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A Case of Uterine Leiomyoma with Intravenous Leiomyomatosis—Histological Investigation of the Pathological Condition—

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Abstract Intravenous leiomyomatosis (IVL) is generally defined as a histologically benign leiomyoma derived from a uterine myoma or intrauterine venous wall that has grown and extended intravenously. We here report on a single case of IVL, and investigate its pathological genesis. Regarding the part of the myoma extending to the vessel lumen, observations found the myoma to be pushing into the vessel. Immunostaining with CD34 antibody gave an image of the area where the myoma pushed into the vessel, showing CD34-positive vessel endothelium cells folded back into a layer covering the myoma, and continuing to line of the surface of the myoma within the vessel. Early pathological genesis of IVL was clarified for the first time that the tumor did not invade the vessel by breaking the venous wall, but rather advanced by stretching the vascular wall and progressing into the vein like a polyp, covered in endothelium cells.

Keywords CD-34 antibody · Immunostaining · Intravenous leiomyomatosis · Pathological genesis · Uterine leiomyoma

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Introduction

Intravenous leiomyomatosis (IVL) is generally defined as a histologically benign leiomyoma derived from a uterine myoma or intrauterine venous wall that has grown and extended intravenously [1]. There are many reported cases of IVL. IVL is exposed to venous blood that flows to the heart and has an unusual pattern of growth, growing slowly and extending into the venous system with the possibility of reaching the heart undetected. This pathological state is named intracardiac leiomyomatosis (ICL) and results in cardiac failure, fainting and in some cases, sudden death [2, 3]. The concepts of IVL and ICL as disorders have gained a wider acceptance, with recently reported cases from the gynecological and cardiovascular fields increased [4]. While the majority of reports simply raise warning with regards to this rare disease, there has been no reexamination of its pathogenesis. We reported on a single case of IVL, and investigated its pathological genesis.

Patient

The patient was a 43-year-old woman with gravida 3 para 2 (2 natural births, 1 natural miscarriage). Her past medical history consisted of an appendectomy at age of 15 years old, with nothing of particular note in the family's medical history. On visiting a practice for internal medicine earlier in August 2008 for upper respiratory inflammation, the patient was found to have a pelvic mass. Referred to our clinic for further testing, the patient was diagnosed with uterine myoma. Pelvic examination on the initial visit found a uterus the size of a child's head, of firm elasticity, with fairly low mobility and a cord-like tumor through the left

fornix of the vagina. At the time, the tumor was thought to be a myoma on the posterior wall. Blood and biochemical tests found only mild hepatic dysfunction, otherwise within normal range of tumor markers such as CA125, CA19-9, and LDH isozyme. MRI examination found a uterine myoma reaching navel height, which seemed partly continuous with the outside of the uterus.

Results

Surgical Findings

The surgery was planned to be an abdominal total hysterectomy under general anesthesia. During operation, induration was constantly felt from within the left ovarian veins to the uterus. Clamping of the left suspensory ligament of the ovary revealed the myoma existing within the left ovarian vein. The myoma had also invaded the left uterine vein, and invaded from the deep uterine vein to inside the cardinal ligament vessels. These vessels were carefully incised and the area confirmed free of any remaining myoma by palpation. The diagnosis was IVL with myoma growth within the uterine vein and left ovarian vein. Contrast CT was carried out from chest to pelvis on the second day after surgery to evaluate for the existence of any remaining myoma within the vessels, with no lesions found in any vessels. The patient was discharged with no complications, such as post-operative venous embolism. Ten months have passed since the surgery with no abnormalities.

Macroscopic Findings

The resected uterus and ovary weighed 680 g (Fig. 1a). The cut surface of the myoma nodules was white, and they were fibrous and hard. There were protrusions from the nodules into the uterine and ovarian veins. The length of the protrusions was approximately 10 cm and 5 cm, respectively (Fig. 1b). Surfaces of protrusions were smooth, and there was no hemorrhage or necrosis.

Microscopic Findings

The myoma nodules consisted of proliferation of spindle cells (Fig. 2a). There was no remarkable increase in the mitotic figures, and the MIB1-index was estimated approximately 1 to 2%, clearly confirming non-malignancy (Fig. 2a). Regarding the part of the myoma extending to the vessel lumen, observations found the myoma to be pushing into the vessel (Fig. 2b). Immunostaining with CD34 antibody gave an image of the area where the myoma pushed into the vessel, showing CD34-positive vessel endothelium cells folded back into a layer covering the myoma, and continuing to line of the surface of the myoma within the vessel (Fig. 2c). No images were found of myoma cells breaking endothelial cells to expose the vessel lumen. The tip of the myoma within the vessel was also covered with vessel endothelium. The histological diagnosis was uterine leiomyoma with intravenous leiomyomatosis.

Discussion

IVL is a pathology that may progress to ICL, a potentially life-threatening disorder [2, 3]. Regarding the pathogenesis of IVL, Knauer [5] suggested in 1903 that this is a leiomyoma originated from the venous wall, while Sitzenfrey [6] hypothesized in 1911 that this is the uterine leiomyoma which invaded into the uterine vein. In 1975 Norris et al. [1] carried out a histological search of 14 cases

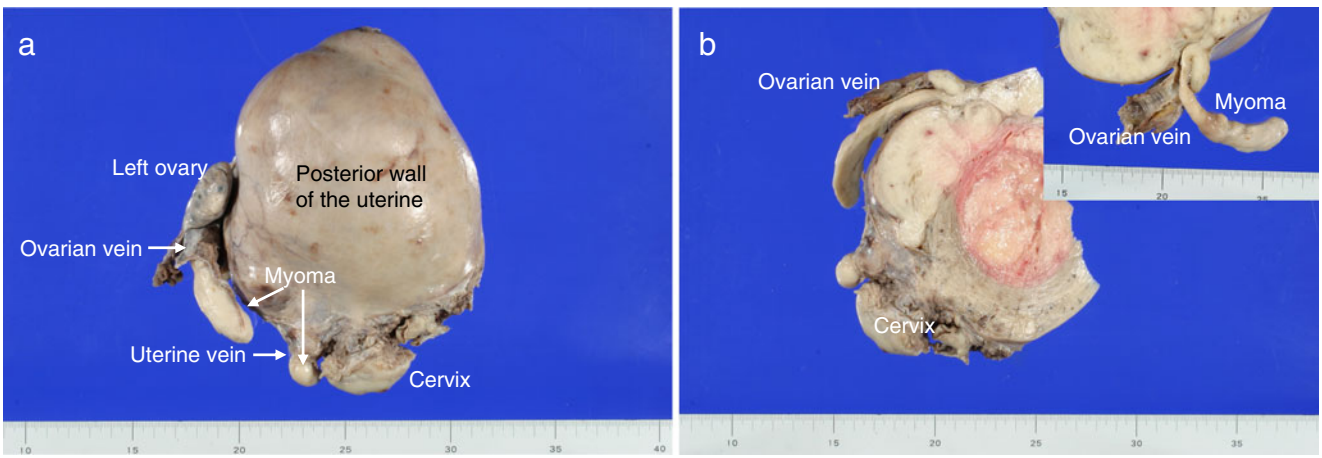

Fig. 1 Macroscopic findings. **a**, Excised uterus and appendages. **b**, Tumor protrudes from left ovarian vein and left uterine vein

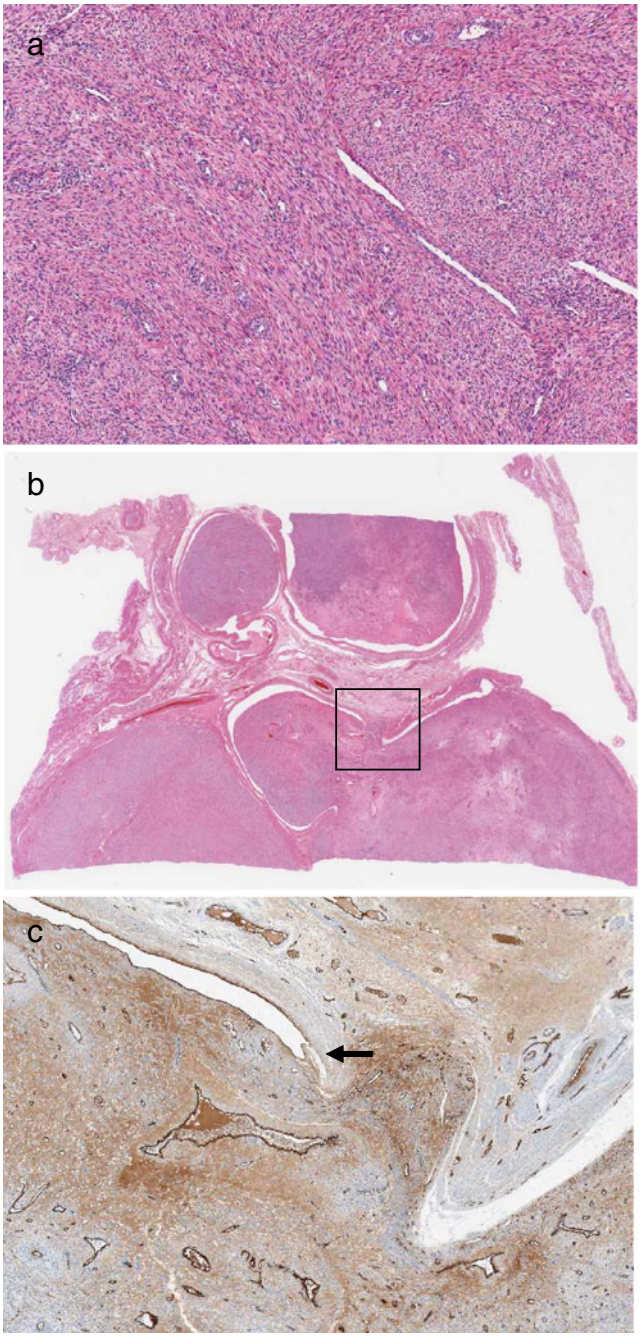

Fig. 2 Pathological findings. **a**, H-E staining of tumor. Refer to main text for findings. Magnification: X100. **b**, Leiomyoma can be seen within the vessel. Observation that leiomyoma seems pushed into the vessel. Magnification: X10. **c**, Immunostaining by CD34 antibody. Enlarged view of area in Figure b surrounded by a black line. The arrow indicates the region where CD34-positive vascular endothelial cells are folded back to cover the tumor. Magnification: X100

of IVL. They defined IVL to be a histologically benign leiomyoma but they still suggested on the origin of this condition being derived from an uterine myoma or venous wall. Merchant et al. [7], on the other hand, reported on a peculiar vascular architecture in IVL and named this as "vessels within vessels" and hypothesized this unique vessel structure may be the reason it is possible for leiomyoma to occur in the arterial wall, within the venous lumen and extend into blood vessels.

Recently, the disease concepts of IVL and ICL have become widely known, with an increased number of cases reported, with one of either above theories supported to explain the mechanism of generation. To date there have been no reports on a pathological condition showing how leiomyoma occurs in the uterine muscle layer and extends inside the vessel. The present study demonstrated that the surface of the intravenous leiomyoma was covered by endothelial cells, suggesting for the first time that the tumor did not invade the vessel by breaking the venous wall (Fig. 3), but rather advanced by stretching the vascular wall and progressing into the vein like a polyp, covered in endothelium cells (Fig. 3). The case shows the tumor to progress a maximum of 10 cm into the veins, but not to what extent a tumor may progress within the vessel with vascular wall covering intact, or when the vascular wall may be broken. It would be reasonable to think that cases of ICL and embolized pulmonary vein are the result of breakage of the vascular wall covering the tumor, or the tip separation at some point. According to a review by Lam et al. [4] 38 out of 68 cases of ICL had history of total hysterectomy, with a median period from total hysterectomy to ICL diagnosis of 4 years. At this point it is difficult to think that IVL derived from a uterine vein or ovarian vein stump, so the scenario of an IVL covered with vascular wall and missed upon hysterectomy, given time to grow and become an ICL can be considered likely. If the tumor had remained in the vessel after separation within the vessel, embolization should have occurred at an earlier stage. In this present case, the possibility of ICL occurring was judged almost none as the tip was observed carefully for any separations during surgery, and CT scan examination was conducted after surgery to confirm no tumors remained in any vessel.

IVL is usually a condition found by chance during surgery [4]. As reported in past cases, if cord-like tumors are felt on the cervix-side [8], and if pre-operative images are inspected with IVL disorders kept in mind [9], it is possible that IVL will be diagnosed prior to surgery. In reality however, pre-operative diagnosis is extremely difficult. Emergency surgery is required if the condition progresses to ICL, but even if some tumor remains after operating for IVL, progression is known to be slow [4], with sufficient time in place to consider measures for ICL prevention that make use of the estrogen-dependent character of IVL [10], such as Gn-RH analog therapy, laparoscopic oophorectomy, and termination of ovarian function by irradiation.

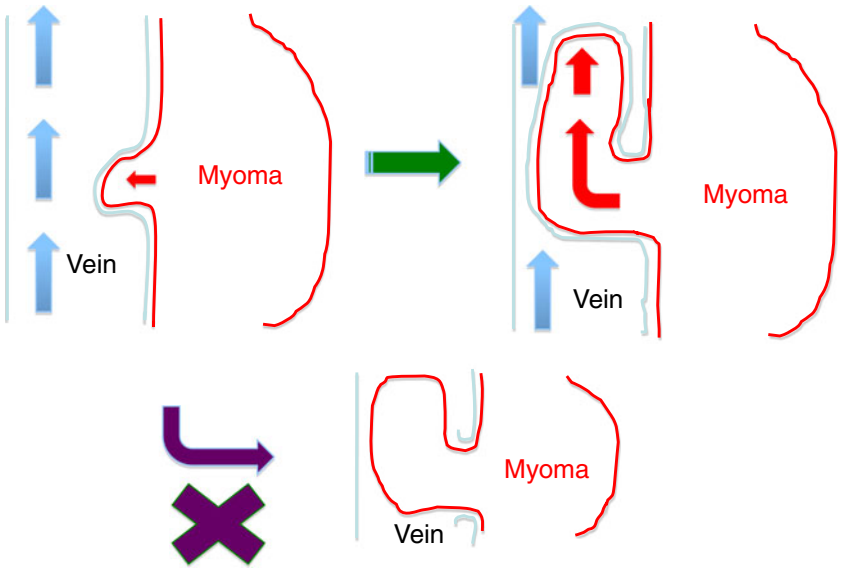

Fig. 3 Schema of IVL pathogenesis for this case. The tumor does not break the venous wall and invade the vessel, but pushes the vascular wall with a covering of endothelial cells as a polyp-shaped tumor

Conclusion

One case of uterine leiomyoma with rare IVL was found. Through morphological investigation, it was shown that a myoma stretched the vascular wall to extend along the vascular lumen while covered in endothelium. Even when discovery of IVL is a chance occurrence, confirming with extreme caution that the tip of the tumor is not broken or separated is most important for prevention of ICL.

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References

1. Norris HJ, Parmley T (1975) Mesenchymal tumors of the uterus. Intravenous leiomyomatosis. A clinical and pathologic study of 14 cases. Cancer 36:2146–2178
2. Timmis AD, Smallpeice C, Davies AC et al (1980) Intracardiac spread of intravenous leiomyomatosis with successful surgical excision. N Engl J Med 303:1043–1044
3. Suginami H, Kaura R, Ochi H et al (1990) Intravenous leiomyomatosis with cardiac extension: successful surgical management and histopathological study. Obstet Gynecol 76:527–529
4. Lam PM, Lo KW, Yu MY et al (2004) Intravenous leiomyomatosis: two cases with different routes of tumor extension. J Vasc Surg 39:465–469
5. Knauer E (1903) Beitrag zur Anatomie der Uterusmyome. Beitr z Gynäk 1:695
6. Sitzenfrey A (1911) Ueber Venenmyome des Uterus mit intravaskulärem. Ztschr f Geburtsh u Gynäk 68:1
7. Merchant S, Malpica A, Deavers MT et al (2002) Vessels within vessels in the myometrium. Am J Surg Pathol 26:232–236
8. Oki A, Yoshikawa H (2007) Intravenous leiomyomatosis. Obstet Gynecol (Tokyo) 74:663–669, In Japanese
9. Nam MS, Jeon MJ, Kim YT et al (2003) Pelvic leiomyomatosis with intracaval and intracardiac extension: a case report and review of literature. Gynecol Oncol 89:175–180
10. Mitsuhashi A, Nagai Y, Sugita M et al (1999) GnRH agonist for intravenous leiomyomatosis eith cardiac extension. A case report. J Reprod Med 44:883–886