

Uterine angioleiomyoma – a rare variant of uterine leiomyoma: review of literature and case reports

Dobrośława L. Sikora-Szczeńniak

Department of Obstetrics and Gynaecology, Specialist Hospital in Radom, Poland

Abstract

Introduction: Uterine angioleiomyoma (AL) is an extremely rare variant of uterine leiomyoma. It is composed of smooth muscle cells and thick-walled blood vessels. Angioleiomyoma usually occurs in middle-aged women, 40-60 years old. Aim of the study was to review of literature research reports on uterine AL. Discussion of nine case reports of uterine AL in the patients operated on in our ward.

Material and methods: The paper presents analysis of accessible research reports on uterine AL, and medical records of the patients operated on in our ward.

Results: Mean age of the patients with uterine AL was 47.11 ± 5.21 , body mass index (BMI) 25.88 ± 3.95 . All women had given birth (1-5 natural deliveries, 2.44 mean). Uterine AL occurred in 0.34% to 0.40% cases of leiomyomas. Angioleiomyoma were located intramurally and subserosally in six and three patients (respectively, 66.7% and 33.3%). Laparotomy was undertaken in seven cases (77.8%), transvaginal access in two cases (22.2%), and myomectomy in one case (11.1%). Blood transfusion was required in four cases (44.4%).

Conclusions: In the group of uterine leiomyomas, uterine ALs occurred in 0.34-0.40% of cases. Angioleiomyoma cases posed a greater risk of complications threatening the patient's health and life. Preoperative differentiation of AL with ovarian tumour was more difficult due to frequent degenerative lesions in the course of uterine AL.

Key words: uterine angioleiomyoma, surgical operation.

Introduction

Angioleiomyoma (AL) is a benign tumour of mesenchymal origin. Among uterine leiomyoma variants, AL in the uterine body is extremely rare [1]. According to a review by Handler *et al.* only 11 cases of uterine ALs were reported in English language literature in 1966-2007 [2]. Diwaker *et al.* quoted 15 cases, and Sharma *et al.* found 16 English language publications on uterine ALs [3, 4].

The aetiology of uterine AL remains unclear. In addition to minor trauma and chronic venous insufficiency, the development of uterine AL can be affected by sex hormones. Pertinent symptoms of the disease speak for hormone-dependent uterine leiomyoma formation in women on hormone replacement therapy (HRT) in the peri- and postmenopausal period [5].

The researchers also postulate the involvement of angiogenesis. Angioleiomyomas form in the process of angiogenesis when vascular walls thicken due to the proliferation of smooth muscle cells [6, 7]. In addition to the transport of blood, blood vessels are essential to the integrity of the entire body. In that respect vascular endothelial cells responsible for restructuring and angiogenesis are very important [8, 9]. Generally, uterine AL

is composed of primitive thick-walled torturous blood vessels surrounded in a chaotic manner by interlaced spindles of well-differentiated smooth muscle cells arising from venous or arterial walls [10, 11].

Contrary to angiogenesis, in arteriogenesis blood vessels form independently of hypoxia. The process is induced by increased shear stress. As a result, "dormant" endothelial cells (ECs) are activated. Growth factors produced by perivascular macrophages transform small collateral vessels into large arteries with diameters 20 times larger [6, 7]. Endothelial cells are essential for the integration of mechanical forces with molecular signals in arteriogenesis [12]. Chemically, arteriogenesis is related to cytokine – basic fibroblast growth factor (bFGF) and angiogenin from the angiopoietin family. Basic fibroblast growth factor encoding gene is located on the short arm of chromosome 4 [13, 14]. The cytokine is produced by myocytes, fibroblasts, macrophages, mastocytes, and tumour cells. It is present in the cytoplasm and transported by leukocytes and thrombocytes [13, 15]. Like platelet-derived growth factor (PDGF), bFGF is a myogene for ECs and smooth muscle cells [7]. The endothelium responds to bFGF via tyrosine kinase receptors from the fibroblast growth factor receptor (FGFR) family [13, 15]. Angiopo-

Corresponding author:

Dobrośława L. Sikora-Szczeńniak, Department of Gynaecology and Obstetrics, Specialist Hospital in Radom, Tochtermiana 1, 26-610 Radom, e-mail: dosiass@wp.pl

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etin-1 exhibits paracrine activity, i.e. it induces migration, adhesion, and survival of endothelial cells [16].

Genetic bases of the leiomyoma cell evolution are not well known yet. Auguściak-Duma *et al.* state that 40% of those benign tumours present abnormal karyotype [17]. In their search of literature on molecular and cytogenetic origin of leiomyomas, Knapp *et al.* found that almost 50% of the tumours presented chromosomal aberrations. Translocation, duplication, and deletion were observed on chromosomes 7, 12, and 14. However, balanced translocations were seen on chromosomes 12 and 14 [18]. Hennig *et al.* found cytogenetic clonal changes in the karyotype in uterine AL, which was never spotted in conventional leiomyoma. Cytogenetic analysis of uterine AL in a 41-year-old patient demonstrated the following karyotype abnormalities: 6,X,t(X;11)(p11.4;p15)/46,idem,inv(2)(p15q13)/46,idem,inv(2)(p15q13),t(5;20)(q13.2) [19].

Microscopically, three histological types were distinguished in AL variant, i.e. capillary of dense structure with narrow vessels interlaced with thick fascicles of smooth muscles, venous type composed of thick vessels interspersed with fascicles of smooth muscles, and cavernous with widened vessels and lesser amount of smooth muscles. In that type vascular muscular walls are difficult to differentiate from intervascular fascicles of smooth muscles [20].

The patients with postoperatively diagnosed uterine ALs usually present with lower abdominal pain and abnormal uterine bleeding. Clinical and radiological differentiation between AL and leiomyoma is difficult [21]. Uterine AL may be suspected preoperatively when imaging scans show signs of vascular damage in patients with uterine bleeding and anaemia [22-24]. In some cases, imaging techniques (USG, CT, MRI) may suggest preoperative diagnosis of uterine AL. The effectiveness of diagnosis is limited to establishing the nature and extent of the lesion [23, 24].

According to many authors, differential preoperative diagnosis of that AL variant with other tumours is extremely difficult, and therefore it is not usually made until microscopic examination has been performed [1, 3, 8]. Differential diagnosis based on histopathological and immunohistochemical findings considers fibroma, angiofibroma, angiolipoma, and angiomyofibroblastoma, which are vimentin- and desmin-positive but smooth muscle actin-(SMA) negative [25]. Perivascular epithelioid cell tumour – PEComa is HMB-45-positive [26].

Immunohistochemical assays use immunoreactivity against SMA, vimentin, desmin, caldesmon, and progesterone receptors. Immunoreactivity of CD10 and oestrogen receptor is weak; however, endothelial cells are CD34- and CD31-reactive.

This paper reviews literature reports on uterine AL. In addition, we present uterine AL cases in the patients operated on in our ward over an 18-year period.

Material and methods

This paper reviews literature reports on uterine angioleiomyoma, a variant of leiomyoma. In addition, medical records of nine patients with postoperative histological diagnosis of uterine ALs were retrospectively analysed.

The patients were qualified for operation on the basis of gynaecological examination, USG, and histological assessment of uterine samples. In one case an operation, i.e. hysterectomy with bilateral appendages, had to be performed on an emergency basis due to the perforation of the uterus at an attempt of diagnostic abrasion. Final diagnoses were made on the basis of postoperative microscopic examinations in the Pathomorphological Laboratory, Regional Specialist Hospital in Radom. In doubtful cases, immunohistochemical assays were done [26].

Results

Sahu *et al.*, Bommanahalli *et al.*, Laximinarayana *et al.*, Garg *et al.*, Kamath *et al.*, Gómeza *et al.*, Demiray *et al.*, Zizi-Serpertzoglou *et al.*, Grigoriadis *et al.*, and Lazarov *et al.*, have recently reported on ALs [1, 10, 21, 27-33].

In Polish literature on the subject ALs in the uterine body were discussed in two reports [34, 35]. In general, the authors reported on single cases of uterine AL. Only two reports presented two and three cases of uterine AL [36, 37].

However, Chinese authors presented clinical analysis of 26 and 29 cases of AL [38, 39]. Thomas *et al.*, Hsieh *et al.*, and Hakverdi *et al.* reported on multiple uterine ALs [22, 40, 41]. The cases of AL in the uterine cervix were presented by Koleskas *et al.*, Al-Sanna *et al.*, and Ye *et al.* [42-44].

The analysis of medical records of the patients treated in our ward over an 18-year period (1998-2015) revealed 1413 cases of leiomyomas and 875 leiomyomas with uterine endometriosis. Among 2270 cases of leiomyomas and leiomyomas with uterine endometriosis there were nine cases of *leiomyoma angiogenes* (0.40%). Mean age of the patients was 47.11 years, SD ± 5.21 , the youngest patient was 43, the oldest was 60 years old. Mean body mass index (BMI) was 25.88, SD ± 3.95 (20.42-33.59). Three women had BMI < 25.0, five women were overweight (BMI 25.0-29.9), and one woman was obese (BMI ≥ 30.0). Moreover, there was a case of superpathological obesity noted, class III (BMI = 54.6) [35]. In the examined group the mean number of deliveries was 2.44 (1-5 deliveries); all 22 deliveries were natural.

In the group of AL in the uterine body six were intramural (66.7%) and three were subserosal (33.3%).

In the group of patients operated on for uterine AL the biggest size of the uterus was 180 × 150 × 120 mm. The excised masses were 25-100 mm in diameter; the big-

gest uterine AL mass (subserosal, myoma nascens) was 130 × 50 × 50 mm.

Other pathologies concomitant to AL included:

- leiomyoma and endometriosis – 1 case,
- multiple leiomyomas – 1 case,
- endometriosis – 2 cases,
- erosion – 3 cases,
- thecoma of the right ovary – 1 case,
- paratubal serous cyst – 2 cases.

Table I presents information about female patients and types, the results of the treatments and operations performed in cases of uterine angioleiomyoma.

Surgical procedures and operations

In the majority of cases, surgical management of uterine AL involved hysterectomy with or without appendages. Myomectomy was rather rare [21, 37, 45].

In the group of nine patients, seven women (77.8%) had laparotomy performed: in six cases (66.7%) hysterectomy (with bilateral appendages – three cases, unilateral – one case, with the right fallopian tube – one case, and without appendages – one case). Myomectomy was performed in one case (11.1%). Angioleiomyomas in the uterine body were transected from transvaginal access: subserosally located – two cases (22.2%).

Generally, microscopic examination of AL samplings found no features of atypia, mitosis, pleomorphism, or necrosis. However, the authors presented individual cases of nuclear atypia [1, 37, 40].

Degeneration in angioleiomyoma often results from ischaemia, and the type depends upon the degree and speed of ongoing vascular insufficiency [46]. Mucoid areas, hyalinisation, calcification, and fatty deposits were also noted [1, 10, 22, 40]. Fibryn accumulation in the widened blood vessels of angioleiomyoma was reported, too [2, 18, 37, 40].

The analysis of patients' medical records revealed the following microscopic examination findings:

- hyalinisation – 2 cases,
- swelling and hyalinization – 1 case,
- necrosis and swelling – 1 case,
- ulceration – 1 case (in subserosal angioleiomyoma nascens).

In the cases qualified for differentiation with uterine angioleiomyoma, histopathological examination was necessary [26].

Literature reports present numerous complications posing a serious threat to the health and life of patients with uterine ALs, such as spontaneous rupture of the uterus with bleeding to the peritoneal cavity, and disordered blood clotting due to consumptive coagulopathy [5, 28].

Tab. I. Cases of angioleiomyoma uterus found on the ward (N = 9)

No.	Date of surgery	Initials	Age [years]	Body mass (BMI)	Preoperative diagnosis	Surgery treatment	Histopathological diagnosis angioleiomyoma	Other diseases genital
9	17.09.2015	I.U.	48	59 (20.42)	Muscles emerging	BUEM	Angioleiomyoma submucosa	
8	12.04.2014	D.B.	44	58 (20.55)	Fibroid uterus	MM	Angioleiomyoma	
7	11.12.2012	K.N.	60	70 (20.04)	Uterine fibroids Perforation of the uterus	TAH + BSO	Angioleiomyoma necroticans and oedematosum	Endometriosis Endometrial polyp Thecoma right ovary
6	10.10.2012	M.I.	43	60 (25.97)	Fibroids uterus Cervical erosion	TAH + RS	Angioleiomyoma subserosa	Intramural fibroids Cyst serous fallopian right
5	01.10.2009	P.H.	48	86 (33.59)	Fibroids uterus	TAH + RSO	Angioleiomyoma submucosa exulcerans	Intramural fibroids Endometriosis
4	21.08.2008	L.H.	47	72 (24.77)	Fibroids uterus Cervical erosion	TAH	Angioleiomyoma hyalinisans	Endometrial polyp
3	08.04.2003	J.M.	46	60 (26.40)	Fibroid uterus Uterine bleeding	BUEM	Angioleiomyoma submucosa	Endometritis chronic
2	02.10.1998	S.K.	43	63 (26.56)	Many fibroids endometrial Cervical erosion Secondary anaemia	TAH + BSO	Angioleiomyoma intramural oedematosum partly hyalinisans	Ovarian follicular cyst
1	14.01.1998	Ś.B.	45	64 (26.64)	Fibroids uterus Cervical erosion	TAH + BSO	Angioleiomyoma hyalinisans	Endometriosis Endometrial polyp Ovarian follicular cyst

TAH – total abdominal hysterectomy, BSO – bilateral salpingo-oophorectomy, MM – myomectomy, RS – rechten salpingectomy, RSO – rechten salpingo-oophorectomy, BUEM – a biopsy of the cervical canal and the walls of the uterus; evacuation myoma

Perioperative transfusion of blood and blood products was required in four patients (44.4%), four units of packed red blood cells (PRBC) in one patient and two units of PRBC in three patients.

The authors generally agree that surgical total removal of angioleiomyoma either by laparotomy or laparoscopy is a sufficient management because no recurrence has been noted so far [21].

In the majority of cases the treatment involved hysterectomy with or without the resection of appendages. Myomectomy was rare, and its decision depended upon the patient's desire to maintain fertility [21, 31, 37, 45].

In one case presented in Polish literature on the subject the patient was operated on twice because the first operation was not total. The recurrence of tumour was diagnosed within a few months following myomectomy. Histopathological examination confirmed that the tumour was not totally removed, and angioleiomyoma was diagnosed. The tumour recurred three years following the second operation and the patient was prescribed radiotherapy [34].

Discussion

At present the World Health Organization (WHO) does not classify uterine AL as a separate entity or leiomyoma variant in the group of uterine cancers [1, 4, 30].

McCluggage *et al.* proposed a motion to the WHO to include angioleiomyoma among benign variants of uterine leiomyomas [37].

In the examined group, ALs in the uterine body were postoperatively diagnosed in 0.40% cases, and its percentage was higher than that noted in Polish reports on the subject (0.34%) [35]. In our group the patients' ages ranged from 43 to 69 years, and it was within the age range quoted in most reports, i.e. 30-69 years according to Garg *et al.* [21].

Koleskas *et al.* and Ye *et al.* reported the cases of AL *colli uteri* with massive bleeding [42, 44].

Moreover, Handler *et al.*, Hsieh *et al.*, and Hakverdi *et al.* presented cases of multiple angioleiomyoma of the uterine body, too [2, 22, 41].

The analysis of our material found no such cases.

In case of uterine AL, pain results from ischaemia in the AL region due to vascular cramps [22].

Researchers believe that abnormal uterine bleeding, often responsible for anaemia, results from dysregulated growth factors and their receptors, which affect vascular morphology and regulate angiogenesis [22]. Basic fibroblast growth factor is said to play a special role in that pathology [5, 13]. Culhaci *et al.* suggested that massive bleeding might be due to hypertension [25]. Those symptoms might be more pronounced in AL cases compared to leiomyoma [2, 25, 28]. In the examined group as many as 77.8% patients presented with such complaints.

Literature reports found that angioleiomyoma was associated with several episodes of massive bleeding from the genital organs, causing a severe life and health threat [4, 22, 44, 47].

Handler *et al.* reported on a rare case of coagulopathy due to large necrotically altered uterine angioleiomyoma [2]. Kamath *et al.* presented a case of hyperfibrinogenaemia in a patient with uterine AL [28]. Culhaci *et al.* observed rupture of the uterine body due to angioleiomyoma [25].

In the examined group of nine patients with uterine AL, transfusion of blood and blood products was required in 44.4% of patients because of post-haemorrhagic anaemia, and that was 5-6 times higher than the percentage noted on obstetric-gynaecological wards in regional and clinical hospitals (8.2% and 6.6%, respectively) in patients with uterine leiomyomas [48].

In general, atypia, mitosis, pleomorphism, and necrosis are absent in benign uterine AL. However, there are individual cases of atypia and mitosis reported. Thomas *et al.* presented atypia in a patient with increased CA-125 and pseudo-Meigs syndrome [40]. Sahu *et al.* presented a case in which they found focal atypia in addition to mucoid areas and hyalinisation [1]. McCluggage *et al.* observed a case of mitosis of 2 per 10 high-power fields [37]. In one case the areas of mild cellular atypia and slight increase in mitotic activity, mean 3-4 mitoses per 10 power fields, were observed by Manimekhala *et al.* [36].

In some cases degeneration in AL mimics ovarian pathology, which makes diagnosis more difficult, especially if the AL is located on the posterior wall of the uterus [28, 36, 41, 46].

Swelling, mucoid lesions, hyalinisation, accumulation of fibrin deposits, and degeneration were also observed in some reports [1, 22, 37, 40].

Mucoid areas and hyalinised degeneration in uterine AL were reported by Kamath *et al.*, Agorastos *et al.* [28, 46], and Manimekhala *et al.* [36].

In the examined group histopathological microscopy of AL samplings found swollen areas, hyalinisation, necrosis, and even ulceration in uterine AL *myoma nascens*.

The analysis of our material and other reported cases revealed that final diagnosis was made postoperatively only when histopathological investigation was performed [21].

Conclusions

The analysis of our material found angioleiomyoma variant in 0.34-0.40% cases of uterine leiomyomas.

Uterine ALs were associated with a larger number of complications in the course of disease, the consequence of which was a high percentage of required transfusions of blood and blood products (44.4%).

Degeneration in uterine AL, which is observed frequently, makes preoperative differential diagnosis with ovarian tumour more difficult.

Disclosure

Author reports no conflict of interest.

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