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Case report

A case of a large leiomyomatous uterus with multiple arteriovenous malformations and subsequent high cardiac output state with severe four chamber cardiac enlargement

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ABSTRACT

Uterine arteriovenous malformations (AVMs) are rare and potentially life-threatening. They can be congenital or acquired. Uterine artery embolization or hysterectomy are considered mainstays of management. AVMs can be associated with leiomyomas, and patients may require both procedures. We present a case of a 42-year-old woman with a massively enlarged leiomyomatous uterus supplied and drained by multiple large AVMs, leading to high cardiac output state with severe four chamber cardiac dilation. Management required a multidisciplinary team of interventional radiology, gynecologic oncology surgery, vascular surgery, cardiac anesthesiology, cardiology, and urology and a 2-day interventional approach of preoperative arterial embolization followed by hysterectomy.

1. Introduction

Arteriovenous malformations (AVMs) are abnormal vascular connections between arteries and veins that disrupt normal blood flow and oxygen circulation. Congenital AVMs usually have multiple vascular connections and involve surrounding structures, whereas acquired AVMs typically have a single connection between an artery and a vein (Shintre and Coelho, 2017). AVMs can also be iatrogenic, or surgically constructed for hemodialysis, and can be a cause of high output heart failure (Zahra et al., 2021). AVMs can be diagnosed by color Doppler, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) or angiography (Samadi and Salazar, 2019). These most commonly occur in the brain or spine but can rarely present in the uterus and cause life-threatening vaginal bleeding (Sato et al., 2015). While the true incidence of uterine AVMs remains unknown, it is estimated to be about 4.5% in women with abnormal uterine bleeding (AUB) (O'Brien et al., 2006). Uterine AVMs can be congenital, resulting from a defect in the differentiation of the primitive capillary plexus during fetal angiogenesis, or acquired, following pregnancy, uterine instrumentation (dilation and curettage, C-sections, other procedures), gestational trophoblastic disease, and gynecologic cancers (Yoon et al., 2016). Management of uterine AVMs depends on patient age, hemodynamic stability, and desire for future fertility. Angiographic uterine artery embolization (UAE) is the treatment of choice, especially in young women who desire to preserve fertility (Vijayakumar et al., 2013).

In contrast to uterine AVMs, uterine leiomyomas or fibroids are the

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most common benign gynecologic tumor. Leiomyomas associated with AVMs, however, are uncommon with only four other cases reported in the literature (Gan et al., 2021; Val-Bernal and Hermana, 2016; Soeda et al., 2012; Anonymous, 2009). Here we describe the multidisciplinary surgical management of a large leiomyomatous uterus with multiple AVMs in a premenopausal woman symptomatic with high cardiac output, heavy AUB, and subsequent chronic iron-deficiency anemia. Surgical management utilized a two-day multi-disciplinary approach of preoperative angiogram with extensive selective arterial embolization, followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy.

2. Case description

A 42-year-old nulligravid woman presented to our Gynecology Oncology Surgery clinic for consultation regarding growing, symptomatic leiomyomata. She had a history of known 2 cm leiomyomas diagnosed in 2004 at an outside institution at 25 years of age. In 2009, her menstrual cycles became shorter and more frequent. Imaging showed that her uterus had multiple very large uterine leiomyomas, with the largest measuring 12 × 11 × 18 cm. Imaging was repeated in 2015 due to worsening bulk symptoms but UAE was not pursued due to concern for multiple collaterals limiting durability of the procedure. She was started on 6 months of Lupron, which resulted in lighter and more regular periods but no reduction in leiomyoma size. In May 2016, an MRI revealed her uterus to extend to the level of the splenic flexure, measuring over 30 cm in length. Due to continued leiomyoma burden, she underwent right UAE; however, her angiogram at the time of that procedure was concerning for arteriovenous shunting of the left uterine artery into the left gonadal vein and left UAE was not performed.

Over the course of the 18 months prior to her presentation to us, she experienced recurrence of her heavy AUB, increasing bloating and abdominal girth, weight loss, urinary frequency, nocturia, abdominal/pelvic pain, and the inability to lie supine. She also began experiencing shortness of breath and was found to have a heart murmur on exam 6 months prior to our encounter. Transthoracic echocardiogram (TTE) at that time showed mitral regurgitation that was interpreted as severe and pulmonary hypertension. She underwent a CT angiogram of the abdomen and pelvis, which again showed a massively enlarged uterus with innumerable leiomyomas. Most notably, however, was the vascularity involving the uterus and adnexa, which was markedly complex with arterial and venous enlargement, including bilateral ovarian vein dilation with the proximal right ovarian vein at 3.3 cm in diameter with evidence of apparent vascular shunting (Fig. 1).

Based on her 17-year history of known uterine masses and imaging showing no extrauterine disease, her growing uterine masses were presumed to represent benign leiomyomas; however, the differential diagnosis included atypical proliferations such as a cellular leiomyoma, or a low-grade sarcoma. Upon presenting to our team for consultation and management, a detailed CT angiogram was completed to better define her unique vascular anatomy, which showed her uterus as a large heterogeneously enhancing mass measuring approximately 31.9 × 27.5 × 13.1 cm with extensive vascularity, multiple large AVMs, and areas of necrosis. Her uterus had recruited additional arterial supply from the internal iliac arteries, ovarian arteries, superior mesenteric artery, inferior mesenteric artery, and abdominal aorta (Fig. 2).

It was initially unclear if her shortness of breath was secondary to cardiac dysfunction or due to mass effect from the uterine mass or a combination of both. Cardiology evaluation and TTE at the time of her multidisciplinary consultation revealed she was in a high cardiac output state (cardiac index 5.33 L/min/mÂ^2), had severe four-chamber enlargement but thus far maintained normal systolic function (ejection

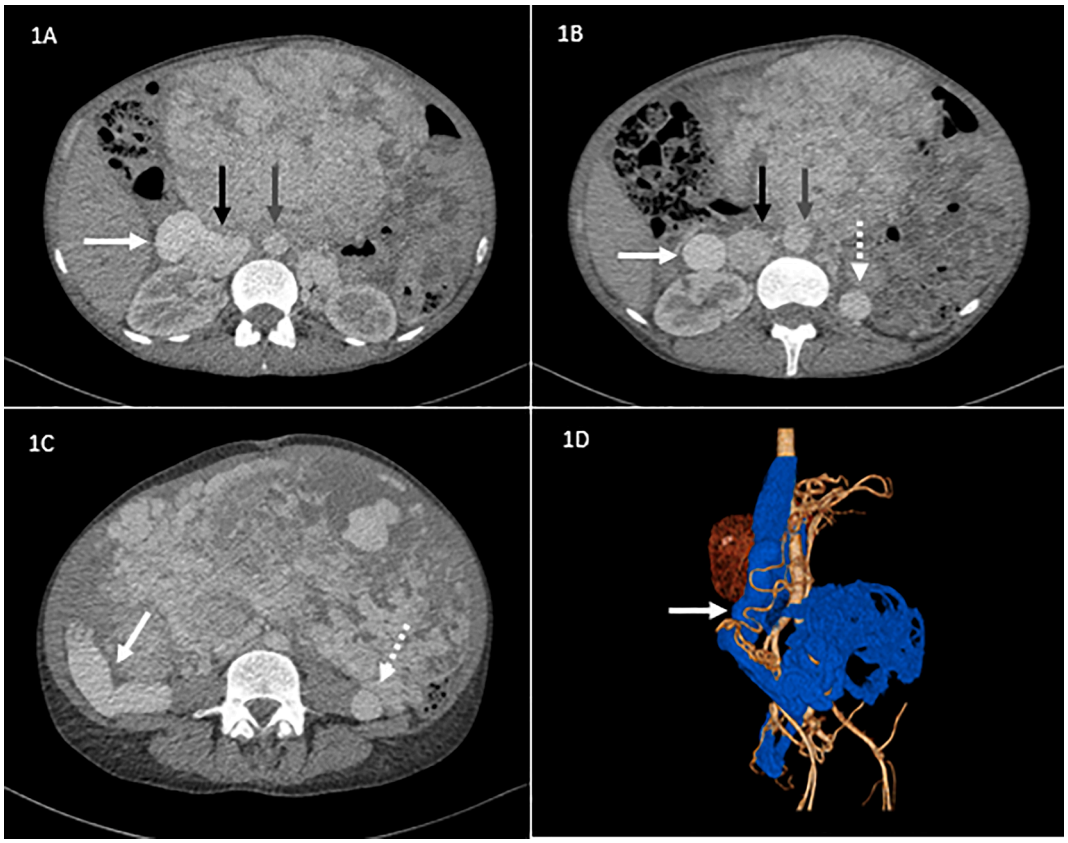

Fig. 1. A, B, C. CTA/CTV showing highly vascular uterine mass; right ovarian vein (white arrow) with evidence of shunting at the level of the IVC (black arrow); aorta (gray arrow) and left ovarian vein (dotted white arrow). Figure D. 3-D reconstruction showing dilated right ovarian vein (white arrow) and marked venous involvement of the uterus.

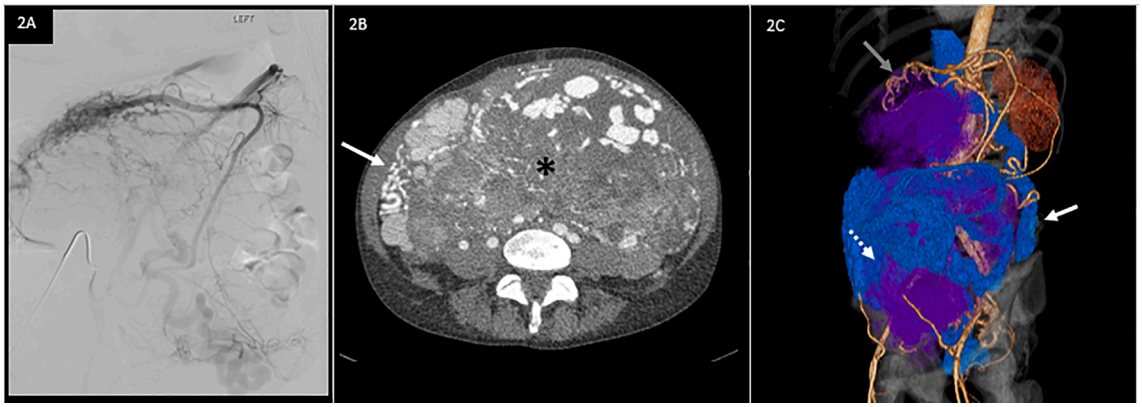

Fig. 2. A. IR angiography showing extensive tumor vascularity from multiple branches of the inferior mesenteric artery. Figure B. CT angiogram showing vascular uterine mass (black asterisk) and dilated right ovarian venous plexus and extensive right ovarian arterial supply (white arrow). Figure C. 3-D reconstruction showing superior mesenteric artery (gray arrow), left gonadal vein (white arrow), and uterine mass (dotted white arrow).

fraction 56%), trivial to mild mitral valve regurgitation, and slightly improved pulmonary hypertension compared to cardiac evaluation 6 months prior. The AVMs involving her uterine leiomyomas were felt to be the culprit for her high cardiac output state. Anticipating the potential for large volume blood loss, fluid shifts, and altered cardiac response, her anesthesia team included subspecialists prepared to utilize Cell Saver, a massive transfusion protocol, and intraoperative monitoring of volume status and cardiac function with transesophageal echocardiogram. Neuraxial anesthesia was avoided given concern for intraoperative coagulopathy and possible epidural vein congestion.

Hysterectomy ± bilateral salpingo-oophorectomy (BSO) was recommended to address the underlying cause of her high cardiac output state which had a near certain probability of progressing to heart failure, relief from the heavy AUB and resultant anemia, and diagnosis of uterine tumor histology. Another important consideration for our patient was ovarian preservation. However, given the extensive involvement of the ovarian vasculature bilaterally, an ovarian sparing procedure appeared unlikely to be feasible. She was evaluated by reproductive endocrinology, but at 42 years of age was not eligible for ovarian tissue cryopreservation or ovarian autotransplantation. As such, estrogen replacement therapy was planned if both ovaries required removal for management of the AVMs.

One day prior to her hysterectomy, the patient underwent extensive angiography and venography to define the arterial and venous supply to

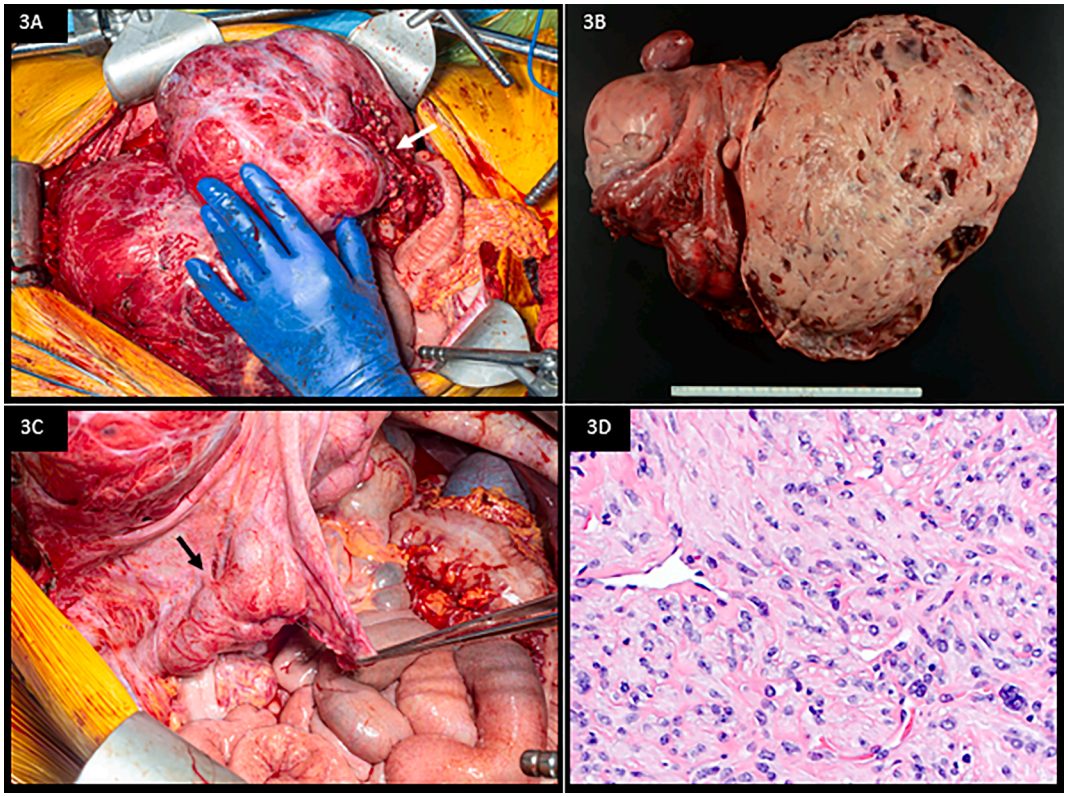

Fig. 3. A. Intraoperative photograph showing vascular connections between the uterus and transverse mesocolon (white arrow). Figure B. Gross pathology of the uterus containing multiple leiomyomas, the largest with a solid cut surface demonstrating cyst formation and focal areas of necrosis. Figure C. Dilated left gonadal vein (black arrow). Figure D. Microscopic evaluation revealed features of an FH-deficient leiomyoma including occasional intracytoplasmic eosinophilic inclusions, prominent nuclei, perinucleolar clearing, binucleated cells and hemangiopericytic vessels.

the uterus, fallopian tubes, and ovaries and guide preoperative embolization. Based on the findings, the interventional radiology team proceeded with embolization of the right ovarian artery, anterior divisions of both internal iliac arteries, the right uterine artery, left inferior epigastric artery, and left deep circumflex iliac artery. However, because of her arteriovenous fistulas, fast flow within the venous side and large size of the ovarian veins, these could not be treated with endovascular measures due to the high risk of embolization to her heart and lungs. The following day, she underwent temporary bilateral ureteral stent placement with urology followed by a midline laparotomy, abdominal hysterectomy, and bilateral salpingo-oophorectomy performed jointly by gynecologic oncology surgery and vascular surgery given the aberrant vessels and massively dilated ovarian vasculature. Intraoperative findings included vascular connections to the uterus and its multiple leiomyomas from neovascularization arising from the left anterior abdominal wall (inferior epigastric vessels), transverse mesocolon (Fig. 3A) and omentum, and bladder. There was an obvious fistula between left ovarian artery and vein (Fig. 3C) with a palpable thrill. The right ovarian vessels appeared to have an arteriovenous fistula as well; however, the right ovarian artery had been embolized the prior day. Neovascularization feeding the uterine masses were ligated in the process of the surgical resection. Bilateral ovarian arteries and veins were ligated separately and near the aortic origins of the ovarian arteries, proximal to the bilateral ovarian vessel AVMs to completely resect the AVMs. Ligation of each vessel was performed using 2-0 silk and the proximal stumps of both the arteries and the veins were oversewn with 4-0 Prolene suture. Preservation of neither ovary was feasible secondary to ovarian vessel AVM involvement. Estimated blood loss was 3100 mL and she received 1.5 L of autologous red blood cell (RBC) salvage as well as 2 units of packed RBCs, 2 units of cryoprecipitate, 4 units fresh frozen plasma, and 1 unit of platelets. She also received IV tranexamic acid at the beginning of the case. She remained hemodynamically stable throughout surgery, cardiac function remained stable, and she was observed in the ICU for one night postoperatively. She remained stable and was transferred to the general care unit on POD 1 until discharge on POD7.

Her uterus weighed 4168 g and contained over 10 pedunculated, intramural and subserosal leiomyomas ranging from 0.4 to 25 cm (Fig. 3B). The largest leiomyoma had a grossly tan solid cut surface with numerous cysts and scattered regions of necrosis (Fig. 3B). Microscopically (Fig. 3D), the tumor showed streams and small fascicles of spindle cells embedded in a hyalinized matrix. The tumor cells had ample pale eosinophilic cytoplasm, rare intracytoplasmic inclusions, variable nuclear atypia including nuclear enlargement, prominent nucleoli with perinucleolar clearing, as well as occasional binucleated forms. The mitotic index was consistently low level. Multiple prominent thin-walled staghorn vessels were present as were regions of hyaline-type necrosis. Immunohistochemical profiling revealed loss of fumarate hydratase (FH) expression and gain of 2SC expression. The tumor was classified as an FH-deficient leiomyoma. This raised concern for the possibility of Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome, a rare, adult-onset tumor-predisposition syndrome characterized by cutaneous leiomyomas, uterine leiomyomas, and renal tumors (Kamihara et al., 2006). After a Clinical Genomics consult, the patient pursued genetic testing, which identified a variant of uncertain significance (VUS) in the FH gene.

Her outpatient postoperative course was complicated by bilateral pulmonary emboli that occurred three weeks postoperatively and were determined to have arisen from a right ovarian vein thrombus. She was treated with the direct-acting oral anticoagulant apixaban. She otherwise recovered smoothly and follow up TTE 17 weeks postop showed normal right atrial, right ventricular, left ventricular chamber sizes, normal pulmonary arterial pressures, unchanged ejection fraction at 56% and normal cardiac index at 3.15 L/min/mÅ^2. It also showed only mild left ventricular diastolic dysfunction, trace mitral, aortic, and pulmonic regurgitation.

3. Discussion

Uterine AVMs are relatively rare vascular lesions that often present with heavy vaginal bleeding. Diagnosis can be challenging due to the obscurity of the condition and its similarity to other benign potentially hypervascular uterine lesions, such as retained products of conception, hypervascular polyp, leiomyoma, hemangioma, or gestational trophoblastic disease (Vijayakumar et al., 2013). Preoperative identification is clinically important because surgical disruption of an AVM may result in life-threatening hemorrhage (Sato et al., 2015) Additionally, the aberrant vascular connections in the setting of AVMs raises the potential for inadvertent outcomes in the setting of procedures commonly used to manage heavy AUB and symptomatic leiomyomas, such as UAE. In fact, fatality from particulate embolization through an unrecognized uterine AV fistula during leiomyoma embolization has been reported (Anonymous, 2009).

When appropriately recognized, imaging such as angiography and venography can be used to define the feeding arteries and venous drainage, elucidate neovascularization, and guide potentially complex preoperative planning. In addition to preoperative selective arterial embolization, venous coiling may also be utilized preemptively to control surgical blood loss. Additionally, intraoperative prophylactic endovascular balloon occlusion of the ipsilateral internal iliac artery during hysterectomy has also been described in managing an AVM associated with large cervical leiomyoma (Shintre and Coelho, 2017). Our premenopausal 42-year-old nulligravid patient had no history of pelvic procedures, pregnancy, or gynecologic cancers prior to her initial AVM diagnosis in 2016; however, she did have a right UAE performed in 2016 which may have contributed to further AVM development. The complex nature of her AVMs at initial diagnosis with no prior inciting occurrence to suggest an acquired AVM setting, suggests a congenital etiology.

Of critical importance, the AVMs involving our patient's ovarian vessels and uterus had led to a high cardiac output state and severe four chamber enlargement, an unsustainable state of cardiac function that could ultimately lead to heart failure (Koyalakonda and Pyatt, 2011). Fortunately, her symptoms, physical exam, and multidisciplinary evaluation identified the critical need for surgical intervention prior to the development of high output cardiac failure and at 4 months following hysterectomy + BSO her cardiac function is improved, with resolving cardiac chamber dilation and stable ejection fraction.

In conclusion, the combination of complex and massive AVMs in the setting of a large leiomyomatous uterus and a high cardiac output state with evidence of early cardiac dysfunction required a careful and stepwise, multidisciplinary approach to ensure optimal surgical and medical outcomes.

4. Consent

Signed informed consent for this case report was provided by the patient and is available upon journal request.

Author contributions

1. Beatriz Vega, BA: manuscript concept, writing, editing, figure design, and approval of final submitted manuscript
2. Andrew H. Stockland, MD: figure design, manuscript editing, and approval of final manuscript
3. Rachel Bramblet, DO: manuscript editing and approval of final manuscript
4. Alexandra L Anderson, MD: figure design, manuscript editing, and approval of final manuscript
5. Rekha Mankad, MD: manuscript editing and approval of final manuscript
6. Zaraq Khan, MD: manuscript editing and approval of final manuscript

7. Mohamed Mustafa, MD: manuscript editing and approval of final manuscript
8. Joan Steyermark, MS, LGC: manuscript editing and approval of final manuscript
9. Amanda R. Fields, MD: manuscript editing and approval of final manuscript
10. Novette J. Berntson, CRNA: manuscript editing and approval of final manuscript
11. Kenneth Schoolmeester, MD: figure design, manuscript editing and approval of final manuscript
12. Jill J. Colglazier, MD: figure design, manuscript editing and approval of final manuscript
13. Jamie N. Bakkum-Gamez, MD: manuscript concept, writing, editing, figure design, and approval of final submitted manuscript

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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