



Case report

Intravenous leiomyomatosis: Case series and review of the literature

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ARTICLE INFO

Keywords:

Leiomyomas
 Leiomyomas beyond the uterus
 Intravenous leiomyomatosis
 Benign metastasizing leiomyomas
 Surgery
 Hormonotherapy

ABSTRACT

Introduction: Intravenous leiomyomatosis (ILV) is a rare pathology, part of leiomyoma beyond the uterus (LBU), characterized by benign smooth muscle cell tumor outside of the uterus and mainly affecting premenopausal woman with a medical history of leiomyoma or gynecologic surgical treatment. The treatment depends on the localization of the tumor, age of the patient, initial size, symptoms and the suitability for surgery but should always aim in toto surgical resection.

Case presentation: Retrospective case series and review of literature.

Clinical discussion: Symptoms presented by the patient were aspecific and only localized in the pelvic area. All cases were fortuitous histopathological diagnosis. No relapse was. Two out of 5 patients have pulmonary nodules, only one was biopsied and diagnosed with PBML (pulmonary benign metastasizing leiomyoma).

Conclusion: IVL and BML are rare disease that can co-exist. Because of tumoral hormonal receptors, hormonotherapy could be an optional treatment but to date no clear efficacy is demonstrated. In case of high recurrence risk such as voluminous initial mass, impairment of broad ligament, failure of total surgical resection, adjuvant hormonotherapy could be useful. Recurrence rate is about 16.6-30% and can occur even dozen years later and even after radical surgery, justifying a regular follow up.

1. Background

Leiomyomas is one of the most common gynaecological benign neoplasia with estimated incidence of 5.4% to 77% of women of reproductive age and characterized by benign smooth muscle neoplasms inside of the uterus [1]. Leiomyomas beyond the uterus (LBU) is defined by benign smooth muscle cell tumor outside of the uterus. Sub classification of this entity is intravenous leiomyomatosis (IVL), benign metastasizing leiomyomas (BML), diffuse peritoneal leiomyomatosis (DPL), retroperitoneal leiomyomas and parasitic leiomyomas [2]. IVL is a rare pathology, first described in 1896 by Birsch-Hirschfeld [3], that affects only woman, and characterized by benign smooth muscle growing within vascular spaces of the venous system [4–6]. Incidence of this disease is about 0.25% to 0.40% of patients who present uterine fibroma [7]. Until now, approximately 300 cases have been reported in the literature.

We hereby present a 20 years retrospective single institution case series of five patients and a review of actual medical recommendations (Table 1).

2. Methods

Respecting the SCARE 2020 criteria we collected the following data of five patients [8].

3. Case 1

A 52 years old nulliparous Caucasian woman known to be overweight (BMI 32), with myomatous uterus, presented to her gynecologist with menometrorrhagia.

Endovaginal echocardiography showed a fundal myoma FIGO 1 of 7x9cm. The thin prep cytologic test and endometrial sampling analysis were normal.

The patient underwent a total hysterectomy with adnexectomy by laparoscopy with no operative complication. The macroscopic operative status was normal. Pathological examination concludes for squamous metaplasia of the endocervical mucosa, leiomyoma and intravenous leiomyomatosis. Microscopic examination revealed no mitosis, no atypia nor necrosis. Immunofixation showed reaction for actin, desmine and

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Received 12 June 2021; Received in revised form 17 July 2021; Accepted 27 July 2021

Available online 31 July 2021

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caldesmon and weak reaction with CD10.

Because of this fortuitous diagnosis, she underwent a cardiac echocardiography which showed no occlusive mass from the inferior vena cava or cardiac dysfunction. A thoracic Computed Tomography (CT) scan pointed well-circumscribed bilateral nodular lung lesions from 4 to 8 mm in the antero-superior and inferior pulmonary lobes (Fig. 1). The patient declaimed no pulmonary symptoms. Because of this highlighting, Positron Emission Computed Tomography (PET-CT) was organized but revealed no metabolic translation of the pulmonary nodules but one posterieur hypercaptive (SUV max 2,2) centrimetric subcutaneous nodule which showed, after cutaneous biopsy, no cellular atypia and was probably lipoma. She underwent a laparoscopic wedge resection of one pulmonary lesion with prior radiological tracking wire. Anatomico-pathological analysis of the pulmonary tissue revealed an intraparenchymal well-defined mass, pushing back the airways tissue to periphery. Final diagnosis is pelvic low grade IVL with pulmonary BML (PBML). Before thoracic surgery, she gets infected by SARSCoV-2 and developed pneumonia with hypoxemic acute respiratory failure but with fast rehabilitation and only needed for oxygen and corticosteroid therapy.

4. Case 2

A 50 years old menopausal woman presented a voluminous uterus with preoperative suspicion of endometrial cancer. She underwent a laparoscopic hysterectomy with adnexectomy without any complication. Macroscopic evaluation of the uterus, fallopian tubes and ovaries was normal. Pathological examination of the uterus showed a quiet well-defined lobulated tumor of 7 cm length inside of the myometrium. The microscopic examination revealed a leiomyomatous tumor with well-developed vascular network and vascular invasion outside of the mass by invasive cords rowing inside of the venous lumen, in direction of the right parametrium. Both adnexa were normal.

No other imaging was organized and the patient was lost to follow up after one year.

5. Case report 3

A 38 years old 1G1P obese (BMI 38) Caucasian woman developed a rapidly-growing uterine mass of 10x8x8cm. The MRI confirmed the uterine origin and objectivated submucosal and subserous development from the mass. Suspecting a sarcoma she underwent an abdominal hysterectomy with bilateral salpingectomy. The post-operative pathological examination denied this diagnosis and revealed IVL.

Immunofixation was negative for CD 10, caldesmon and actin positive. Progesterone and estrogen receptors were highly positive. The surgical margins were free from tumoral invasion. She underwent a complete check up with echocardiography and thoracic CT which found three sub pleural nodules in the apical segment and the inferior part of the laterobasal segment, measuring from 6 to 8 mm. She never underwent pulmonary biopsy, and the control 3 years later showed no progression of those nodules without any hormonal treatment and the

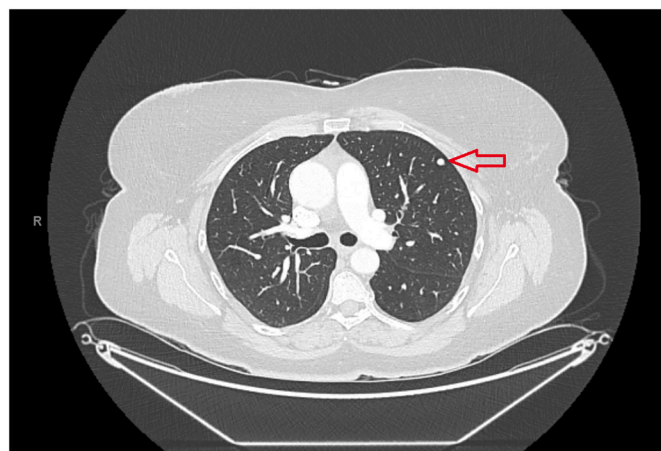


Fig. 1. CT scan showing well-circumscribed millimeter nodular lung lesion of the left antero-superior pulmonary lobe.

patient never complained about respiratory symptoms.

6. Case 4

A 46 years old 3G2P woman with amenorrhea due to intrauterine progestogen device presented with pelvic pain. The endovaginal ultrasound concludes to a myomatous uterus. She had undergone a total laparoscopic hysterectomy with bilateral salpingectomy. Uterus was about 680 g and showed a voluminous whitish fasciculate in appearance mass of 10x8x8cm. Pathological examination concluded with intravascular leiomyomatosis. A thoracic CT showed no other lesions and she was lost to follow up.

7. Case 5

A 43 years old woman suffered from hypermenorrhea. Multi-myomatous uterus was diagnosed with endovaginal ultrasound. Because of failure of a hormonal medical treatment, she underwent a subtotal hysterectomy by laparoscopy with intra-abdominal morcellation. The post-operative pathological examination showed intravascular leiomyomatosis and because of the grinding of the surgical specimen, it was not possible for the pathologists to pronounce if the excision was in healthy tissue.

Six years after diagnosis, she presented no sign of recurrence without any other treatment.

8. Results

Median age at diagnosis of our series is 45.2 years. Symptoms presented by the patient were aspecific (abnormal bleeding and/or pelvic pain) and only localized in the pelvic area. The median uterus weight was 446 g (from 160 g to 752 g). One patient presented a rapidly

Table 1.

Case	Age (yrs)	Menopausal status	Clinical presentation	G & P	Surgical procedure	Tumoral size (cm)	Weight (g)	Histological findings	Staging	Follow up (mo)
1	52	Yes	Menorrhagia	G1P0	TLH + BSO	3	160	Actin, desmin, caldesmon + Factor VII, CD31 +	1	5
2	50	Yes	Pelvic mass	U	TLH + BSO	7	300	Actin, desmin, caldesmon +	1	NED (12)
3	35	No	Pelvic mass rapidly growing	G1P1	TAH + BS	10	752	CD 10 negative, caldesmon, actin +, progesterone 100%, estrogen 80%	1	NED (48)
4	46	No	Pelvic pain	G3P2	TLH + BS	10	680	CD 31, CD34 +	1	LFU
5	43	No	Hypermenorrhea	G53P	STLH + BS	5	340	CD 10 negative, CD 34 et 31 +	1	NED (72)

Abbreviations: BML, benign metastasizing leiomyomas; BS, bilateral salpingectomy; BSO, bilateral salpingo-oophorectomy; LFU, lost to follow up; mo, months; NED, no evidence of disease; TAH, total abdominal hysterectomy; STLH, subtotal laparoscopic hysterectomy; TLH, total laparoscopic hysterectomy, U, unknown, yrs., years.

growing uterine mass suspected for sarcoma.

All cases were fortuitous histopathological diagnosis.

No relapse was identified but two of our patients were lost to follow up and one is a very recent case. Two out of 5 patients have pulmonary nodules, only one was biopsied and diagnosed with PBML.

Patient with PBML get infected with SARSCoV-2 in Mai 2021. She required a short hospitalization 10 days after the first positive Polymerase Chain Reaction (PCR) test. No other case of PBML patient with SARSCoV-2 infection is actually described.

9. IVL: review of literature

9.1. Pathogenesis

Etiology of IVL remains unclear. Two theories postulates for the pathological development: Steinmetz et al. thought that IVL growth form a preexisting uterine leiomyoma which grows and progressively invade vascular lumen [9]. Knauer pretend that IVL could develop by metaplasia from the smooth muscle cells from uterine venular walls [10]. The second hypothesis seems unlikely for Ma et al. because of the absence or rarity of endothelial marker such as CD10, CD 31 or CD34 [7]. However those markers were positive for some of our patients (Fig. 2).

9.2. Histological characters and genetics dysregulation

Histologic description corresponds to typical uterine myoma with immuno-histological reaction for actine, desmin, caldesmon which are muscular markers. Cells exhibit positivity for estrogen or progesterone receptors and mitosis rate is rather low [11].

Some molecular difference are observed in between uterine myoma and IVL such as dysregulation of HOXA13 - a specific gene for embryonic development and cell differentiation [12], or MED12 mutation, which has a critical and central role in RNA polymerase II transcription [13]. A higher rate of chromosomal aberration is observed in IVL despite the fact that both share some molecular characteristics. High-mobility group AT-hook 2 (HMGA 2), a protein acting for mesenchymal differentiation, is suspected in pathogenesis of IVL transformation [14].

Sampling is very important for IVL diagnosis especially to observe not only the tumor but also the smooth muscle tissue surrounding for exact diagnosis [15]. Thanks to the vigilance and the actual attention paid by the pathologist to this diagnosis, IVL is no more underdiagnosed.

9.3. Clinical manifestations

Although IVL is a histologically benign condition, it might have a malignant behavior and typically spreads unilaterally by two possible venous ways from the uterus: through the uterine veins to the iliac veins and then to inferior vena cava (IVC) or from the ovarian veins directly reaching the IVC. IVL never shows any vascular adhesion [6,16] and obstruction of the vascular lumen is never complete [17]. Depending on the localization of the invasion, symptoms are non-specific and can mimic uterine myoma or be as worth as chest pain, dyspnea or cardiac arrest when the tumor invades the cardiac chambers [11]. Risks factors to develop IVL are uterine myoma, previous surgical procedure of the uterus such as hysterectomy or myomectomy and a prior IVL diagnosis [18].

9.4. Imagery

Diagnostic imagery for IVL or follow up is MRI, CT scanner, or echocardiography [19–21]. Echography is useful for IVL with cardiac extension with visualization of intravascular long serpentine, such as multiple stripe-like hyperechogenic lines, filled with colored blood flow [22]. If extension of IVL is restricted inside of the small veins of the uterus, detection is very challenging [15]. It seems that CT is superiors to

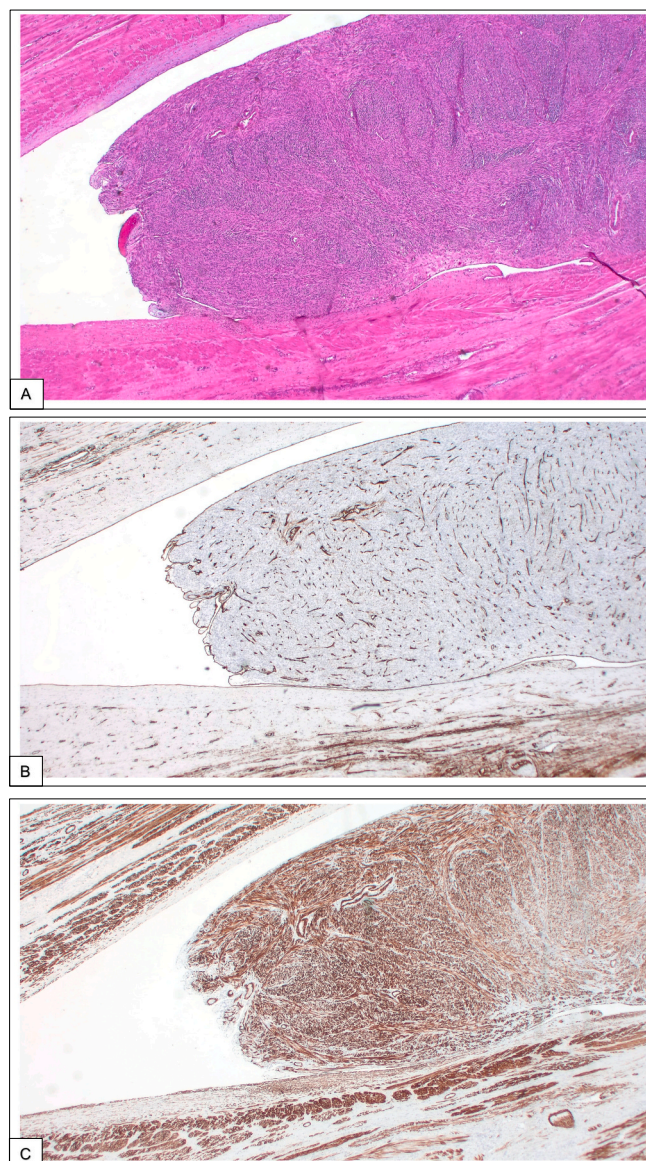


Fig. 2. A, Intravascular tumor almost completely filling the lumen of a small vein with a dense cellular proliferation of uniform spindle-shaped smooth muscle cells (hematoxylin and eosin (H&E), magnification $\times 50$). B, Immunohistochemical brown staining for factor VIII, an endothelial marker, showing an endothelial recovering of the intravascular leiomyoma (magnification $\times 50$). C, Immunohistochemical brown staining for caldesmon, a marker of smooth muscle, showing an intense staining of the intravascular leiomyoma as well as the muscular wall of the vein (magnification $\times 50$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

MRI or US in mapping the full path of tumor extension [19].

Classified in 4 level of extension by MRI or CT, staging is very useful for the pre-operative assessment and organization of a multidisciplinary approach (Fig. 3) [7,23]. In this case series, we only described patients with stage I. PET CT imagery for IVL diagnosis point low metabolic activity in contrast to malignant lesions but shows no other advantage [24].

The differential diagnosis of IVL should include benign myoma, thrombus, leiomyosarcoma, soft tissue sarcoma, lymphoma, cardiac myxoma, tumor thrombosis of Wilms tumor or metastasis [2,25–27].

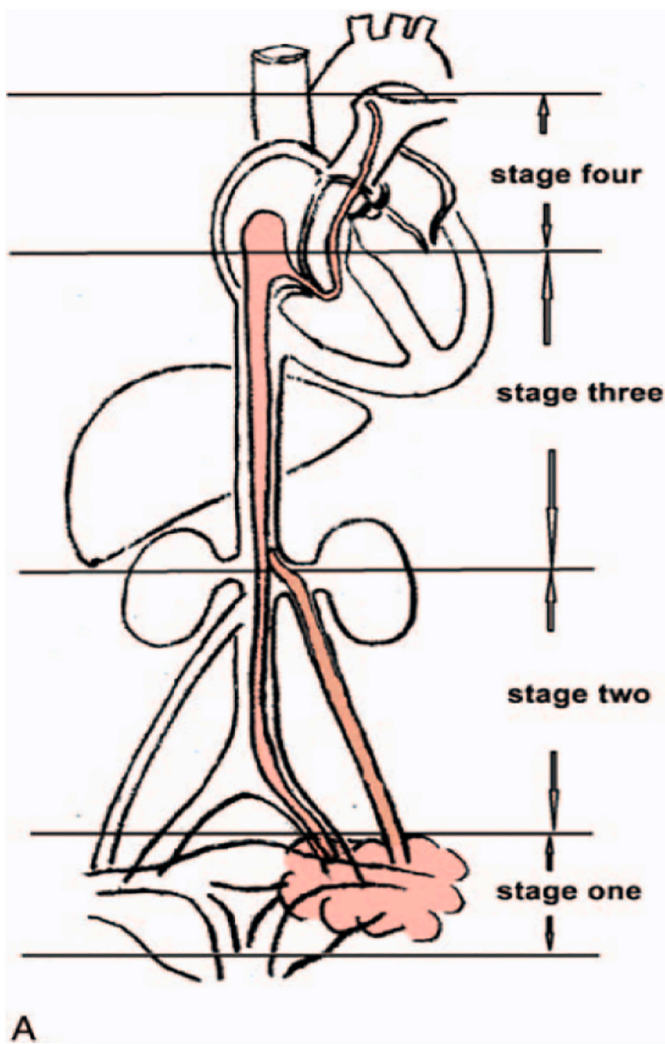


Fig. 3. Stage of intravenous leiomyomatosis was categorized into 4 stages helping surgical management. Stage I corresponds to a penetrative tumor towards the uterine venous wall, but confines to the pelvic cavity. Where tumor has extends into the abdominal cavity, but without reaching the renal vein, categorization is a stage II. If the tumor reaches the renal vein and IVC, or the right atrium, but without reaching the pulmonary arteries, patients were categorized as stage III. Stage IV corresponds to metastases or invasion of the pulmonary arteries.

9.5. Treatment

Treatment of IVL is usually surgery [28]. There is no consensus for the optimal approach for IVL resection [29] but current recommendations for any stages are complete surgical resection such as total hysterectomy. A few cases with simple myomectomy are reported, especially young patients with desire of fertility preserving. Choice of surgical technics (laparoscopy versus laparotomy) seems to have no impact on the recurrence rate and varies among surgeons and mainly depends on the tumors size and the health condition of the patient that impact her tolerance to surgery [7,11]. Few studies propose as gold standard adjuvant therapy to proceed to bilateral salpingoophorectomy followed by hormonotherapy [30].

For more advance stages, depending on the tumoral vascular extension and the suitability for the patient to surgery, early treatment is recommended with a single or double procedure by multidisciplinary team [31,32]. If the tumor reaches cardiac level, sternotomy is followed by abdominal resection by laparotomy. Recent study shows that thoracotomy could be avoided by gently pulling the tumor from the

abdominal level [28]. Nowadays one-stage approach are more frequently proposed because of increased knowledge of this disease [30,33]. Most of the one-stage procedures are performed with cardiopulmonary bypass and total circulatory arrest but it is possible to proceed with heart beating surgery because of the absence of adhesion to the IVC or the heart [34,35]. One stage operation avoid the risk of tumor embolism in between the two operation, tumoral progression or repeated surgery [28,29].

Difficulty of surgery depends more on the degree of tumors invasion and deformation of the vessel walls, than with its length. Complications of major surgical operations are death, hemorrhage due to peri-tumoral hypervascularization, infections, embolism and the usual post laparotomy complications [31,36,37]. To prevent hemorrhage, preoperative embolization of the uterine arteries or uterine arteries ligation may be appropriate [28].

9.6. Quick update on BML

100 cases have been reported [23] with first reported case in 1939 [38]. Despite being also histologically benign, BML shows the metastatic potential of LBU. Reported metastasizing sites are spine, skull, rib, vertebra, parametria, appendix, lymph nodes, retroperitoneum and most of time; lungs [23,24,39,40].

Most accepted hypothesis for PBML is a cell dislodging from the uterine wall during myomectomy or hysterectomy [23], but exact etiology still also unclear. Another hypothesis is that PBML metastasizes because hits low grade malignant power, considering PBML as a differentiated leiomyosarcoma. Third theory states that PBML is neither more a smooth muscle hamartoma nor a metastasis because of its multiple origins sometimes without uterine fibroma [24].

Because of the small interval between IVL and PBML diagnosis, our first case proves that no previous surgical intervention is required for developing BML which was already observed in a small case series [18]. Metastatic potential of LBU is probably inherent at any stage of this disease. A recent publication suggests that the type of surgery does not determine the risk of future incidence [18]. Mean time from primary surgery to BLM diagnosis is often longer with a median of 8.8 years and most of time diagnosis is only made after patients reporting pulmonary symptoms such as cough, dyspnea, chest pain, or even pneumothorax rather than routine imaging monitoring after BML diagnosis [18]. Rarely, PBML causes respiratory failure [41].

10. Discussion

IVL recurrence rate is estimated of 16.6% to 30% [5,42–44]. A few risk factors are nowadays identified such as initial voluminous mass (>7 cm), impairment of broad ligament or failure of total surgical resection [45]. No recurrence was observed in our study. Literature reviews contradict each other if young patient presents a higher risk of recurrence [46,47] but IVL is more frequent in premenopausal woman.

Because of estrogen and progesterone receptors, tumoral growth seems to be related to the hormonal level [47] and exogenous estrogen must be avoid [48]. To date regarding treatment for IVL, no clear efficacy was demonstrated for adjuvant hormonal treatment such as gonadotropin-releasing agonist, aromatase inhibitor or selective estrogen receptor modulators (SERM). Hormonal medication might be considered in case of high risk of recurrence such as a big initial tumors size or incomplete surgical resection. Some study recommend the use hormonal therapy, especially if the patient is premenopausal, in case of recurrence or in order to reduce the tumor size if the patient declines surgery [49–57], but the side effects of premature menopause have to be balanced with the eventual benefices of this medication [58]. A case with increase of tumor burden was described after Tamoxifen treatment emphasizing the necessity to consider carefully the indication of hormonal therapy [59]. Radiotherapy at low doses is described in patients at high risk of recurrence [60].

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