Surgical treatment of intravenous leiomyomatosis involving the right heart: a case series

Guangze Luo¹,²,*, Hongrui Pan¹,²,*, Jiaxue Bi¹,*, Yudong Luo¹, Jiechang Zhu¹, Zhou Feng¹, Hailun Fan¹, Yiwei Zhang¹ and Xiangchen Dai¹,²

Abstract

Objective: This study was performed to investigate the surgical treatment of intravenous leiomyomatosis involving the right heart.

Methods: The clinical data of five patients with intracardiac leiomyomatosis treated from April 2002 to October 2017 at a single center were retrospectively analyzed.

Results: All five patients underwent successful intravenous and right atrial tumor removal via abdominal and inferior vena cava incisions. In three patients, these incisions were combined with thoracotomy and a right atrial incision, and in two patients, they were combined with uterine and bilateral fallopian tube and ovarian resection. One patient with advanced disease underwent a one-stage procedure and died thereafter. Of the remaining four patients who underwent follow-up for 1.5 to 12.0 years, one developed recurrence at 1 year postoperatively. The recurrent tumor, which was pathologically confirmed to be an intravenous leiomyoma, was removed via inferior vena cava and internal iliac vein incisions without subsequent recurrence.

Conclusions: The main treatment goal for inferior vena cava leiomyomas involving the right heart is to first address the severe obstruction of cardiac blood flow and then pursue second-stage surgery. Concurrent thoracotomy appears unnecessary because moderately sized right heart tumors can be gently removed via the inferior vena cava.

¹Department of Vascular Surgery, Tianjin Medical University General Hospital, Tianjin, China
²Tianjin General Surgery Institute, Tianjin Medical University General Hospital, Tianjin, China

*These authors contributed equally to this work.

Corresponding author:
Xiangchen Dai, Department of Vascular Surgery, Tianjin Medical University General Hospital, No. 154 Anshan Road, Heping District, Tianjin 300052, China.
Email: 13302165917@163.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Introduction

Intravenous leiomyomatosis (IVL) is a rare and histologically benign-appearing but malignant endovascular disease that can be caused by invasive uterine fibroid tissue or venous smooth muscle cells.\(^1\) The high recurrence rate and poor prognosis render correct preoperative diagnosis, complete resection, and close postoperative follow-up important in the management of IVL. Growth of IVL beyond the uterus, through the ovarian and iliac veins to the inferior vena cava, and into the right heart and pulmonary artery results in intracardiac leiomyomatosis (ICL), which causes severe and potentially lethal circulatory disorders.\(^2\) Two hundred cases of ICL have been reported to date.\(^3,4\) We herein summarize and analyze the clinical manifestations, imaging features, surgical treatment, and long-term postoperative outcomes of five cases of ICL treated at the General Hospital of Tianjin Medical University, China, from April 2002 to October 2017. This study was performed to help clinical surgeons more thoroughly understand IVL and to achieve a correct diagnosis and perform rational treatment of such diseases in clinical practice.

Methods

Baseline sociodemographic and clinical characteristics

The five patients with ICL in the present study were women aged 34 to 60 years (mean, 45.8 years) with a history of uterine leiomyomas. Three had undergone hysterectomy for uterine fibroids (one simple hysterectomy and two uterine combined with bilateral fallopian tube and ovarian resections). All five patients presented with congestive heart failure or arrhythmia-related symptoms such as chest tightness, hernia, or syncope. Two patients had lower extremity edema affecting mobility, and one had severe ascites, a poor general status, orthopnea, and New York Heart Association grade IV cardiac function. In all five patients, cardiac ultrasound revealed IVL involvement of the heart that was not apparent on chest X-rays. In three patients, the tumor mass was confined to the right atrium. In two, however, the large tumor mass also involved the right ventricle and oscillated between the right ventricle during diastole and the right atrium during systole, causing both diastolic and systolic dysfunction. A similarly echogenic mass was also present in the inferior vena cava; this mass was thick, cord-like, and continuous with the tumor in the right atrium (Figure 1). Computed tomography (CT), including multiplanar reconstruction using the sagittal, cross-sectional, and coronal planes, showed a wide soft tissue mass spanning from the uterine or ovarian veins through the iliac veins and inferior vena cava to the right atrium. Magnetic resonance imaging (MRI) revealed a widened, longitudinally irregular inferior vena cava with irregular soft tissue signals in the lumen and in the right atrium. Abdominal color Doppler ultrasound showed solid masses in the pelvic area and inferior vena cava (Figure 1). Two patients underwent positron emission tomography (PET)/CT at
another hospital, which showed mild metabolite activity consistent with vascular-derived malignant and slow-growing tumors. Overall, these imaging examinations revealed right internal iliac vein–inferior vena cava–right heart extension in two patients, left internal iliac vein–inferior vena cava–right heart extension in one patient, and gonadal vein–inferior vena cava–right heart extension in two patients. All patients underwent surgical treatment followed by hormonal treatment.

**Combined transthoracic and abdominal surgery**

Three patients underwent thoracoabdominal surgery under general anesthesia, hypothermia, and cardiopulmonary bypass. Through a right-sided chest incision, the
heart was examined by thoracoscopy-assisted direct visualization. After insertion of an ascending aortic cannula and intubation and blockage of the superior and inferior venae cavae via the right atrium, an incision was made in the right atrial wall. The tumor, which extended from the inferior vena cava to the right atrium, was examined. In two of the patients, ICL involved the right ventricle. The anterior end of the tumor mass was freed into the right ventricular cavity, and the intracardiac mass was removed. A mid-abdominal incision was then made layer by layer up to the xiphoid process and down to the pubic symphysis. After entering the abdominal cavity, opening the posterior peritoneum, and exposing the inferior vena cava and applying a tourniquet to it, the tumor tissue filled the inferior vena cava and was released upward to the renal veins, to which tourniquets were applied. After the inferior vena cava was blocked about 3 cm above the vena cava bifurcation, a longitudinal incision was made, through which the proximal inferior vena cava mass was gently and completely pulled out. The distal mass in the inferior vena cava was stretched as far as possible. The tumor was then removed. The abdominal iliac vein or ovarian vein mass, uterus, bilateral attachments, and uterine lesions were removed, and pelvic dissection was performed.

**Simple transabdominal surgery**

Two patients underwent abdominal surgery alone (Figures 2, 3). A mid-abdominal incision was made up to the xiphoid and down to the pubic symphysis under general anesthesia and moderate to low body temperature. The procedure was performed following the same steps up to the incision of the inferior vena cava as described above. Transesophageal echocardiography (TEE) was then used to examine the intracardiac mass, guide the gentle and complete removal

![Figure 2](image-url)
of the proximal intracardiac and inferior vena cava tumors, and stretch and remove the distal tumor mass. Finally, the iliac vein or ovarian vein mass, uterus, bilateral attachments, and uterine lesions were removed through the abdomen, and pelvic dissection was performed.

**Ethics**

This report describes a retrospective clinical study and includes no personal information about any patient. All patients and their families provided written informed consent before surgery. The study was authorized
by the ethics committee of Tianjin Medical University General Hospital.

Results

In all five patients, the primary tumor as well as the intracardiac and inferior vena cava tumors were completely removed. Two patients concurrently underwent uterus and bilateral fallopian tube and ovarian resection. During the operation, frozen sample pathological examination showed extensive fibrosis with spindle-shaped cells; combined with the patients' clinical symptoms, this finding was consistent with intravenous leiomyomas. Postoperative pathological examination revealed leiomyomatosis with mucosal and red degeneration, a retroperitoneal inferior vena cava mass, and venous leiomyomatosis, confirming the diagnosis of intravenous leiomyoma of uterine or internal iliac vein origin. Immunohistochemical staining showed smooth muscle actin (++), progesterone receptor (++), estrogen receptor (++), desmin (++), and calponin (-); endothelial cell expression of CD31 and CD34; vimentin and smooth muscle actin staining; low p53 protein and cytokeratin expression; and negative staining for progesterone receptor and Bcl-2 (Figure 3).

One patient died of excessive intraoperative hemorrhage and multiple organ failure after surgery, one developed jaundice 1 week after surgery, and one had intestinal adhesions after 6 months and recovered with conservative treatment. Of the four patients who were followed up for IVL recurrence from 1.5 to 12.0 years, one patient developed recurrence 1 year postoperatively; the tumor was removed via inferior vena cava and internal iliac vein incisions without recurrence thereafter.

Discussion

ICL is the spread of IVL along a venous access route to the right ventricle, pulmonary artery, or lung.6,7 IVL is highly aggressive, and most reported tumors appear to invade the inferior vena cava (93.1%), right atrium (87.4%), and right ventricle (47.1%).7 Diagnosing IVL, especially ICL, is sometimes difficult because of the lack of specificity in its clinical symptoms. In this case series, the most common symptoms were chest tightness, herniation, and lower extremity edema. In two patients, these symptoms were secondary to leiomyomas involving the hepatic vein and posterior inferior vena cava and manifested as portal hypertension, suggesting Budd–Chiari syndrome. Even when IVL has affected the right heart, no particularly serious symptoms may occur in the early stage; however, right heart failure, pulmonary embolism, or cardiac arrest may occur in later stages, possibly leading to sudden death.8,9 Chest tightness and suffocation suggest that the IVL has affected the right heart system, leading to tricuspid regurgitation or right ventricular inflow obstruction. Symptoms such as bloating, fatigue, and an abdominal mass are nonspecific and are easily overlooked clinically. Therefore, for women who are around 40 years of age or have a history of uterine fibroids, the inferior vena cava and heart must be evaluated upon occurrence of chest tightness, hernia, and lower extremity edema to avoid a missed diagnosis. Examinations for such patients should include CT or MRI, echocardiography, and, if necessary, CT pulmonary angiography, PET/CT, or PET/MRI. These imaging techniques not only highlight the possibility of tumor malignancy but can also accurately display the worm-like extension in the veins. These methods, as illustrated here for inferior vena cava CT
(which was performed preoperatively in all patients), can inform the treatment strategy for refractory venous leiomyomatosis and provide data on the tumor size, tumor location, degree of adhesion, and tumor extent. Echocardiography can be used to identify atrial occupancy and mobility (floating or adhesion), assess the size of the cardiac chambers and function of the tricuspid valve and overall heart, and provide a diagnosis. Intraoperative TEE is useful to guide intracardiac mass removal and to clearly show whether a tumor plug is adhered or detached. IVL should be distinguished from right atrial myxoma, leiomyosarcoma, Budd–Chiari syndrome, and deep vein thrombosis with inferior vena cava extension.

Surgical treatment should be the first choice for patients with ICL, and complete removal of the tumor is the key to successful treatment. The difficulty of surgery is mainly determined by the degree of adhesion of the tumor to the vessel wall, not by the length of the tumor. The disease recurrence rate is high; therefore, complete removal of the tumor is the key to preventing recurrence. In 1974, Mandelbaum et al. reported the successful removal of intravenous leiomyomas involving the right heart. In 1982, Ariza et al. reported the first complete use of staged surgery to remove ICL. Consistent with most literature reports in both China and worldwide, all patients in our case series were treated with concurrent surgical resection with participation of a multidisciplinary team comprising vascular surgeons, cardiac surgeons, obstetricians, and gynecologists. Three patients in the present case series underwent combined thoracic and abdominal surgery, and in one of these three patients, no tumor was found after the chest and right atrium were opened. After exploration, we found that the tumor had retracted into the inferior vena cava, and we removed it by abdominal surgery. In the other two patients with a tumor involving the right ventricle, the tumor had retracted into the right atrium, and the part of the tumor within the inferior vena cava was pulled through the right atrium and excised. TEE was used in the two patients who underwent simple transabdominal surgery to gently and completely excise the tumor involving the right heart, incise the inferior vena cava, and finally remove the tumor. Therefore, preoperative examination of patients with IVL involving the right heart must involve a comprehensive assessment regarding whether the tumor is adhered to the vessel wall and involves the right ventricle or pulmonary artery. If the tumor has no adhesions to the vessel wall or endocardium, or if the right ventricle is not affected, the surgeon can first open the inferior vena cava via simple transabdominal surgery and then gently pull out the proximal cardiac tumor thrombus and remove it under TEE guidance. Simple laparotomy shortens the operation time, reduces the surgical trauma and the coagulation dysfunction caused by intraoperative heparin, and lowers the rate of postoperative complications. Detailed preoperative discussions with multidisciplinary physicians and a high skill level of the surgeon are also critical.

The two currently available surgical methods for treating ICL are a one-stage operation or a staged surgery. In a one-stage operation, two procedures are performed concurrently to remove the intracardiac tumor thrombus through the inferior vena cava, the pelvic abdominal tumor, and the uterus and bilateral attachments. In a staged surgery, the intravenous mass above the renal vein is removed first; 4 to 6 weeks later, the lower segment of the renal vein and
the primary tumor are removed. Kocica et al.\textsuperscript{9} reported their experience with 113 patients with ICL, including 33 (29.2\%) treated by a one-stage operation, 49 (43.4\%) treated by staged surgery, and 20 (17.7\%) treated by total incomplete resection. All patients in our case series underwent a one-stage surgery with successful removal of the intravenous masses and primary lesions. The key to surgery is to reduce the amount of bleeding and prevent the tumor plug from falling off. For primary lesions in the pelvic cavity, performance of a total hysterectomy with concurrent ligation of the ovarian arteries and veins at a high position is recommended to prevent tumor migration and residue and ensure removal of bilateral attachments. For patients in whom the tumor cannot be removed completely, ligation of the proximal vascular end of the tumor is recommended to prevent the tumor thrombus from entering the inferior vena cava.

In the present series, the patient who died after the procedure had undergone two previous gynecologic surgeries, the more recent one of which had been performed 5 years prior. The patient had been repeatedly evaluated at other hospitals and refused surgery, and 3 months before admission to our hospital, she developed heart failure, herniation, orthopnea, severe ascites, and lower extremity edema. Cardiac ultrasound showed IVL involvement of the right ventricle with tricuspid regurgitation and right ventricular inflow obstruction. CT showed that the tumor involved the hepatic and renal veins, and MRI indicated that the primary lesion had adhesions and that the tumor had extensively invaded the tissue. Preoperative blood biochemical examination showed hypoproteinemia, thrombocytopenia, and abnormal blood coagulation. Before the operation, the patient’s condition was discussed with several specialists, who determined that the ventricular inflow obstruction should be resolved as soon as possible to alleviate heart failure symptomatology. The patient and her family agreed to the surgery. Incision of the inferior vena cava was performed through the abdomen, and the proximal cardiac tumor thrombus was gently removed under TEE guidance. The pelvic mass was then removed because the left internal iliac vein was strongly adhered to the surrounding tissue, and a large number of collateral vessels had arisen due to tumor invasion. Separation and cutting of the internal iliac vein was difficult, as was locating the tumor pedicle along the leiomyomas and removing it. The operation time was long with a large amount of bleeding. The patient died of multiple organ failure after surgery. Because of the patient’s poor physical condition, a staged procedure might have been more appropriate; the first phase would have mainly addressed the heart failure symptomatology, and the second phase would have been performed to remove the primary lesion and the extended mass.

The efficacy of hormonal therapy for IVL remains controversial.\textsuperscript{15,19,20} Some authors have proposed that IVL is a hormone-dependent tumor and that the presence of ovaries can increase the chance of recurrence.\textsuperscript{21–23} Tamoxifen, gonadotropin-releasing hormone agonists, medroxyprogesterone, and other drugs are used postoperatively because of their antiestrogenic effects to control possible residual tumors or preoperatively to inhibit tumor growth and thereby reduce the tumor volume and facilitate complete resection. Four patients in our case series were treated with hormone therapy, and one patient developed recurrence of a small, slowly growing tumor 1 year after surgery. Radiotherapy at low doses might also be used in patients who are prone to recurrence.\textsuperscript{24}
Conclusions
For IVL involving the heart, timely and accurate preoperative diagnosis, adequate preoperative preparation, reasonable selection of surgical methods, and complete tumor removal are the keys to successful treatment and prevention of recurrence. Postoperative maintenance therapy and follow-up are very helpful for a good prognosis and prolonged survival. For patients with severe right heart blood flow obstruction, the main treatment goal should be to address the heart failure symptoms first; a second-stage surgery should then be performed after the patient’s cardiovascular status has improvement.

Acknowledgement
We thank all of the patients and their families, the investigators, and the medical staff. We also thank Dr. Roberto Patarca for editing the English text of a draft of this manuscript.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD
Guangze Luo https://orcid.org/0000-0002-2984-9281

References
1. Ordulu Z, Nucci MR, Dal Cin P, et al. Intravenous leiomyomatosis: an unusual intermediate between benign and malignant uterine smooth muscle tumors. Mod Pathol 2016; 29: 500–510.
2. Doganci S, Kaya E, Kadan M, et al. Huge intravascular tumor extending to the heart: leiomyomatosis. Case Rep Surg 2015; 2015: 658728.
3. Li B, Chen X, Chu YD, et al. Intracardiac leiomyomatosis: a comprehensive analysis of 194 cases. Interact Cardiovasc Thorac Surg 2013; 17: 132–138.
4. Clay TD, Dimitriou J, McNally OM, et al. Intravenous leiomyomatosis with intracardiac extension - a review of diagnosis and management with an illustrative case. Surg Oncol 2013; 22: e44–e52.
5. Marcus SG, Krauss T, Freedberg RS, et al. Pulmonary embolectomy for intravenous uterine leiomyomatosis. Am Heart J 1994; 127: 1642.
6. Carr RJ, Hui P and Buza N. Intravenous leiomyomatosis revisited: an experience of 14 cases at a single medical center. Int J Gynecol Pathol 2015; 34: 169–176.
7. Matsuo K, Fleischman F, Ghattas CS, et al. Successful extraction of cardiac-extending intravenous leiomyomatosis through gonadal vein. Fertil Steril 2012; 98: 1341–1345.e1.
8. Wu CK, Luo J, Yang CY, et al. Intravenous leiomyomatosis with intracardiac extension. Intern Med 2009; 48: 997.
9. Kocica MJ, Vranes MR, Kostic D, et al. Intravenous leiomyomatosis with extension to the heart: rare or underestimated? J Thorac Cardiovasc Surg 2005; 130: 1724–1726.
10. Chino Y, Tsuyoshi H, Tsujikawa T, et al. A novel diagnostic strategy using 16alpha-[18F]-fluoro-17-beta-estradiol (18F-FES) PET/MRI to achieve complete resection of intravenous leiomyomatosis in reproductive-age women. Clin Nucl Med 2017; 42: e335–e336.
11. Xiao J, Liu G, Cheng D, et al. The value of (18)F-FDG PET/CT in the diagnosis of uterine intravenous leiomyomatosis extended into the right atrium. Hell J Nucl Med 2016; 19: 179–181.
12. Zeng H, Xu Z, Zhang L, et al. Intravenous leiomyomatosis with intracardiac extension depicted on computed tomography and magnetic resonance imaging scans: a report of two cases and a review of the literature. Oncol Lett 2016; 11: 4255–4263.
13. Harris LM and Karakousis CP. Intravenous leiomyomatosis with cardiac extension: tumor thrombectomy through an abdominal approach. *J Vasc Surg* 2000; 31: 1046–1051.

14. Virzi G, Ragazzi S, Bussichella F, et al. Intravenous leiomyomatosis extending from the inferior caval vein to the pulmonary artery. *J Thorac Cardiovasc Surg* 2007; 133: 831–832.

15. Esmaeilzadeh M, Tavakolli A and Safaei A. Recurrent intracardiac leiomyomatosis. *Can J Cardiol* 2007; 23: 1085–1086.

16. Schafer HM, Isaak A and Gurke L. Case report of an intracaval leiomyomatosis 10 months after complete hysterectomy. *Int J Surg Case Rep* 2017; 35: 1–3.

17. Mandelbaum I, Pauletto FJ and Nasser WK. Resection of a leiomyoma of the inferior vena cava that produced tricuspid valvular obstruction. *J Thorac Cardiovasc Surg* 1974; 67: 561.

18. Ariza A, Cerra C, Hahn IS, et al. Intravascular leiomyomatosis of the uterus. A case report. *Conn Med* 1982; 46: 700–703.

19. Nam MIS, Jeon MJ, Kim YT, et al. Pelvic leiomyomatosis with intracaval and intracardiac extension: a case report and review of the literature. *Gynecol Oncol* 2003; 89: 175–180.

20. Nishizawa J, Matsumoto M, Sugita T, et al. Intravenous leiomyomatosis extending into the right ventricle associated with pulmonary metastasis and extensive arteriovenous fistula. *J Am Coll Surg* 2004; 198: 842–843.

21. Clement PB. Intravenous leiomyomatosis of the uterus. *Pathol Ann* 1988; 23: 153.

22. Cea-Calvo L, Lozano F, Pombo M, et al. Images in cardiovascular medicine. Uterine intravenous leiomyomatosis extending through the inferior vena cava into the right cardiac cavities. *Circulation* 2000; 101: 581.

23. Low HY, Zhao Y, Huang KS, et al. Intravenous leiomyomatosis of the uterus: a clinicopathological analysis of nine cases and literature review. *Taiwan J Obstet Gynecol* 2017; 56: 362–365.

24. Zhang Y, Clark LH, Sheng X, et al. Successful en bloc venous resection with reconstruction and subsequent radiotherapy for 2 consecutive recurrences of intravenous leiomyoma–a case report. *BMC Cancer* 2016; 16: 6.