

# Natural history of leiomyomas beyond the uterus

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## Abstract

**Rationale:** Most leiomyomas are located in the uterus. Leiomyomas are rarely found outside the uterus and classified as leiomyoma beyond the uterus (LBU). This group consists of disseminated peritoneal leiomyomatosis, benign metastasizing leiomyoma, intravenous leiomyomatosis, parasite leiomyoma located in the broad ligament and retroperitoneal space. The descriptions of the patients who suffer from these types of leiomyomas are presented mainly in case reports.

**Patient concerns:** A 34-year-old multiparous woman was operated on multiple recurrent uterine leiomyoma in parametrium. At one time, 32 leiomyomas were removed. Thirteen months following it, in next laparotomy, 132 leiomyomas were excised. Histologically, both were intravenous leiomyomas (IVLs).

**Diagnosis and Interventions:** In follow-up, computed tomography (CT) and magnetic resonance imaging scans were performed to look for next recurrent leiomyoma. Accidentally, the mass was found in inferior vena cava which was diagnosed as intravenous vena cava leiomyoma. The mass was removed and the final diagnosis of intravenous myoma was confirmed in histopathology.

**Outcomes:** CT scan performed 3 months after the surgery for leiomyoma in vena cava revealed no pathology. Next 10 months' follow-up was uneventful.

**Lessons:** The recurrent multiple uterine leiomyoma precede LBU. The uterine leiomyoma spreads intravenously route to parametria as parasite leiomyoma, then to vena cava. It has to be taken into account in follow-up.

**Abbreviations:** Approx = approximately, BML = benign metastasizing leiomyoma, CT = computed tomography, IIV = internal iliac vein, IVC = inferior vena cava, IVL = intravenous leiomyoma, LBU = leiomyomas beyond the uterus.

**Keywords:** case report, chronology of appearance, leiomyomas beyond the uterus

## 1. Introduction

Uterine leiomyomas are very frequent pathology, which affect 20% to 30% of female population over the age of 35. Leiomyomas may also arise outside the genitourinary tract that is in the vulva, the ovaries, the urethra, and the urinary bladder. But there are some unusual locations and growth patterns of leiomyoma, which are

classified as: disseminated peritoneal leiomyomatosis, benign metastasizing leiomyoma (BML), intravenous leiomyomatosis, parasite leiomyoma located in the broad ligament, retroperitoneal leiomyomatosis.<sup>[1]</sup> The descriptions of the patients who suffered from these types of leiomyomas are presented mainly in case reports. The history of surgery for uterine leiomyoma was documented in most articles. The association between the types of surgery and the time elapsed from the primary surgery of uterine leiomyomas to occurrence of leiomyomas beyond the uterus was analyzed in one of the reports.<sup>[2]</sup>

However, consecutive occurrences of different types of leiomyoma beyond the uterus (LBU) have not been described in the literature. Some reports describe only synchronous occurrence of different types of LBU.<sup>[3,4]</sup> The case reports describe different types of LBU as an individual event in the history of the disease.<sup>[5–8]</sup>

The aim of this study was to present the chronology of occurrence of different types of LBU.

## 2. Case report

The study covers the period of treatment from 2014 to 2018 in the multiparous woman. Sequence of LBU occurrences and surgeries performed in the patient is presented in Table 1.

The patient was first admitted to the gynecology clinic in September 2014 due to leiomyoma recurrence after myomectomy performed in other health care facility in 2012. A repeat myomectomy revealed a leiomyoma of 11 cm in diameter—its microscopic image is presented in Fig. 1.

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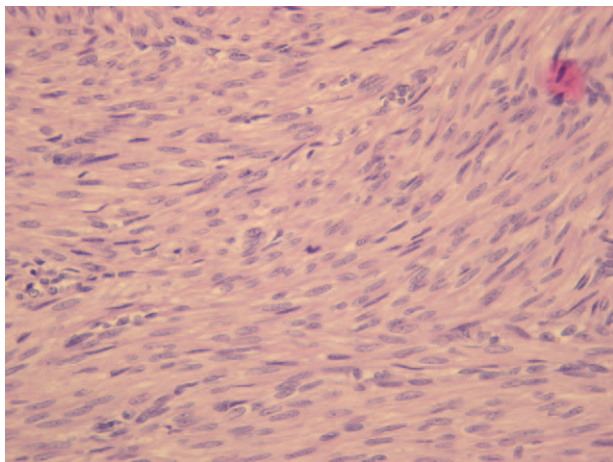
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**Table 1**  
**Chronological sequence in the patient with leiomyoma beyond the uterus.**

Number	Year	Patient age	Type of surgery	Histopathology diagnosis	Lesions location
I	2014	34	Myomectomy	2 myomas (11 cm)	Intramullar
II	2015	35	Parametrectomy with excision of parasitic leiomyoma	Myoma conglomerate	Parasitic
III	2016	36	Adnexectomy + leiomyoma excision of LBU	132 Myomas in retroperitoneal space and cardinal ligament	IVL + parasitic
IV	2017	37	Adnexectomy + myomectomy	Myoma in parametrium	IVL + parasitic
V	2018	38	Excision of tumor in the vena cava inferior	Intravenous leiomyomatosis	IVL

IVL=intravenous leiomyoma, LBU=leiomyomas beyond the uterus.

A year after the myomectomy, the patient reported lower abdominal pain and gynecological examination revealed a leiomyoma conglomerate in the left parametrium. Computed



**Figure 1.** Hematoxylin and Eosin, objective ×10. A typical microscopic view of a benign leiomyoma, with sparse mitosis (2 mitosis/10 HPF), with no necrosis and without marked atypia.

tomography (CT) of October 21, 2015 was suggestive of LBU (Fig. 2A and B). Left parametrectomy was performed and 32 leiomyomas were excised. One of these leiomyomas was present inside the vein—which corresponds to the intravenous leiomyoma (IVL) (Fig. 3)

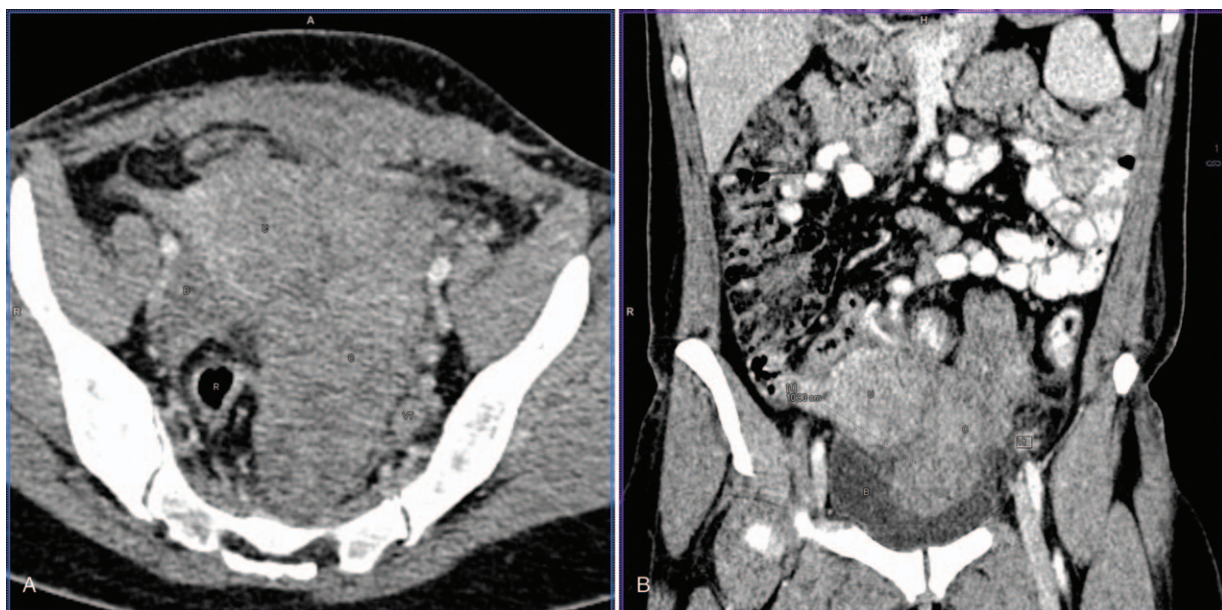
Thirteen months after the above-mentioned surgery the patient started complaining of abdominal pains again. Palpation revealed tumor conglomerate in the left parametrium. CT confirmed the presence of tumor conglomerate of 400 mL in volume (Fig. 4A and B).

During laparotomy, 132 leiomyomas were excised, which corresponded to parasitic leiomyoma. The postoperative view of leiomyomas dissected from the veins of parametrium is presented in Figure 5.

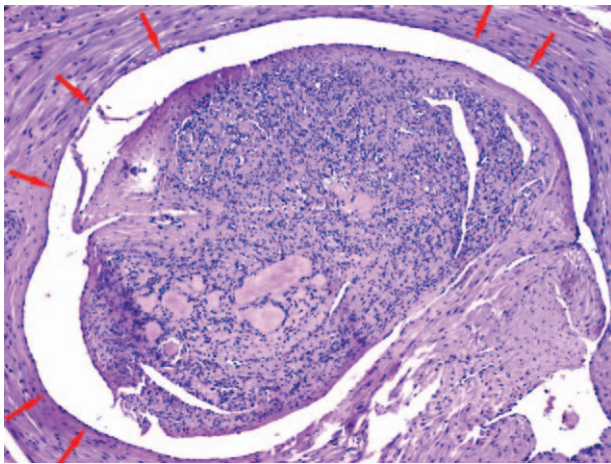
The follow-up CT and nuclear magnetic resonance imaging 1 month after this operation revealed the mass within the inferior vena cava (IVC) (Fig. 6A and B).

The patient was admitted to the cardiac surgery clinic, where the presence of an intravenous lesion was confirmed. The lesion begins in the basin of distal internal iliac vein (IIV) and extended through the common iliac vein to the IVC reaching to the level of the renal veins (Fig. 7).

The laparotomy was performed with median incision and the conventional adhesiolysis was performed, which enabled the



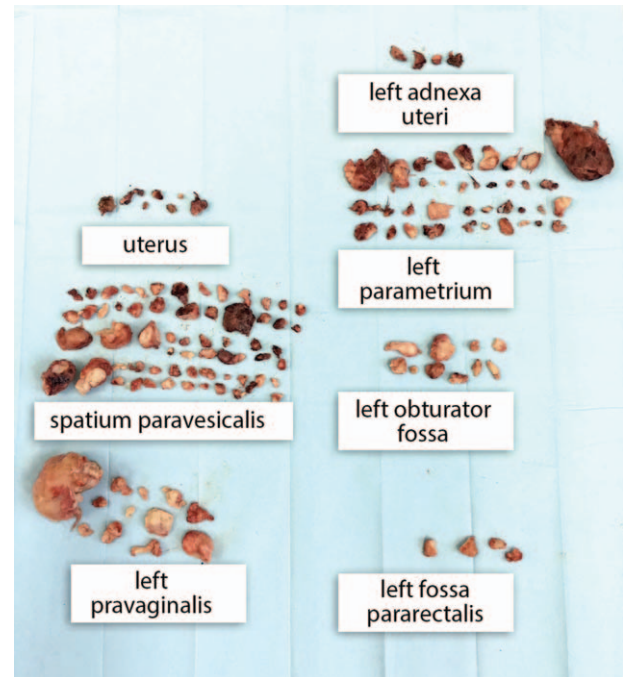
**Figure 2.** (A) Pelvic axial scan ( B=bladder, C=leiomyoma conglomerate, R=rectum U=corpus uteri, VT=dilated venal plexes wider,). (B) Pelvic and lower abdominal frontal scan (B=bladder, C=leiomyoma conglomerate, U=corpus uteri, VT=dilated venal plexes).



**Figure 3.** Hematoxylin and Eosin, objective  $\times 5$ . This very small in size leiomyoma is within the vascular lumen (the arrows show the thin wall of this vascular space)—the phenomenon called intravenous leiomyomatosis.

access to IVC owing to extensive intra-abdominal adhesions caused by the previous surgical procedures. The exploration during laparotomy revealed the solid mass within IVC beginning in the left IIV and reaching below the level of the renal veins as it was shown in Figure 7.

The temporary ligations of the IVC were placed above the lesion to reduce the blood loss during the procedure. The right internal jugular vein was cannulated as a preparation for possible extracorporeal circulation in the case of massive hemorrhage. Additionally, the access to the right femoral vein was protected. Owing to its size, the mass was removed in a 3-step surgical procedure. In the first and the second step, the upper and middle section of the lesion was removed, which appeared to be free-floating within the lumen of IVC (Fig. 7). The lower most



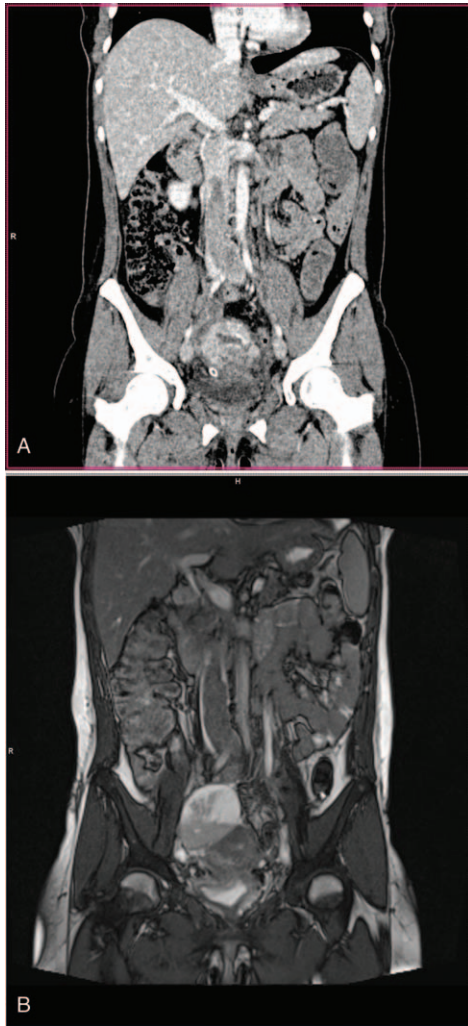
**Figure 5.** Postoperative view of removed leiomyomas which constituted the conglomerate on the Figure (A and B).

cephalad fragment of the lesion was adherent to the IVC wall and had to be peeled off the vein wall. The involved wall of IVC was secured with staplers. Intraoperative view of the evacuated mass is presented in Figure 8A and B.

The frozen section examination describes the lesion as “most probably benign, of leiomyoma characteristics.” The left ureter was injured during dissection of the left iliac veins. It was



**Figure 4.** (A) Sagittal lower abdominal and pelvic scan (B=bladder, C=leiomyoma conglomerate sized 6, 5  $\times$  8, 5, OS=os sacrum, R=rectum, U=corpus uteri). Fig. 4B. Axial pelvic scan (B=bladder, C=leiomyoma conglomerate, U=corpus uteri, VT=dilated venal plexes).



**Figure 6.** A Anterior lower abdomen and pelvic scan (IVL=intravenous leiomyomatosis inside the vena cava posterior). (B) NMR frontal scan.

managed by placing a ureteral doubleJ stent with additional interrupted suturing. During surgery Cell Saver System (Autotransfusion System Xtra Sorin Group Deutschland GmbH) was used to reduce blood loss.

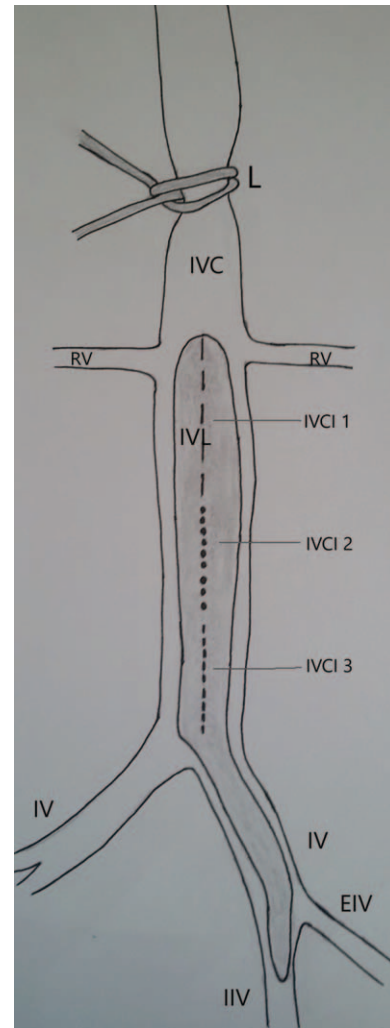
Three months after the surgery, the patient had follow-up examination and CT scan, which revealed no pathology in IVC (Fig. 9). Next 10 months' follow-up was uneventful.

Informed written consent was obtained from the patient for publication of this case report and accompanying images. In our case, the patient consented regular and proved diagnosis and therapy in Obstetrics and Gynecology and Cardio Surgery Clinic, so the ethical approval was not necessary.

### 3. Discussion

Fasih et al<sup>[1]</sup> enumerated leiomyomas outside the uterus according to the locations describing them as a separate disease entity referred to as LBU.

Recently, attempts have been made to find connection between them. Ma et al<sup>[3]</sup> based on the description of 76 cases suggested an LBU classification similar to Fédération Internationale de

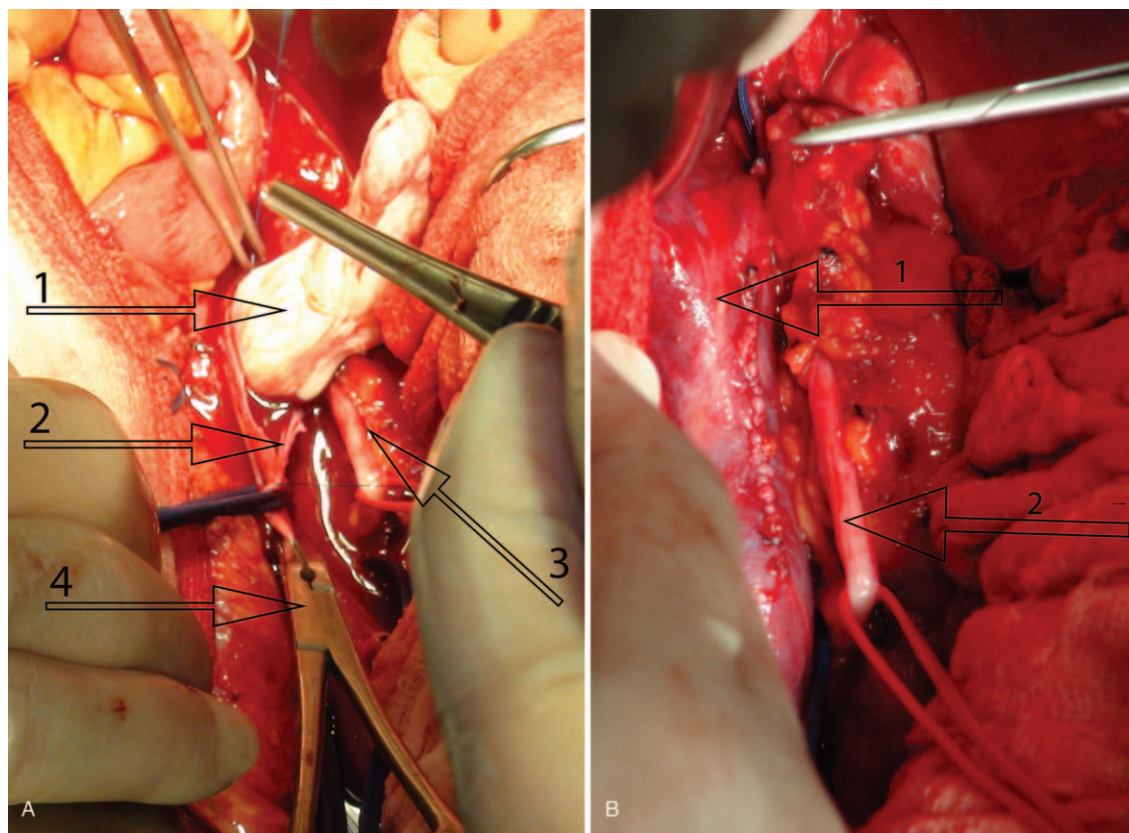


**Figure 7.** Scheme illustrated location of intracaval leiomyoma and basic steps during its removal. 1,2,3=subsequent internal vena cava incisions, EIN=external iliac vein, IIV=interior iliac vein, IV=common iliac veins, IVC=inferior vena cava, IVL=intravenous leiomyoma, L=temporary ligature, RV=renal vein.

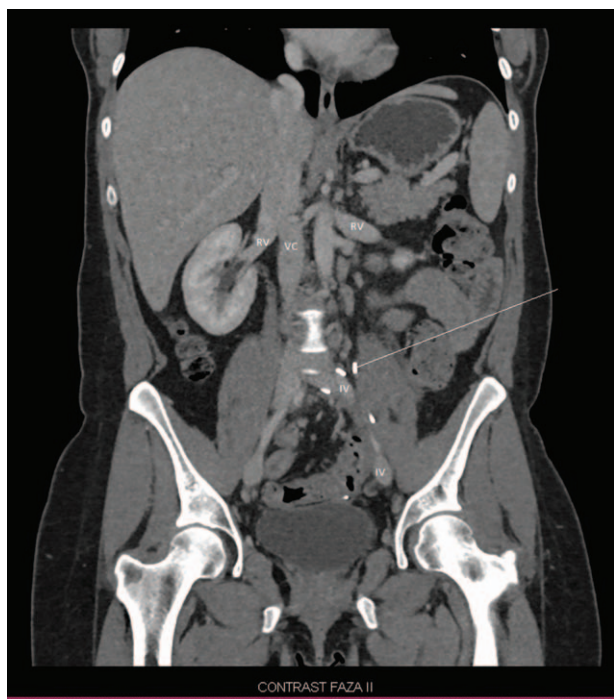
Gynécologie et D'obstétrique oncological ones. This classification assumes that LBU spreads from the pelvic veins to the IVC, the heart, and the lungs. According to this classification, the case described by us is stage II. One of the LBU types is IVL. It may be the link between uterine leiomyoma and LBU, because IVL extending through small veins may develop as parasitic leiomyoma in parametrium or retroperitoneal space.

More currently small pelvic veins unknown in classical gynecological anatomy were "discovered" during studies of the anatomical background of surgical oncological techniques with nerve-sparing.<sup>[9]</sup> Their existence explains how leiomyomata are spreading in these veins creating the picture of parasiting leiomyomas.

According to the literature, >50% of IVL tumors spread through the uterine and IIV, ~25% through the ovarian vein, and ~5% through the internal ovarian and iliac veins.<sup>[5]</sup> According to Castelli et al and Baca Lopez et al,<sup>[6,7]</sup> IVL in the IVC develops in approximately 10% of patients, and in some of them the lesion reaches the heart. In the presented case, 132 parasitic leiomyomas



**Figure 8.** (A) IVL evacuation— intraoperative view: (1) cephalad leiomyoma section, (2) dissected vena cava inferior, (3) the ureter on the right, (4) vessel clump closing the lumen of the vena cava inferior. (B) Status post IVL evacuation— intraoperative view: (1) the vena cava inferior sutured after IVL evacuation, (2) ureter on the right. IVL=intravenous leiomyoma.



**Figure 9.** Computed tomography frontal scan of the abdomen and pelvis 3 months after the surgery of IVL evacuation in vena cava. arrow=staplers on IVL, IV=left iliac vein, RV=renal vein, VC=vena cava.

were myomas inside these veins. Ma et al<sup>[3]</sup> posed an interesting hypothesis that IVLs metastase through the IVC, the right heart to the pulmonary arteries to manifest as BML.

Our study also documents intravascular metastasizing which is in line with Sitzenfrý's theory of pathogenesis of these lesions.<sup>[8,10]</sup> In our patient, the occurrence of intravenous LBU were preceded by four myomectomies in anamnesis. Two of them were recurrent uterine leiomyomas. The other two were multiple recurrent parasie leiomyomas. In the previous study, we did not observe any relationship between certain types of surgeries and increased risk of LBU extension.<sup>[2]</sup>

Our study did not provide a clear answer why some uterine leiomyomas cause metastases described in some articles as benign.<sup>[1-4]</sup>

Leiomyoma characteristics that increase the risk of metastases are difficult to find; however, Quade et al, Kir et al, Biri et al observed that tumor growth was more advanced and the rate of mucoid degeneration was higher in younger patients. Probably that tumor growth may be related to estrogen level.<sup>[11-13]</sup> Notably, uterine leiomyomas and LBU in our case have histopathological image identical to typical uterine myoma.

Some studies suggest that, for example, chromosomal changes may predispose to the extension of leiomyomas via an ectopic route. Dal et al<sup>[14]</sup> observed chromosome abnormality of translocation between 12q15 and 14q24, although no similar abnormality was found in patients with uterine myoma. According to Buza et al,<sup>[15]</sup> recurrent chromosomal aberrations are an important finding likely related to the pathogenesis of this

disease. Ordulu et al<sup>[16]</sup> explained the pathogenesis of IVL with molecular analyses. They suggested that dysregulation of the non-histone chromatin-associated architectural factor high mobility group AT-hook 2, which affects the differentiation and proliferation at 12q14, plays a role in the development of IVL. A cytogenetic and molecular biological study by Quade et al<sup>[11]</sup> revealed an abnormal karyotype of 45XX, der(14)t(12;14)(q15;q24),-22 in all of 12 intravenous leiomyomatosis specimens.

An important conclusion from our case is that the key moment of LBU formation is the identification of leiomyomas in the small pelvic veins. And then the leiomyomas are already proliferating through the continuity of vessels. Therefore, when searching for the etiology of LBU, it is necessary to search for the mechanism of their intravasation to veins. According to Sachdeva et al<sup>[17]</sup> epigenetic factors, in particular microRNA-182, which increases the expression of genes encoding metalloproteins, are responsible for mesodermal sarcoma, which metastasize. It is interesting whether the same microRNA is responsible for the metastasis of other mesodermal tumors such as LBU.

The venous way of proliferation is supported by the fact that in our case, as in other cases,<sup>[10,18]</sup> leiomyomas spread unilaterally, that is, left-sided. There are reports in which the extension pathway occurred through the right ovarian vein<sup>[8,10,19–21]</sup> or bilaterally.<sup>[20,22–24]</sup>

Literature analysis showed that LBU can spread from the internal femoral vein to the IVC directly through the ovarian veins.<sup>[5]</sup> The knowledge of the lesion proliferation through the ovarian vessels is justified by the fact of a smaller number of metastases recorded after removal of the adnexa and gives the same hints on the appropriateness of removing adnexa to prevent relapse. Only Zhang et al<sup>[23]</sup> suggest that the scope of surgery (hysterectomy + bilateral salpingoophorectomy) is debatable and the issue remains to be clarified.

According to Dulu et al,<sup>[10]</sup> the question about the frequency of IVL relapses seems important—it amounted to be 16.67% and concerned young patients, which suggests that the tumor size and age of the patient may be a recurrence factor.

The number of publications on LBU has been increasing during the last 20 years.<sup>[25]</sup> One of the possible explanations is an increase in access to imaging techniques and awareness of a possible diagnosis of this condition. In the presented case, leiomyomas from the IVC have been removed by laparotomy, as in other studies.<sup>[3,5–7]</sup> In our case during surgery the lower most caudal fragment of the lesion was adherent to the IVC wall and had to be peeled off the vein wall. We secured this place by staplers. This step was performed to avoid postoperative bleeding from the veins. In literature there have been 4 reports of death owing to the bleeding from this place.<sup>[26–29]</sup>

Interestingly, ureter injury occurred in our case just like in the study by Yu et al,<sup>[30]</sup> who reported 2 cases of ureter injury in 8 patients.

Our description of an individual case does not allow to draw conclusions about the time between appearances of different types of LBU.

According to the authors, the LBUs have been preceded by the recurrence of uterine leiomyomas followed by the intravenous leiomyomatosis. The intravenous leiomyomatosis spreads through the iliac or ovarian veins to the IVC. Current article provides a basis for taking into account risk factors as an indication for screening.

## Author contributions

**Conceptualization:** Andrzej Skręt.

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**Visualization:** Justyna Filipowska, Mariusz Książek.

**Writing – original draft:** Edyta Barnaś, Andrzej Skręt.

**Writing – review & editing:** Joanna Skręt Magierło.

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