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Case Report

Intravenous leiomyomatosis: A case study and literature review☆

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ABSTRACT

The dissertation presents a case of intravenous leiomyomatosis and conducts the literature review. A 31-year-old woman with a hysteromyomectomy history presented with abnormal uterine bleeding and anemia, a large pelvic tumor, underwent excision of the uterine and bilateral salpingo-oophorectomy. A pathological diagnosis determined it as intravenous leiomyomatosis. The patient recovered well, and no recurrence was noted after 1 year of follow-up. Intravenous leiomyomatosis is rare. Imaging is helpful, but the final diagnosis of intravenous leiomyomatosis is usually made following surgical excision and histopathology. Early surgical resection is a better treatment modality.

Introduction

Intravenous leiomyomatosis (IVL), a rare leiomyoma condition, is characterized by nodular masses of histologically benign potential malignant muscle cells growing within veins. The IVL incidence is low; fewer than 300 patients with IVL were reported before 2018. However, its recurrence rate is high, and its mechanism remains unclear. In the early stages of IVL, patients may be asymptomatic despite extensive IVL. When symptoms manifest, IVL would have reached the pelvic involvement stage. Hence, early diagnosis is difficult and always needs imaging methods. Complete surgical resection is one of the treatment options for IVL, with pathological diagnosis as the gold diagnosis criteria. Difficulty in early diagnosis and extremely low incidence results in a high preoperative misdiagnosis rate. We analyzed the clinical features, pathogenesis, pathological characteristics, surgical techniques, and prognosis through a case study and literature review. This study aimed to assess a better surgical strategy for treating

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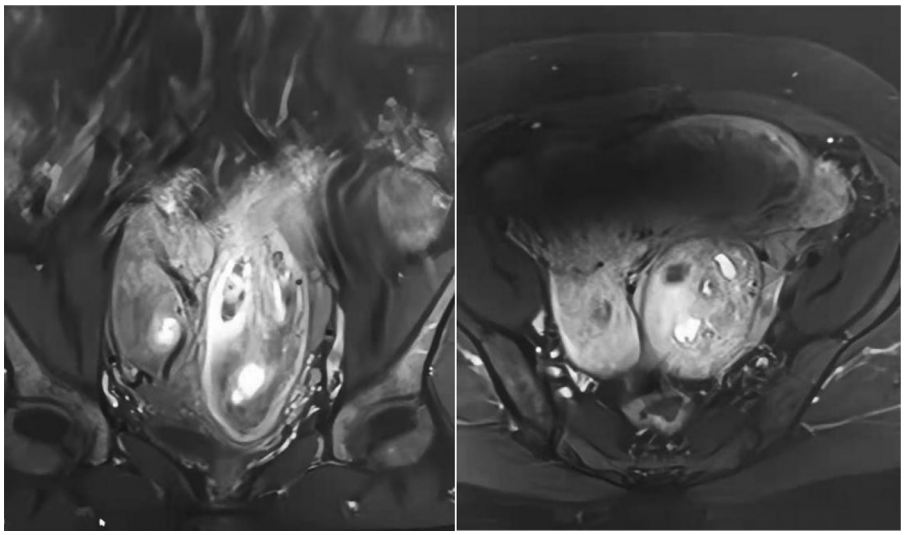

Fig. 1 – The magnetic resonance imaging of intravenous leiomyomatosis.

IVL. We also noted the limitations in disease management of the case study to suggest a new guide for similar cases.

Case presentation

A 31-year-old woman (gravida 0, para 0) was admitted to the hospital in 2016 for a giant mass and excessive bleeding for 1 year. The pelvic examination showed a uterus as large as 5-month pregnant, uneven surface, and poor activity. The hysteroscopic examination showed a prominent anterior uterine wall and no noticeable fibroid nodules. Abdominal ultrasound revealed a huge multiple uterine fibroids tumor, intrauterine solid heterogeneous echo 10.0 × 8.8 × 7.4 cm (submucosal fibroids?). Hemoglobin was found to be 80 g/L. The subject had undergone uterine myomectomy on September 1, 2016, because she was childless. During the operation, the fibroids were soft, round, finger-like, and cord-like, with no obvious boundary between the fibroids and the surrounding pseudo-envelope. The freezing pathology during surgery resulted in degenerated uterine fibroids with an intraoperative blood loss volume of about 1200 mL. Paraffin pathology: uterine leiomyoma. After the surgery, the patient was treated with gonadotropin-releasing (GnRH-a) hormone for 3 months, and it was observed that 1 month after the last GnRH-a, menstruation recovered, with the amount of bleeding equaling the preoperative bleeding. The ultrasound examination revealed uterine fibroids. The regular follow-up review showed a gradual increase in fibroids, severe anemia requiring intermittent blood transfusion. She was admitted to the hospital once again in July 2020 because of severe anemia. A magnetic resonance imaging (MRI) scan confirmed these ultrasonic findings, suggesting IVL. The tumor had invaded the left iliac crest, the common iliac vein, and the inferior vena cava (Fig. 1). During the second surgical operation, the pelvic adhesions were dense. After separating the adhesion, the uterus looked 5-month pregnant, with a purple surface, rich blood vessel, thickened bilateral pelvic funnel ligament, and touching multiple cord-like tissues in the vein (Fig. 2A). Hysterectomy was done because of the rapidly growing fibroid. During the hysterectomy, many rope-like muscle tissues were observed in the pelvic vein (Fig. 2B). When forceped, the rope muscle tissues were worm-like that could shrink by themselves. The freezing pathology during surgery, IVL, and bilateral salpingo-oophorectomy were performed on the patient. Higatured ovarian arteriovenous in the high-level surgery called for pulling out the muscular tissue gently from the pelvic funnel ligament vein, uterine vein, and vaginal vein (Fig. 3). The intraoperative blood loss volume was about 2000 mL.

Vena caval angiography after surgery indicated the pelvic vein filling defect, approaching iliac vascular level. Several nodules were observed between the uterine muscle walls, separated from the surrounding tissue, in the official cavity with gray-white sections and medium texture. The tumor microscopic image showed long spindle-shaped tumor cells woven into a bundle-like arrangement, which was rich in cytoplasm, eosinotropic, located partially in the vein with low nuclei division (1-2/10 HPF). The IVL immunohistochemistry examination revealed tumor cell vimentin, calponin, smooth actin, platelet-endothelial cell adhesion molecules 31, platelet-endothelial cell adhesion molecules 34, estrogen and progesterone receptors (+), MyoD1, actin, broad-spectrum cytokeratin, CD10 (–), and low Ki67 (3%). No drug supplements were given after the surgery, and the patient was reviewed every 3 months; no abnormalities were reported.

Pathogenesis

Histologically, IVL, closely associated with hormones, resembled typical benign uterine leiomyomas at the gross and microscopic levels. The aggressive invasion of IVL, such as malignant tumors extending outside the uterus along the vasculature, spreading to the iliac vein and inferior vena cava. It eventually affected the right atrium and pulmonary and seriously impacted the patient's prognosis, which could be life-

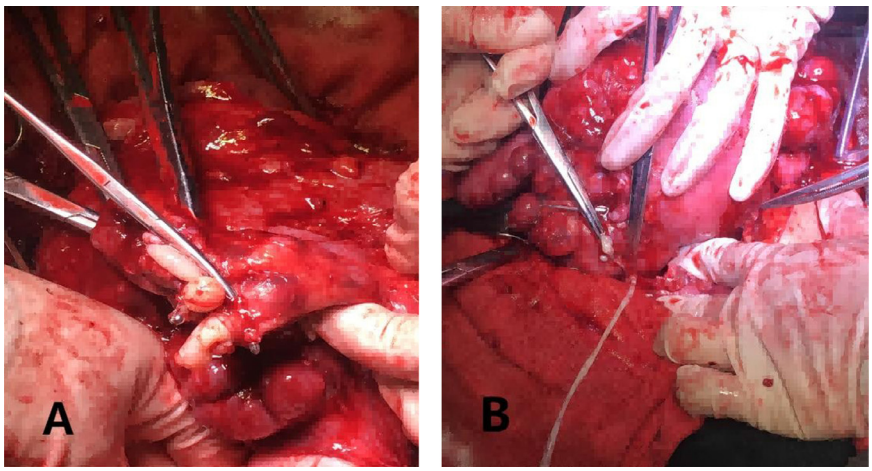

Fig. 2 – (A), the intravenous leiomyomatosis in the uterine vein (B), the worm-like intravenous leiomyomatosis.

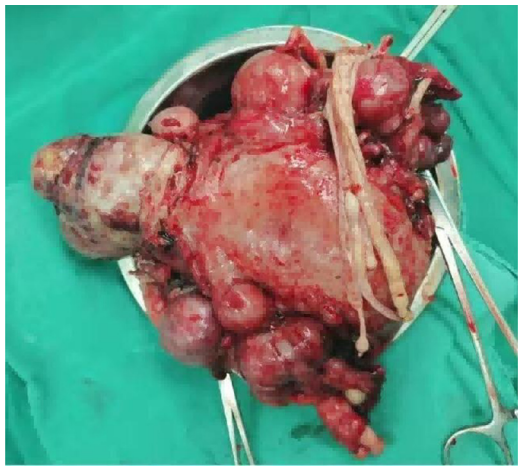

Fig. 3 – The vast muscular tissue from the pelvic funnel ligament vein.

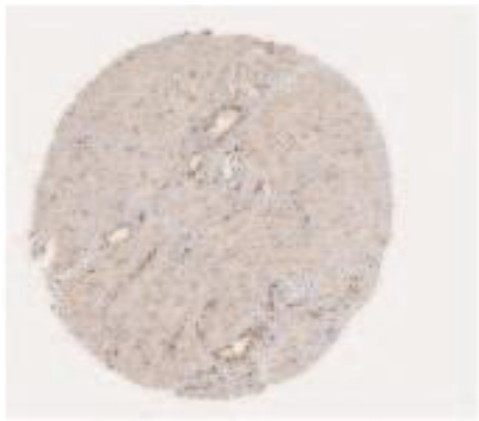

Fig. 4 – MED 12 in the smooth muscle.

threatening [1]. The IVL, first reported by Birch-Hirschfeld in 1896 [2], had more than 200 cases worldwide by 2013 [3]. With increased awareness of the disease, Hu et al. [4] reported 52 cases in 2013 and Fang et al. [5] reported 64 cases in 2015. However, only one case had been reported in our hospital for nearly 30 years.

Currently, there are 2 hypotheses regarding IVL origin; the first one traces IVL's origin from the muscular tissues, whereas the other one contends IVL's origin from myoma tissue infiltrating into the myosphere, or maybe the concurrence of 2 hypotheses [6]. Simple IVL without uterine fibroids has been rarely reported, and most scholars are inclined to the first view at present [7]. Our case showed a continuation of intravenous and intravascular smooth myoma tissues with no adhesion to the vascular wall. Furthermore, the patient's first pathology suggested uterine fibroids only, agreeing with the first hypothesis. However, IVL with cardiac involvement without extending to inferior vena cava indicated that the tumor cell cultivation in the vascular endothelium was one of the possible reasons for the dissemination within the venous system [8]. The expression of HMGA2 (locus 12q14.3) in IVL might be associated with chromosomal rearrangement [9]. The loss of 22q12.3-q13.1 and the absence of the G>A transition at nucleotides c.130 or c.131 were associated with a high-level genetic instability [10]. Wang et al. [11], through RNA sequencing analysis, suggested that IVL and uterine fibroids were different solid tumors. Therefore, a specific IVL pathogenesis remains unclear till now.

MalaCards disease database with a high authority was used for predicting the genes. Through the MalaCards database mining, the important gene associated with IVL are Mediator Complex Subunit 12 (MED12), Estrogen Receptor 1 (ESR1), Desmin (DES), High Mobility Group AT-Hook 2 (HMGA2), Membrane Metalloendopeptidase (MME), GATA6 Antisense RNA 1 (Head To Head)(GATA6-AS1), Progesterone Receptor (PGR), Caldesmon 1(CALD1), CD34 Molecule (CD34). Among these genes, MED12 is the main gene. Its expression in the smooth muscle is high (Fig. 4). We expect to validate the gene in the experimental next.

Pathological characteristics

About 94.34% of IVL patients had uterine fibroids or previous history of uterine fibroid surgery as reported. The gross uterine specimen showed an irregular mass enlargement. Fan et al. [5] reported mass as large as 8-month pregnant. The incision revealed a vortex, tough or somewhat soft texture, and the winding and widened surface veins. The typical gray worm-like structures were visible in the local and surrounding myometry—along the pulse lumen to under the uterine plasma membrane. The present case study reported purplish-red uterine surface, rich in blood vessels, with thickened bilateral pelvic funnel ligaments. Multiple stripe cord-like tissue inside the vein during the surgery was touched. The worm-like tissue could be pulled out from the broken end of the ovarian vein (Fig. 4) that persisted weakly after being touched and was considered for smooth myoma tissue after stimulation. All these features were in accordance with the characteristics mentioned by Fan et al. [6]. The microscopic appearance varied significantly, even within the same tumor. Several histological variants exist based on the cell type, including epithelioid leiomyoma, myxoid leiomyoma, and lipoleiomyoma. None or very few nuclear division images, generally <2/10 high field, without nuclear atypia have been reported. Malignant degeneration of IVL has not been reported. The positive expression of several factors, such as smooth actin SMA, the peritumor vascular endothelial markers (CD31, CD34), or factor VIII, constituted an important IVL diagnostic basis, in addition to being the primary identification point from the ordinary uterine leiomyoma. The patient's first operation was fibroidectomy, and the postoperative pathology was uterine leiomyoma. However, earlier literature reported misdiagnosis due to removal of the surrounding tissue along with the fibroid tissue if the fibroid mass is pulled out blindly. The screening sample is crucially important for the early diagnosis of the disease. The important points to consider for accurate diagnosis include detecting the whole pelvic before opening the uterus, scrutiny of the intrauterine tissue and whole uterus, and correct removal and burial of the uterus (cut the normal muscle layer parallel to the tumor and embed the tissue mass preventing the section of the vein from avoiding misdiagnosis). The first surgery diagnosed the tumor as intravenous leiomyoma, which is due to the misdiagnosis of the surgeon or pathologist.

Imaging characteristics

The misdiagnosis rate is exceptionally high due to the lack of specificity in the clinical manifestations of IVL. A review of nearly 200 domestic documents showed only 9 IVL preoperative cases. Most preoperative cases were misdiagnosed as uterine fibroids and used color Doppler ultrasound for detection. A typical acoustic image showed multiple low-echo nodules between the muscle wall that fused with one another, and the dendritic or bar blood supply at the fibroid site. When the lesion involved the iliac vein, ovarian vein, and inferior vena vein, there was significant lumen expansion, visible moderately echo mass of uneven bars, and no deformed veins during the pressurized probe [11]. The tumor in the right heart of the lesion was multi-boundary and tasteless, showed a uniform equal echo, and did not attach to the right or venous wall of the heart. The mobile tumor often moved [12] back and forth near the tricuspid valve of the right atrium [13]. Computed tomography (CT) and MRI are used to characterize the complex abdominal mass for the origin of the tumor and its site of venous invasion. CT is rapid and less expensive, while MRI differentiates soft tissue composition better, facilitating identification points for the intravenous component attachment. A retrospective analysis by He et al. [14] reported that foci transferred to the inferior vena vein showed continuous uneven filling defect shadow on phase III enhanced CT, with lesions showing "sieve hole" changes on the transverse axial position and "flesh"-like changes on the coronal images after multiplanar recombination. Thus, in cases of highly skeptical IVL, CT and MRI combined with the patient's medical history, color Doppler test, and the preoperative speculative diagnosis can be used to develop the surgical method and to make preoperative preparation.

Common complications

Early stages IVL can be asymptomatic, and the first symptoms of IVL are often isolated syncopal episodes, pelvic mass, abdominal pain, more menstrual volume or a combination of these [15]. When it invades the lower vena cava, right atrium, and the pulmonary artery, syncope, and dyspnea could occur. The IVL's special growths are different from an ordinary uterine leiomyoma and have histopathologically benign manifestations characterized by aggressive behavior such as invading venous and lymphatic vessels. In some cases, it can even involve the right heart or form lung metastases in the direction of venous reflux and cause sudden death [16]. It grows not only along the uterine and ovarian vessels but also along the traffic branches of bladder vessels, cervical vessels, and vaginal vessels. Leiomyoma tissues were also observed in the vessels of the vaginal wall. Therefore, the IVL intraoperative cervix treatment should involve steps to prevent damage to the bladder, ureter, and other structures and avoid misdiagnosis caused by recurrence or embolism. If the tumor in the blood vessels adheres tightly to the vessel wall making its removal difficult, it is advisable not to pull out the tumor forcefully. It may lead to blood vessel rupture, threatening life and even causing death. Huang et al. [17] reported a case where doctors removed the tumor in the right atrium and inferior vena cava vein successfully, but trying to remove the tight pelvic tumor caused uncontrolled bleeding in the pelvic vein and eventually resulted in the death of the patient. Therefore, clinicians should evaluate the operational difficulties and risks accurately. If needed, the operation should be stopped when faced with challenges. In cases where the lesion cannot be removed completely, the blood vessels above the lesion should be firmly tied up to prevent the spread of the tumor.

Treatment

The ILV treatment has 2 goals: (1) to remove the tumor, and (2) to prevent the recurrence [18]. A literature review reveals that recurrence rates are very low for simple hysterectomy and bilateral salpingo-oophorectomy [19]. Myomectomy is suitable

only for young women who need to remain reproductive because of its high recurrence. The tumor recurrence time shows a close relation to thrombolysis. However, no exact recurrence rate has been reported so far. Therefore, it is necessary to have a long-term follow-up after the surgery. Given that estrogen and progesterone receptors are present in the leiomyoma cells, bilateral salpingo-oophorectomy is the essential modality for tumor removal. However, exogenous estrogens must be avoided to prevent subsequent growth of microscopic or unresected foci of intravenous leiomyoma. For the non-castration cases, post-surgery hormone therapy should also be considered. GnRh-a or antiestrogen therapy has also been used to prevent tumor growth and reduce the tumor mass but with little success. The patient in the present case study was given GnRh-a for 3 months after the surgery, and the progression-free duration was only 1 month, suggesting that GnRh-a had little effect on the IVL treatment. Some scholars believe that fast-growing tumors are ineffective against estrogen treatment. Short-term recurrence after the first surgery may be related to the residual lesion [20]. The second surgery involved hysterectomy and bilateral salpingo-oophorectomy, with the ovarian arteriovenous vein tied at a high level. The vascular color ultrasound postoperation indicated the iliac-vein-filling defect, but there was no recurrence, which could be related to the resection of bilateral ovaries.

Case limitations

This was the first case of IVL in our hospital in the last 20 years. We had no experience with this disease, especially when it was confirmed after the second surgery. The case review showed that some fibroids described during the operation were finger and cord-like. However, we should also consider some special types of fibroids related to the disease. If the diagnosis confirmed IVL and estrogen sensitivity, an extended GnRh-a supplementary therapy should be given in addition to observing the menstrual flow closely. The second surgery was at the age of 31 only; the patient still went ahead with uterine removal and bilateral salpingo-oophorectomy due to rapid growth of fibroids and severe symptoms. Moreover, there was no angiography before the second operation. Better evaluation of the lesion location in the blood vessels could assist in endovascular lesion removal at the same time as the uterus. The patient's postoperative vascular color ultrasound still indicated the iliac vein filling defect, and hence needed life-long close follow-up considering the lesion residue. Alexandra et al. [21] reported a case of cardiac metastasis characterized by progressive dyspnea and syncope, misdiagnosed by thrombus, and reported no improvement in symptoms after anticoagulant therapy, reflecting the lack of understanding of the disease. The author believes that the IVL possibility should be considered when the irregular swelling of the uterus and the surrounding area extends along the vascular system and thickens the pelvis. Comprehensive imaging should be done, followed by a perfect surgical plan and near-accurate risk estimations of the operation. The IVL concealment causes ambiguous clinical evaluation, and the lesions become widespread, vascular microthrombosis occurs when hysterectomy is done. Alternatively, the recurrence rate is as high as 16.6% due to lack of experience and ignoring the uterus, ovary, and inferior vena cava lesions, necessitating a long-term follow-up. The present case has been followed up for more than 1 year and reported no recurrence. It is possibly because the follow-up time was short, which needs to continue for life.

Discussion

IVL is a benign smooth muscle tumor of the uterus that grows within the veins but does not invade the surrounding tissue. It often occurs in perimenopausal women with symptoms such as pelvic mass, abnormal bleeding, phlebothrombosis, or a right atrial mass. IVL usually starts in the veins of the uterus and can extend into the inferior vena cava and ultimately into the right side of the heart, resulting in death. Early detection and accurate diagnosis are imperative for appropriate treatment. The abnormal smooth muscle cells that cause IVL express estrogen and progesterone receptors, and tumor growth thus appears to respond to these hormones. Although this is a benign condition, many affected individuals require surgery to remove the excess tissue in the uterus and heart. Complete resection in cases of IVL has been essential for a good prognosis regarding remission/recurrence. For cases in which a complete surgical resection is impossible, bilateral salpingo-oophorectomy or hormone therapy using GnRh-a following surgery has also been recommended, although neither has been able to produce as good a prognosis as a complete resection. The drugs Ethanol and Sirolimus have been mentioned in the context of this disorder. Long-term follow-up is suggested owing to the possibility of recurrence.

In conclusion, IVL is rare and may be located in the uterine and vessels, and ultrasound or MRI may aid in the diagnosis. Differential diagnosis includes uterine leiomyoma, benign metastasizing leiomyoma, adenomysis, or myofibroma. The primary treatment should be surgical excision with long-term follow-up.

Patient consent

We have obtained the written informed consent of patient permission for the publication of the case report.

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