Case Report

Intravenous Lipoleiomyomatosis Mimicking Malignant Degeneration of Leiomyoma

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1. Introduction

Intravenous leiomyomatosis (IVL) is a rare condition in which a benign smooth muscle neoplasm is found extending into pelvic vessels. The frequency of IVL is difficult to ascertain due to its potential to be overlooked on routine pathologic assessment of leiomyoma, but it has been reported to be as few as 0.097% of all smooth muscle tumors [1]. While IVL is a benign neoplasm, extension from the pelvic vessels to the inferior vena cava (IVC) and even into the right heart or pulmonary vasculature have been observed [2-5]. Lipoleiomyoma (LPL) is an uncommon, benign uterine tumor distinguished by a mixture of smooth muscle and adipose tissue with little to no mytotic atypia. Both LPL and IVL are rare diagnoses and the combination of the two is exceedingly uncommon with only 8 being reported in the English literature [6-11]. Our case describes a patient with intravenous lipoleiomyomatosis who presented with concern for malignant degeneration of leiomyoma after an incidental finding of a large pelvic mass located at the sight of a previously imaged leiomyoma.

2. Case Report

A 37-year-old nulliparous woman initially presented to her primary gynecologist for routine exchange of her levonorgestrel intrauterine (IUD). The device's strings were not visualized on exam so an ultrasound was ordered to

assess its positioning. Patient's medical history was notable for nephrolithiasis and a left lower-extremity deep vein thrombosis that occurred during a period of immobilization while taking combined oral contraceptives (COC). Her surgical history included a laparoscopic left ovarian cystectomy performed 15 years prior to presentation. She had no family history of breast, ovarian, or colon cancer. Transvaginal ultrasound demonstrated a 25.7 × 11.5cm mass with solid components in the right adnexal region and complex cystic components in the left adnexal region. Solid components demonstrated flow on color and spectral Doppler interrogation. Neither ovary was visualized and the uterus was noted to be 9.6 × 3.9 × 8.0cm with IUD in proper position.

A CT scan of the abdomen and pelvis with contrast was obtained to further assess the mass (Figure 1). This confirmed a 18 × 22 × 29cm heterogeneous mass with primarily solid components located in the right side of the pelvis. An additional multi-loculated complex cystic mass was noted arising from the left ovary and measured 18 × 24 × 23 cm. The right ovary was not identified. A few mildly enlarged retroperitoneal para-aortic lymph nodes were noted (largest 22 mm). There was no evidence of omental or mesenteric tumor infiltration and no ascites. When compared to an ultrasound and MRI performed approximately 5 years prior (images not available), the large solid mass was found to originate in the same location as a 5.4cm intramural or subserosal fibroid.

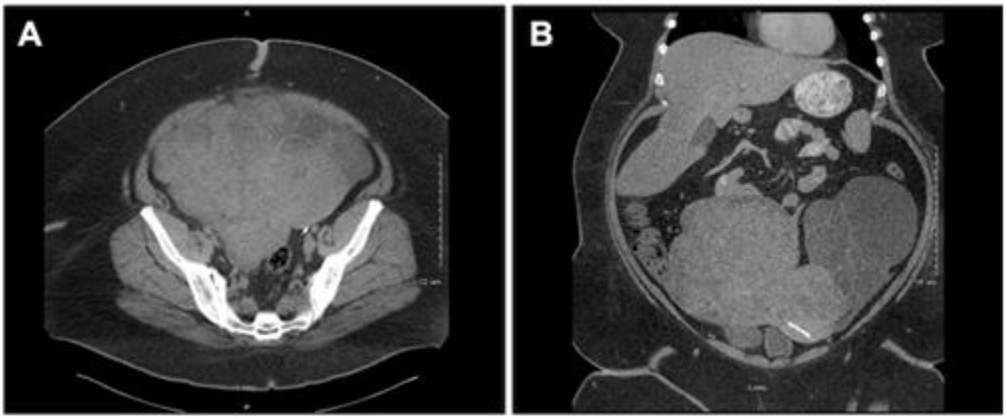

Figure 1: Preoperative CT abdomen and pelvis with IV contrast performed in 2016. (A) Transverse and coronal images demonstrating right-sided pelvic mass contiguous with uterus and left-sided cystic mass. (B) Intrauterine device visible on image B.

Patient had additional abdominal imaging 3 years prior to presentation in the setting of nephrolithiasis and sepsis (Figure 2). The non-contrast CT of the abdomen and pelvis at that time noted "slightly bulbous contour of the uterus…bilateral enlargement of the adnexal regions" with left adnexa measuring 9.8 × 8.7 × 7.7cm and right adnexa measuring 10.2 × 9.2 × 8.2 cm. Tumor markers revealed an elevated CA 125 (106 U/mL) and normal alpha-fetoprotein and CEA (1.1 ng/mL and <0.5 ng/mL, respectively). Given concern for a malignant transformation of the leiomyoma noted on prior imaging, the patient was referred to gynecologic oncology for further treatment. Surgical exploration and removal of the mass was recommended.

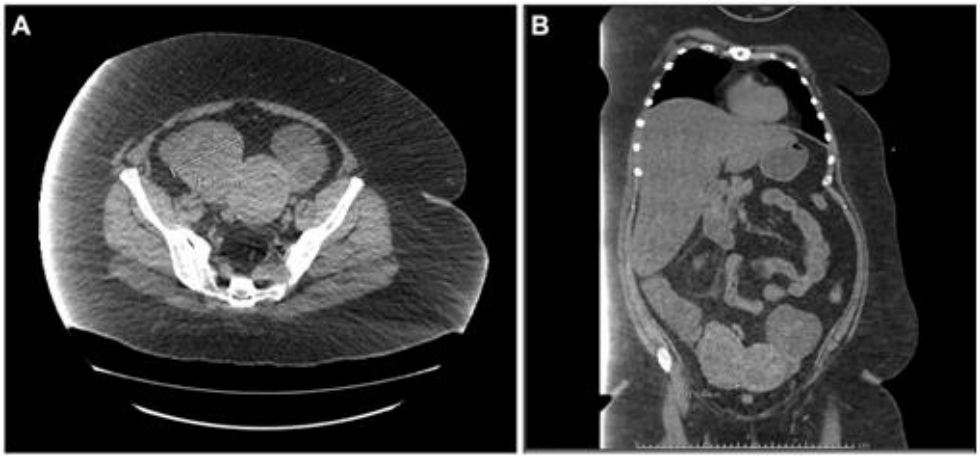

Figure 2: Non-contrast CT performed in 2013, 3 years prior to presentation for non-gynecologic indications. Imaging demonstrates similar orientation and distribution of pelvic masses at an earlier stage.

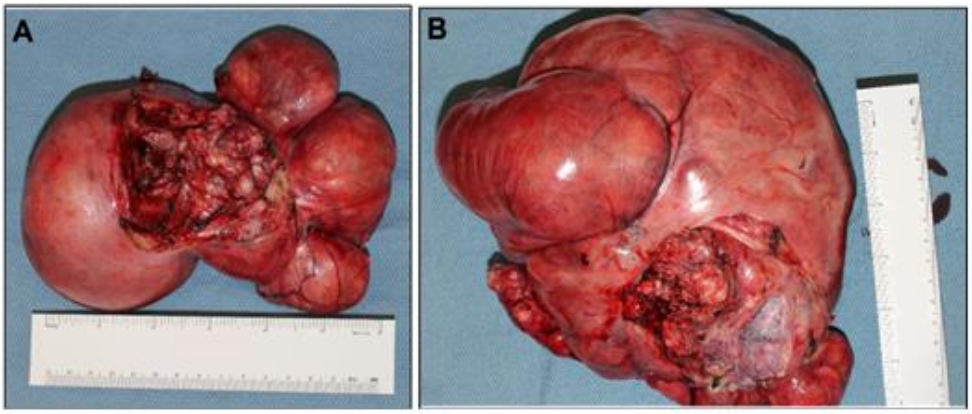

Figure 3: Gross surgical specimen. (A) showing cut edge of right lateral surface of uterus (anterior surface oriented toward top of page) and (B) showing cut edge of right-sided mass.

Laparotomy was performed via a midline vertical incision. Intraoperative findings demonstrated massive enlargement of both ovaries (>25 cm). The right ovary was visibly abnormal and neoplasm was noted to involve the right broad ligament and uterus (Figure 3). The left ovary was independent from this mass and appeared multi-cystic. All other peritoneal and visceral surfaces appeared grossly normal. A right salpingo-oophorectomy was performed and the specimen sent for intraoperative frozen section, which demonstrated a low-grade spindle cell neoplasm. Due to the gross involvement of the uterus with the right-sided neoplasm and the markedly abnormal left ovary, decision was made to proceed with hysterectomy and left salpingo-oophorectomy. Omental biopsy was also obtained. Her surgery was otherwise uncomplicated and had an estimated blood loss of 800 mL.

Histologic assessment of the right adnexal mass and uterus demonstrated intravenous lipoleiomyomatosis (Figures 4). Immunohistochemical staining of the right-sided solid mass was positive for smooth muscle actin (SMA), desmin, and CALD and negative for CD10. Cytogenetics showed 46

XX, t(9;12)(p22;q14) with reciprocal translocation identified in all cells from culture. Left ovary was found to be a benign serous cystadenoma.

Patient's postoperative course was unremarkable and she was discharged on postoperative day three. Given her history of DVT while using COC, estrogen replacement was deemed to be contraindicated so she was started on Effexor to treat menopausal symptoms. She was seen at routine postoperative visits and was found to be recovering appropriately. At her final clinic visit two months after her initial surgery, the patient was recommended to follow up with her regular OB/GYN for routine care.

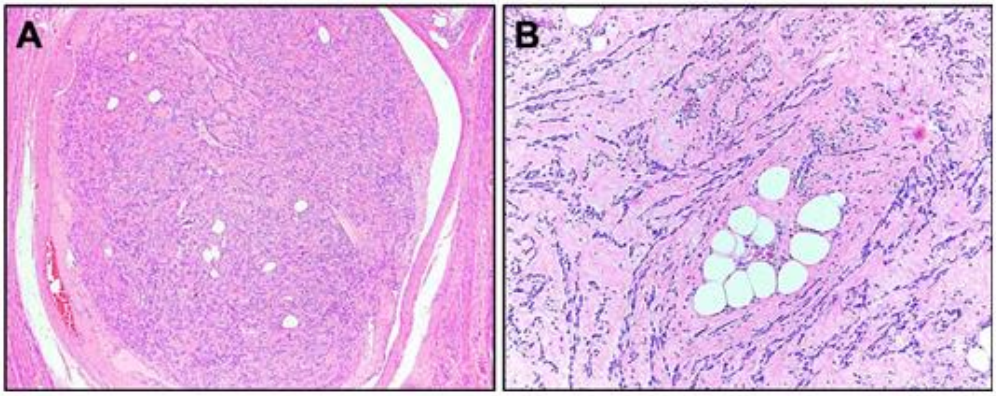

Figure 4: Histologic section (A) demonstrating intravascular component of smooth muscle within vessel on H&E staining. Higher-power representation (B) of lipomatous component within smooth muscle on H&E staining.

3. Discussion

Intravenous lipoleiomyoma is a very rare diagnosis and our case is the first in the literature to provide serial imaging of this condition. Intravenous leiomyomatosis has been reported to account for 0.097% of all smooth muscle tumors [1]. The exact rate of IVL is less clear given its apparent rarity and the potential for very early cases to be missed or misdiagnosed. Many case reports of IVL in the literature highlight cases of cardiac extension given the novelty of benign pelvic disease causing cardiopulmonary pathology. While the neoplasm itself is benign by definition, it has the potential for serious complications as it extends proximally through the vasculature and has even been attributed as the cause of death in several patients [12-14]. The pathogenesis of IVL is unclear and several hypotheses have been advanced. Based on early observations by Knauer, it has been suggested that IVL arises directly from smooth muscle in the vessel wall [15]. Alternatively, Sitzenfry, a contemporary of Knauer, supported IVL deriving from direct extension of primary leiomyoma into the vasculature [16]. Later case reports and evidence of immunohistochemical staining with desmin or ER/PR on tumor, but not vessels walls support the process of direct extension [17, 18]. Our case provides additional evidence for direct extension of the tumor into the vasculature based on the progressive growth and expansion of a uterine mass on imaging, which ultimately demonstrated intravenous components on pathology.

	Number of patients	Number of recurrences (%)	Age range (years)	Surgical treatment	IVC involvement	Number of incomplete tumor excision	Follow up (months)	Primary surgery in recurrent cases	
								Complete excision	Incomplete excision
Yu [34]	58	18 (31.0%)	24-60	8 TAH 37 TAH/BSO 6 TAH/USO 7 myomectomy	31	0	1-116 (median 11.5)	1 TAH 15 TAH/BSO 2 myomectomy	n/a
Mulvany [32]	22	1 (4.5%)	23-66	8 TAH 10 TAH/BSO 2 TAH/USO 2 myomectomy	None	Not noted	2-204 (median 90)	1 myomectomy	
Du [1]	18	3 (16.7%)	33-54	8 TAH 5 TAH/BSO 1 TAH/LSO 1 SCH 1 myomectomy	None	1	22-104 (median 42.5)	8 TAH	1 myomectomy
Clement [9]	16	2 (12.5%)	28-76	1 TAH 8 TAH/BSO 2 TAH/USO 1 SCH 2 TVH 1 USO 2 hysterectomy NOS	None	4	12-228 (median 72)	1 TAH/BSO	1 TAH/USO

Carr [30]	14	2 (14.3%)	35-64	4 TAH 7 TAH/BSO 1 TVH 1 SCH 1 myomectomy	2	Not noted	2-194 (median 30)		1 myomectomy 1 TAH
Norris [33]	14	2 (14.3%)	36-70	2 TAH 3 TAH/BSO 6 TAH/USO 2 SCH/BSO 1 noted at autopsy	1	3	12-250 (median 50.4)		1 TAH/USO
Tang [17]	13	0 (0%)	28-56	2 TAH 3 TAH/BSO 2 TAH/USO 6 SCH	None	0	6-90 (median 20)	n/a	n/a
Low [31]	9	2 (22.2%)	32-52	1 TAH 4 TAH/BSO 2 SCH/BSO 2 myomectomy	None	5	60 (no median provided)	n/a	1 TAH 1 myomectomy
Nogales [35]	7	0 (0%)	29-80	2 TAH 4 TAH/BSO 1 TAH/USO	None	0	12-60 (median 16)	n/a	n/a
Total	171	30 (17.5%)							
TAH total abdominal hysterectomy, BSO bilateral salpingooophorectomy, USO unilateral salpingooophorectomy, SCH supracervical hysterectomy, TVH transvaginal hysterecto NOS not otherwise specified									

Table 1: Summary of patient data from nine largest case series.

Previous cytogenetic analysis of IVL has suggested that rearrangement or deletions of 12q14-15 and possibly 14q24 may contribute to the development of IVL [19-21]. Additionally, cytogenetic characterization of lipoleiomyoma has described reciprocal translocation of t(5;12)(q12;q24) [22] and t(12;14)(q15;q22),der(1),der(5) [23]. Our case demonstrated a karyotype with 46 XX, t(9;12)(p22;q14). While the translocation of 12q14 in our patient does coincide with prior anomalies found in IVL, there have only been two other reports of uterine leiomyomas with translocation of chromosomes 9 and 12 in the literature, both with t(9;12)(p22;q15) [24, 25]. Of note, our patient's cytogenetic abnormality has been previously reported in only three lipomas and one myolipoma, which is interesting considering the coexistence of lipoleiomyoma in this case [26-29]. Long-term surveillance of patients with IVL is important due to the potential for recurrence. Recurrence of IVL has been reported to range from 0.0% to 50.0% (Table 1) [1, 9, 17, 30-35]. The largest retrospective study of 58 cases from a referral center in China found an association with IVC involvement and recurrence (OR 13.33, 2.68-66.26) in patients who had complete resection of tumor, but no association between age >50 years old, adjuvant hormonal therapy, hysterectomy vs tumor resection, or ovarian conservation. [34] Smaller case series have suggested association between patient age <40 years old, [1] myomectomy instead of hysterectomy [1, 31], and complete resection of tumor [31, 36].

Although IVL is a benign neoplasm, the potential for fatal obstruction of the heart or pulmonary vasculature warrants monitoring for recurrence. One study reviewed atypical histologic variants of IVL (including two cases of LPL) and concluded that histologically benign tumors with intravenous involvement should be managed and monitored in the same manner as typical IVL [9]. Different modalities and frequencies of surveillance have been suggested by different authors, but, most are in agreement that serial imaging is indicated [1, 34, 37, 38].

Lipoleiomyoma presenting with intravascular extension is exceedingly rare. A total of 8 were identified in the English literature since 1988 [6-11]. Lipoleiomyomas are uncommon variants of smooth muscle tumors with a mixture of smooth muscle and mature adipose tissue and no significant nuclear atypia. While there have been a few case reports describing malignant transformation into sarcomas [39, 40], LPL are benign by definition and are managed similar to typical leiomyomas. Imaging findings for IVL or LPL have some classic findings. Intravenous leiomyomatosis beyond the pelvis is most often identified as a continuous, heterogeneous mass originating in the pelvis and extending to the IVC [3, 41]. While IVL that has progressed to the main vasculature is often apparent on imaging, early disease may have less obvious findings or even sub-centimeter vascular involvement that is not visible. One series noted that approximately two thirds of the 22 cases they evaluate had either minimal vascular involvement (≤3mm) or vascular involvement limited to the myometrium [32].

Lipoleiomyoma may have a variable appearance on imaging, which makes radiologic diagnosis sometimes difficult. Ultrasound studies may demonstrate a hyperechoic mass surrounded by a thin, hypoechoic ring of normal myometrium [42, 43]. This presentation is more typical of LPL and may facilitate preoperative diagnosis [44]. Lipoleiomyoma can also present as a heterogeneous uterine mass with less clear margins. Using fat suppression techniques with MRI may help demonstrate the presence of both adipose and non-adipose tissue, but a histologic

diagnosis would be necessary to evaluate for a possible liposarcoma [45, 46].

This case is the first to provide serial imaging of intravenous lipoleiomyomatosis over years and additionally provides cytogenetic information that corroborates prior studies.

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