



Multimodality imaging applications in the diagnosis of and surgical treatment strategy for intravenous leiomyomatosis: a case description and literature analysis

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Introduction

Intravenous leiomyomatosis (IVL), which predominantly affects premenopausal, parous women, is a rare but histologically benign tumor exhibiting aggressive venous and cardiac extension. Its non-specific symptoms often lead to a complicated diagnosis. Multimodality imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), plays a crucial role in its identification. Treatment typically involves total hysterectomy, bilateral salpingo-oophorectomy, and resection of the intravenous tumor, demanding multidisciplinary surgery, especially for intracardiac involvement.

Case presentation

During a routine body check-up at a local hospital, an incidental finding of a large pelvic mass was identified in a 49-year-old female patient. The patient was subsequently transferred to Wuhan Union Hospital for comprehensive evaluation. Upon admission, her vital signs were normal.

She had a history of two vaginal deliveries, and the physical examination was largely normal, with the exception of hypertension. Her results were as follows: blood pressure: 154/107 mmHg; weight: 61 kg; height: 156 cm; and body mass index: 25.07 kg/m² (overweight). Tumor marker carbohydrate antigen 125 (CA 125) and other blood and biochemical markers remained within normal ranges. ST segment and T wave changes were observed on the electrocardiogram.

Comprehensive diagnostic imaging of the chest, abdomen, and pelvis, including CT and MRI, was conducted. Contrast-enhanced CT scans revealed a hyperattenuating mass originating from the left genital vein, extending sequentially through the ovarian vein, renal vein, inferior vena cava (IVC), and finally into the right atrium of the heart (*Figure 1*). Cardiac cine MRI revealed a free-floating, solid mass in the right atrium that moved into the right ventricle during diastole and retracted during systole (*Videos 1,2*). Enhanced MRI revealed a substantial lesion with heterogeneous enhancement on the anterior wall of the uterus. Additionally, consistent linear filling defects

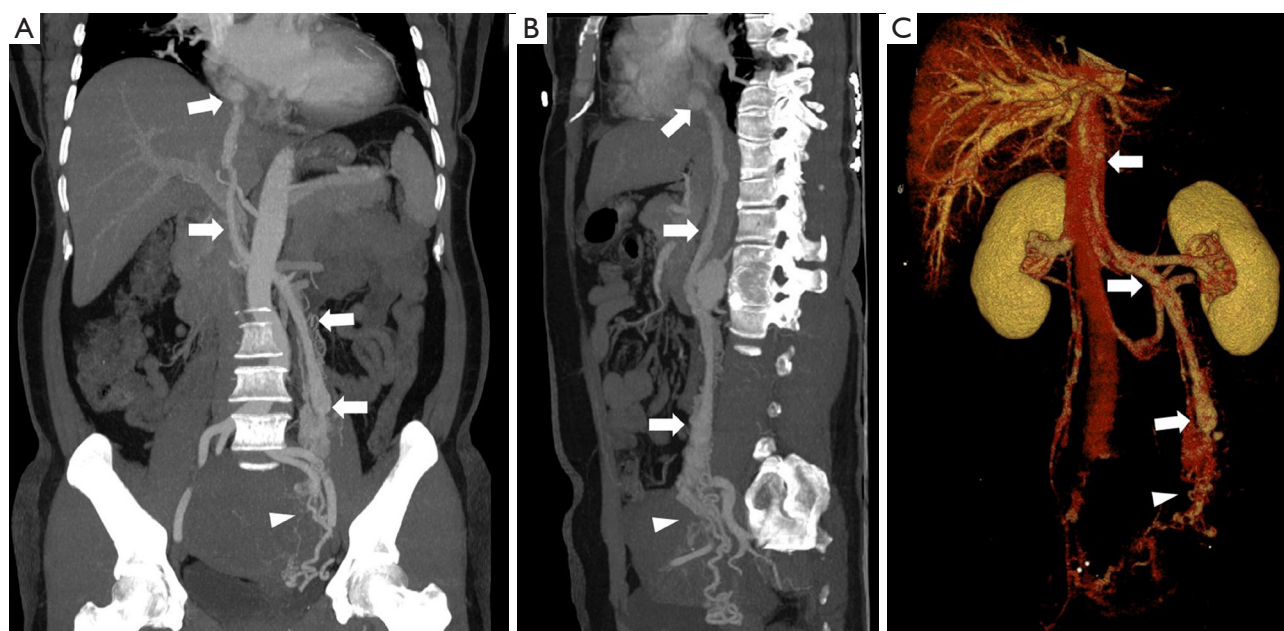
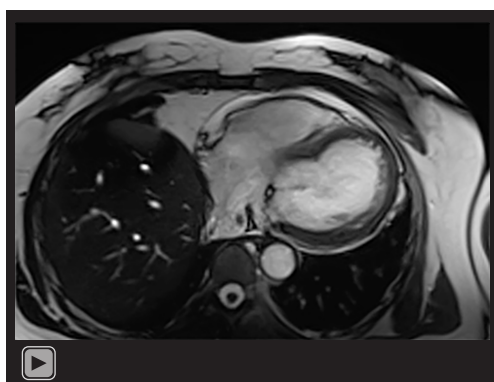
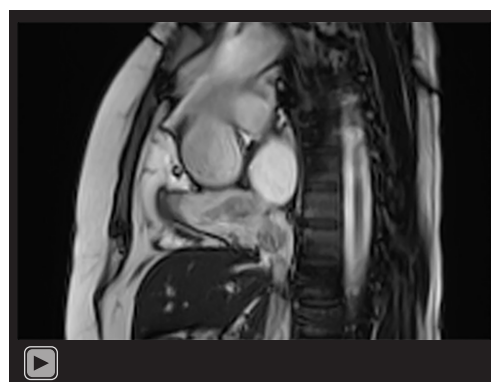


Figure 1 Contrast-enhanced computed tomography scans. The coronal reconstruction (A), sagittal reconstruction (B), and volume rendering (C) images showed a cord-like mass (arrows) in the lumen of the left ovarian vein, extending to the inferior vena cava and right atrium. Varicosity and dilatation of the left genital vein were observed (triangles). No significant enhancement was observed in the enlarged uterus.



Video 1 Cardiac magnetic resonance imaging cine of the four chambers revealed that the mass in the atrium traversed the outflow tract from the right atrium to the right ventricle during diastole, and returned during systole.



Video 2 Sagittal cardiac magnetic resonance imaging cine revealed that the mass ascended from the inferior vena cava into the right atrium, exhibiting regular movement with the cardiac cycle and protruding into the right ventricle during diastole.

were observed in the left ovarian vein, left renal vein, and proximal IVC (*Figure 2*). On axial imaging at the level of the IVC and left renal vein, the lesion demonstrated moderate intensity on T1-weighted imaging and low intensity on T2-weighted imaging. Following contrast enhancement, it exhibited marked enhancement with a sieve-like appearance

(*Figure 3A-3D*).

These findings cumulatively led to a diagnosis of uterine IVL. A multidisciplinary team, including cardiothoracic surgery, gynecology, vascular surgery, urology, and anesthesiology specialists, collaboratively discussed treatment strategies to ensure a comprehensive therapeutic

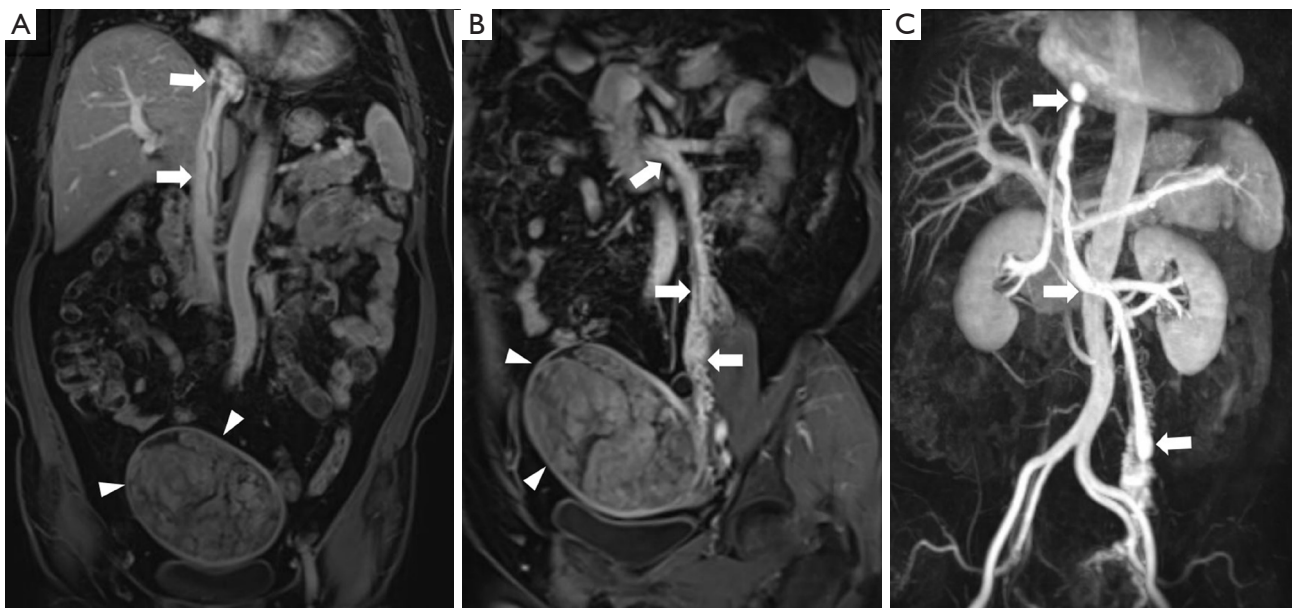


Figure 2 Gadolinium-enhanced magnetic resonance imaging scans. The enhancement of the cord-like mass was more discernible on the magnetic resonance images than the computed tomography scans due to the superior soft tissue contrast (arrows), and linear filling defects were also prominently visible. An inhomogeneously enhanced, enlarged soft tissue mass was identified on the anterior wall of the uterus (triangles). (A) Coronal reconstruction. (B) Oblique-sagittal reconstruction. (C) Maximum intensity projection in magnetic resonance angiography.

approach. The patient underwent a successful single-stage surgery, comprising bilateral salpingo-oophorectomy and hysterectomy, followed by the excision of intravenous tumors from the IVC and right heart, facilitated by cardiopulmonary bypass.

The postoperative pathology results corroborated all the prior examination findings (*Figure 3E,3F*). The immunohistochemical (IHC) results demonstrated positivity for smooth muscle actin (SMA), desmin, human caldesmon (h-caldesmon), partial positivity for cluster of differentiation 10 (CD10), estrogen receptor (ER), progesterone receptor (PR), and fumarate hydratase (FH) without loss of expression. Conversely, cluster of differentiation 34 (CD34) and S100 protein were negative, and the Ki-67 labeling index was 1%. Follow-up examinations at 1- and 3-month post-surgery showed excellent recovery without complications.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

IVL was first documented by Birch-Hirschfeld in 1896 (1). In 1907, Durck reported the earliest known case of IVL with cardiac extension (2). This histologically benign smooth muscle tumor originates either from the direct extension of a uterine leiomyoma into adjacent veins or from vascular intimal smooth muscle proliferation (3,4). IVL is rare, especially when it extends into the heart, which occurs only in 10–40% of cases (4). Despite its benign nature, IVL can behave aggressively, extending to the IVC through various routes, such as the iliac and ovarian veins, and can reach the right heart chambers and occasionally the pulmonary artery, posing a fatal risk (4,5).

In our case, the IHC analysis results revealed a set of key molecular markers, which enriched our understanding of the biological nature of the tumor cells. The positivity for SMA, desmin, and h-caldesmon indicated marked smooth muscle differentiation of the tumor cells, underscoring its nature as a benign tumor, originating from smooth muscle tissue. The partial positivity for CD10 suggested specific enzymatic activity on the tumor cell surface. While not typical, this finding provided additional clues about the possible cellular origin and biological behavior of the

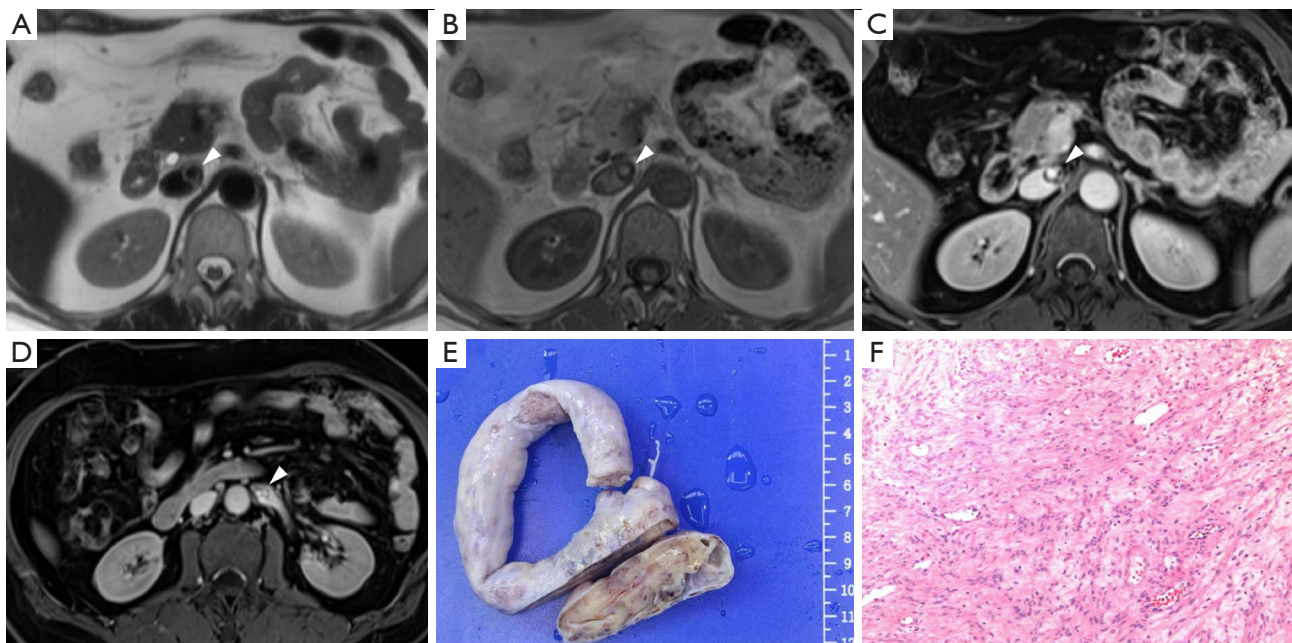


Figure 3 Magnetic resonance axial images and pathological images. (A) Axial T2-weighted imaging showing a lesion with low signal intensity in the IVC (triangle). (B) On the axial T1-weighted images, the lesion in the IVC exhibited moderate signal intensity (triangle). (C) The enhanced axial T1-weighted fat-suppressed images demonstrated pronounced enhancement of the lesion in the IVC, characterized by a sieve-pore appearance (triangle). (D) On the axial T1-weighted fat-suppressed enhanced images, a lesion in the left renal vein demonstrated marked enhancement, resembling a sieve pore (triangle). (E) A gross pathological specimen showed a cord-like mass. (F) The histopathological analysis confirmed the cord-like mass to be intravenous leiomyomatosis (hematoxylin and eosin staining, $\times 100$ magnification). IVC, inferior vena cava.

tumor. The positive expression of ER and PR indicated the sensitivity of the tumor cells to hormones, which might be significant for understanding the hormone-dependent growth of the tumor, and its potential responsiveness to hormone therapy. The positive expression of FH (without loss) suggested the normal functioning of FH in the tumor cells. This finding was critical in excluding tumors caused by FH gene mutations, especially given the role of FH as a tumor suppressor gene whose loss is associated with specific tumor types, such as hereditary leiomyomatosis and renal cell cancer. The negativity for CD34 and S100 helped to rule out characteristics of hematopoietic stem cells, early lymphocytes, endothelial cells, and neurogenic, chondrogenic, and certain soft tissue tumors in the tumor cells. This negative expression further refined our classification of the tumor, eliminating a range of potential non-smooth muscle origins. The Ki67 labeling index of 1% indicated the low proliferative activity of the tumor, which was consistent with the characteristics of benign or low-grade malignant tumors, and which suggested a potentially

favorable prognosis. In summary, the IHC analysis in this case revealed the molecular characteristics and biological behavior of the tumor, providing crucial molecular-level evidence for further understanding its pathologic mechanism and for devising treatment strategies. These results not only supported the diagnosis of the tumor as benign but also identified important biomarkers for future research and therapeutic interventions.

In recent years, research on the molecular characteristics and pathogenesis of IVL has advanced. IVL and uterine leiomyoma exhibit similar patterns of chromosomal rearrangements and protein expression according to cytogenetic and IHC analyses (6,7). For example, rearrangements in the chromosome 12q14-15 region leading to high mobility group protein AT-hook 2 (HMG2) activation have been observed in both IVL and uterine leiomyoma (8-10). Similar expression patterns of the ER and the PR have also been detected (6-10). This evidence supports the theory that IVL originates from uterine leiomyoma. However, IVL also exhibits unique

molecular alterations that are potentially associated with its distinct invasive clinical behavior. Mediator complex subunit 12 (MED12) mutations are prevalent in uterine leiomyoma but are less frequent in IVL, indicating the existence of divergent molecular mechanisms associated with this gene (6,11,12). Two novel mutations in MED12 exon 2 have been identified in IVL [i.e., a synonymous mutation (c.141C>T), and a deletion mutation (c.133_147del15)], which suggests that there may be potential variations in the MED12 mutation pattern between IVL and uterine leiomyoma (11-13). The expression of homeobox A13 (HOXA13), a transcription factor associated with cell differentiation and tissue development, is elevated in IVL at the messenger RNA level (6,14). This elevation may serve as a biomarker for differentiating between IVL and uterine leiomyoma. Expression levels of cyclin E and Ki-67 remain low in IVL, but are high in uterine leiomyosarcoma, which is consistent with the low malignancy of IVL (6,7). Elevated protein expression of p16 and cyclin D1 has been detected in IVL through IHC, indicating the involvement of this pathway in IVL pathogenesis (7). The expression levels of anti-apoptosis-related genes BCL2A1 and CDKN2A, as well as the angiogenesis-related gene CXCL8, are upregulated in IVL, underscoring the enhanced pro-angiogenic capacity of IVL relative to uterine leiomyoma (7,8). The cancer stem cell surface marker CD44 has been shown to be positively expressed in IVL, which suggests that cancer stem cells could be involved in the vascular invasion process of IVL (6,15). Elevated expression levels of hyaluronan, which serves as a principal ligand for CD44, have been observed in IVL. Conversely, hyaluronan levels are notably lower in uterine leiomyomas, which further highlights the differences in the pathogenesis of IVL and uterine leiomyoma (15,16). All these molecular characteristics are pivotal in understanding the unique pathogenesis of IVL, distinguishing it from other uterine leiomyomas, and providing potential targets for future research and therapeutic strategies.

The incidence rate of IVL is estimated to be between 0.25% and 0.40%, with the disease onset typically occurring between the ages of 20 and 70 years, and a median age of onset of 45 years (17,18). IVL is predominantly observed in women of childbearing age, particularly those with a history of uterine leiomyoma or who have undergone surgical interventions, such as myomectomy, hysterectomy, or cesarean sections. Factors such as elevated estrogen levels, venous blood stasis, and local injuries, including those from previous uterine surgeries, are believed to

play significant roles in the onset of IVL (18,19). Surgical intervention is the primary treatment modality for IVL; however, the postoperative recurrence rate for IVL is notably high, with individuals under 45 years of age, especially those with incomplete tumor resection, at an increased risk of recurrence (20). The involvement of large veins, including iliac veins (both internal and external), and the IVC, has been identified as a critical factor contributing to the increased risk of recurrence (21). This underscores the complexity of managing IVL and highlights the necessity for comprehensive vascular assessments during diagnosis and treatment planning. These findings stress the paramount importance of meticulous surgical planning, vigilant postoperative monitoring to effectively manage the risk of IVL recurrence, and adopting a holistic approach to patient care. Additionally, long-term follow up is crucial due to the potential recurrence risk, even post complete surgical resection (19,21).

In the diagnosis and preoperative evaluation of IVL, CT and MRI are essential. CT, which is renowned for its high-density resolution and multiplanar imaging, is indispensable in delineating tumor continuity and pinpointing its precise location, particularly in visualizing IVL distribution in the IVC and cardiac chambers. MRI, which is distinguished by its superior soft tissue contrast and sensitivity, provides comprehensive insights into tumor signal characteristics, which is vital for differentiating between IVL and similar conditions. Further, cine MRI allows for the dynamic monitoring of intracardiac mass movements during the cardiac diastole and systole phases.

In conclusion, multimodality imaging offers a comprehensive and nuanced perspective in the diagnosis of IVL, enabling clinicians to accurately assess the extent and characteristics of the lesion. Specifically, in the surgical management of IVL, multimodality imaging is invaluable, as it offers critical preoperative insights that facilitate complete tumor excision and assist in minimizing the risk of recurrence.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.>

amegroups.com/article/view/10.21037/qims-23-1772/coif. The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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