not be distinguishable on ultrasound, it is not

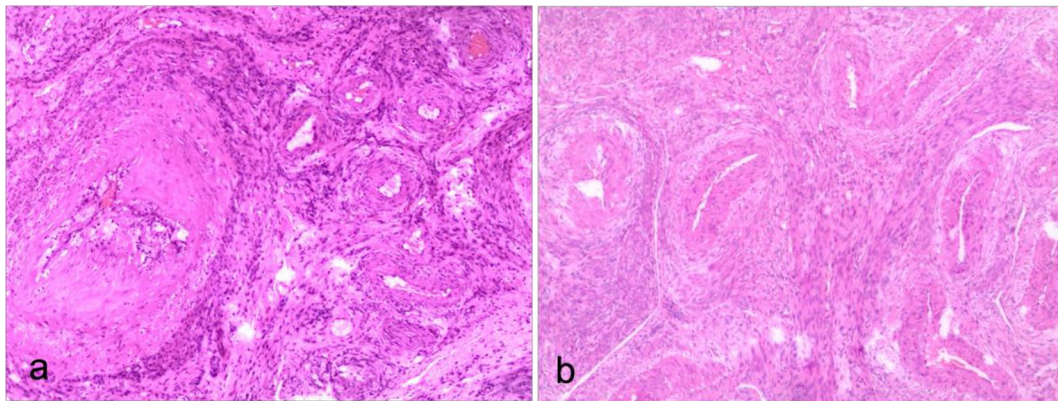


Fig. 1 The HE images of angioleiomyoma showed smooth muscle cells and thick-walled vascular vessels ($\times 100$)

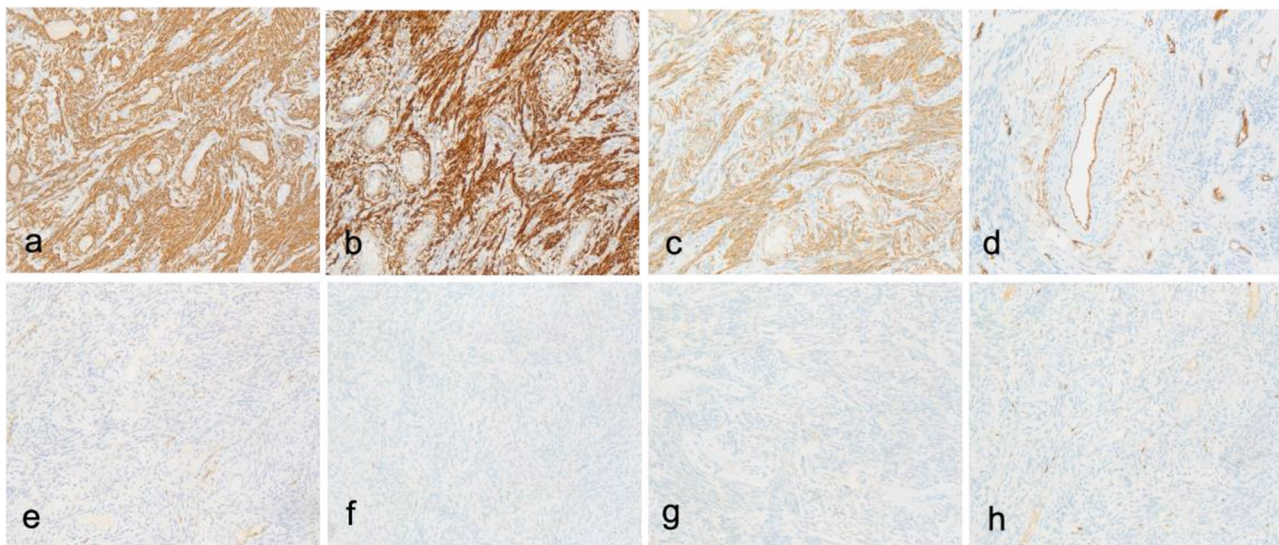


Fig. 2 Immunohistochemistry of angioleiomyoma showing positive with smooth muscle antigen ($\times 200$, **a**); positive with desmin ($\times 200$, **b**), positive with h-caldesmon ($\times 200$, **c**); positive CD 34 staining in vascular endothelium ($\times 200$, **d**); negative reaction with CD 10 ($\times 200$, **e**); negative reaction with HMB45 ($\times 200$, **f**); negative Melan-a staining ($\times 200$, **g**); staining with Ki 67 ($\times 200$, **h**)

possible to determine whether these patients had recurrent angioleiomyomas. Of the 30 patients who underwent hysterectomy, 29 patients had no recurrence, and one underwent reoperation. A 37-year-old patient with angioleiomyoma underwent the first operation in January 2016. During the operation, multiple angioleiomyomas were observed in the anterior wall of the uterine body, posterior wall of the cervix and left broad ligament; the largest was located in the anterior wall of the uterus. Laparoscopic total uterine and bilateral salpingo-resection was performed. There was no abnormality at 1 month or 3 months after surgery, but ultrasound showed a solid mass of about 6 cm in diameter on the left side of the pelvic cavity 6 months after surgery. Laparoscopic surgery was performed in January 2017. A tumour was found in the left broad ligament during the operation and was resected completely. The postoperative diagnosis

was angioleiomyoma. There was no recurrence after follow-up.

Discussion

Angioleiomyomas are rare benign tumours of the female reproductive tract and are considered a distinct variant of leiomyomas. To our knowledge, fewer than 100 cases of uterine angioleiomyoma have been reported to date, and previous studies have suggested that uterine angioleiomyomas account for 0.34–0.40% of common leiomyomas [15]. In this study, angioleiomyomas accounted for 0.6% of all patients with leiomyomas in the female genital tract. Given our large sample size, this number can roughly estimate the proportion of angioleiomyomas.

The aetiology of angioleiomyoma remains unclear. Some studies have speculated that angioleiomyoma in the uterus arises from perivascular smooth muscle cells rather than myometrial smooth muscle cells, suggesting

that its pathogenesis is related to vascular endothelial injury and chronic venous obstruction. In addition to minor trauma and chronic venous insufficiency, the development of uterine angioleiomyomas can be affected by sex hormone stimulation [15]. Most of these tumors are similar with uterine leiomyoma by histology and positive hormone receptors [7]. In our study, 93.2% of the patients were premenopausal, and the condition is found mainly in women of childbearing age, suggesting that it may be related to sex hormones. Seventy women (78.7%) had a history of uterine surgery, but further studies are needed to determine whether uterine surgery is a risk factor for uterine angioleiomyoma.

Previous studies have reported that female reproductive tract angioleiomyoma is often manifested by pelvic mass [11, 16]. In some patients, AUB is the main symptom. It is speculated that AUB in angioleiomyoma is due to dysregulation of vascular growth factors and their receptors, which affect morphology and regulate angiogenesis [14]. The high vascular density of angioleiomyoma may increase the risk of spontaneous rupture of the tumour, leading to massive, life-threatening haemorrhage. Some patients present with abdominal pain, which may be caused by ischemia or vascular contraction. In the present study, we found that the clinical manifestations of angioleiomyomas were closely related to the location of the lesions, similar to common leiomyomas. The main clinical manifestation of angioleiomyomas located in the broad ligaments were pelvic masses, and some patients experienced abdominal distension and abdominal pain due to pelvic mass. While AUB is the main clinical manifestation of angioleiomyoma in the uterine body or cervical canal due to uterine enlargement, numerous vascular growths or affect uterine contractions. Notably, one patient in this study suffered from haemorrhagic shock due to massive vaginal bleeding resulting from cervical angioleiomyoma rupture, suggesting that such cases are at risk of massive bleeding. Similar cases have been reported in previous studies [12]. Moreover, this study for the first time reports a case of angioleiomyoma originating from the vagina of an adult woman. The main clinical manifestation of this patient was massive haemorrhage after sexual intercourse. The symptoms were relieved after angioleiomyomectomy.

The diagnosis of angioleiomyoma depends mainly on pathology. In this study, none of the patients showed angioleiomyoma on preoperative ultrasound or MRI. This may be related to the small number of cases of the disease, as sonographers and radiologists lack relevant experience. Histologically, angioleiomyoma is composed of interlacing fascicles of monotonous spindled smooth muscle cells surrounding abundant thick-walled blood vessels. This is in contrast to the conventional leiomyoma, in which the density of the vascular network is similar to

or less than that of the normal myometrium. Most angioleiomyomas rarely show pleomorphism, mitosis, hyperchromatic nuclei or necrosis [17]. Other mesenchymal tumours that may resemble angioleiomyoma and have prominent blood vessels include angiofibroma, angiolipoma, endometrial stromal tumour (EST) and perivascular epithelioid cell tumors (PEComas). Although each has characteristic morphological features, the sometimes overlapping histological features may require the use of immunohistochemistry to reach the correct diagnosis [18]. In immunohistochemistry, ESTs are typically positive for CD10 and WT-1 but negative for h-Caldesmon, and these immunohistochemical features can distinguish them from angioleiomyoma. PEComa shows an admixture of spindle and epithelioid cells. In immunohistochemistry, PEComas express HMB-45 and Melan-A, which are negative in angioleiomyoma. In this study, all the cases had the morphological features of angioleiomyoma, and no malignant features were found. Immunohistochemistry showed positive for SMA, desmin and h-Caldesmon and negative for HMB-45 and Melan-A. The endothelial cells expressed positive for CD34. CD10 was weakly positive or negative, and the Ki67 index was relatively low. Several studies have asserted that this tumour must be categorised as a benign leiomyoma variant and included in the World Health Organization's classification of tumours of the female genital tract. According to the pathological characteristics of angioleiomyoma in this study, we support this view [1].

Although angioleiomyomas are benign tumours, surgery is recommended for symptomatic patients. The definitive treatment of choice is complete surgical removal of the tumour. Previous studies have shown that hysterectomy or myomectomy are effective treatments, depending on the patient's age, symptoms and desire to preserve fertility. In cases preserving fertility, complete resection of angioleiomyoma including a free margin should be performed [1]; however, resection of angioleiomyoma has been somewhat rare [19]. Simple hysterectomy should be performed if the symptoms are severe and persist or it appears impossible to differentiate angioleiomyoma from malignant gynaecologic tumour. No case of recurrent uterine angioleiomyoma after surgical resection has been previously reported. In this study, two patients had undergone laparoscopic myomectomy in other hospitals but came to our hospital for recurrence.

Fifty-nine patients in our study underwent surgery to preserve the uterus. Among them, 10 showed multiple uterine fibroids during follow-up. Because uterine leiomyomas and angioleiomyomas are difficult to distinguish by preoperative examination, it was not possible to determine whether these patients had recurrent angioleiomyomas. Of the 30 patients who underwent hysterectomy, only one patient underwent reoperation. Because of

the multiple angioleiomyomas in this patient, some of the lesions were located in the broad ligament, so we could not completely rule out the possibility that a small amount of intraoperative residue caused recurrence. After reoperation, the patient has had no recurrence to date. This suggests that such patients still have the possibility of recurrence. Complete removal of the lesion during surgery is particularly important. However, for patients with multiple lesions and large tumour volume, whether undergoing total hysterectomy or myomectomy, the risk of massive haemorrhage during the operation should be recognised [20], and necessary preventive measures should be taken.

The study has several limitations. First, it is a retrospective study, further prospective studies to validate these findings and explore preventive measures for intraoperative bleeding is needed. But the disease is rare, and it is difficult to conduct prospective studies. Secondly, for patient {Sato, 2023 #1099}s with uterine fibroid recurrence indicated by ultrasound during follow-up, pathology could not be obtained to determine whether angioleiomyoma recurred, so the recurrence rate after surgery cannot be provided. However, these patients had no obvious symptoms during follow-up, suggesting that myomectomy is still an effective treatment.

Conclusion

In summary, angioleiomyomas accounted for about 0.6% of female reproductive tract leiomyomas. Patients may present with diverse symptoms, which are related to the location of the tumour. Hysterectomy and myomectomy are both effective treatment methods, but for lesions with multiple and large diameters, the risk of intraoperative bleeding should be recognised. Relapse may occur in some patients.

Abbreviations

AUB	Abnormal Uterine Bleeding
MRI	Magnetic Resonance Imaging
SMA	Smooth Muscle Actin

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Author contributions

SLH and JFJ collected data and performed statistical analysis, data interpretation and drafted the manuscript; JFJ designed the study and revised the manuscript. All authors have read and approved the manuscript.

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Data availability

All data generated or analyzed during this study are included in this article.

Declarations

Ethical approval

This study was approved by the ethics committee and institutional review board of Third Xiangya Hospital of Central South University (No. E24038). Informed consent for participation was obtained from all subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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