A broad ligament solitary fibrous tumor with Doege–Potter syndrome

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Abstract

Introduction Solitary fibrous tumors (SFTs) are uncommon mesenchymal neoplasms and are particularly rare in the female genital tract. Doege–Potter syndrome is a paraneoplastic syndrome involving SFT-associated hypoglycemia. We report, for the first time, on a broad ligament SFT with Doege–Potter syndrome; additionally, we review 30 cases of women with SFTs reported in the literature.

Patient concerns A 37-year-old woman who presented with life-threatening hypoglycemia and a pelvic mass (16 × 15 × 15 cm).

Diagnoses The patient was diagnosed with broad ligament SFT with Doege–Potter syndrome.

Interventions Tumor resection, sub-extensive hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy were performed, and 6 cycles of adjuvant chemotherapy were administered.

Outcomes Serum glucose levels returned to normal as soon as the tumor was resected. Forty-three months after operation, there was recurrence in the posterior peritoneal tissues. She underwent tumor resection and has remained tumor-free 28 months after this excision.

Conclusion Even though it is extremely rare, SFT should be quickly identified to prevent undue treatment delay and avoid unnecessary examination; surgery and long-term follow-up are recommended. SFT can be considered a highly invasive cancer, and intraoperative bleeding may occur. Although no correlation between adjuvant therapy and improved prognosis was found, further studies are required because of the small number of cases reported to date.

Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging, SFTs = solitary fibrous tumors.

Keywords: broad ligament, Doege–Potter syndrome, female genital tract, solitary fibrous tumor

1. Introduction

Solitary fibrous tumors (SFTs) are an uncommon mesenchymal neoplasm with an incidence rate of 2.8 per 100,000\textsuperscript{1,2} Paraneoplastic syndrome of hypoglycemia (Doege–Potter syndrome) is observed in 5% to 10.4% of all patients\textsuperscript{3} While this tumor type can be found in any organ, its occurrence in the female genital tract is extremely rare. There were more than 2000 cases of SFTs reported in the English-language literature; approximately 80 of these cases involved hypoglycemia, and 30 originated in the female genital tract. We here reported for the first time a broad ligament SFT with Doege–Potter syndrome.

1.1. Case report

A previously healthy 37-year-old woman presented at our institution with an enormous pelvic mass and severe hypoglycemia. Beforehand, she had visited the Department of Sleep and Endocrinology complaining of occasional drowsiness and confusion for 1 month. She had never complained of any symptoms related to the gynecologic or gastrointestinal organs.

Laboratory data revealed persistent hypoglycemia (glucose 6.61–2.97 mmol/L [normal, 3.90–6.10]), insulin 0.20 μU/mL [normal, 1.50–15], C-peptide < 0.01 mmol/L [normal, 0.48–0.78], and insulin-related growth factor-1 36 ng/mL [normal, 94–358]). Test results ruled out a functional islet cell tumor, thyroid dysfunction, or adrenal dysfunction. Computed tomography (CT) of the pelvis showed that the right iliac vessels were pressed against the congruous pelvic wall by an enormous pelvic mass, and intravenous blood flowed from the mass towards the womb (Fig. 1A, 1B). Meanwhile, CT scans of the brain, thorax, and stomach were normal. A mass as large as a 16-week pregnant uterus with no tenderness was found through bimanual examination on the right pelvis, and the patient’s actual uterus was pushed to the left. A presumptive diagnosis of a broad ligament leiomyoma was made.

A massive lesion covered by dense thumb-wide vasculum within the right broad ligament was observed under exploratory laparotomy, which was consistent with CT data. Tumor resection, sub-extensive hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy were subsequently performed by the most experienced group at our institution since the tumor appeared to be a poorly differentiated endometrial stromal sarcoma (ESS) on frozen sectioning. The surgery lasted 400 min, and the volume of blood loss was 5000...
mL in total while that of the mass resection was 4900mL; 12 units of packed red cells and 1000mL of plasma were administered. Serum glucose levels soared to 17.10mmol/L as soon as the tumor was resected. The patient subsequently recovered well and was discharged on day 5 post-surgery.

Macroscopically, the tumor measured 16 × 15 × 15cm with clearly defined margins. It exhibited a rotten fish, meat-like, and jelly-like appearance and was grayish-white in color with multiple cystic components containing brown liquid. Microscopically, the atypical neoplastic tumor cells were in a poorly formed arrangement with approximately 14 mitotic figures per 10 high-power fields (Fig. 2A); branching vessels (Fig. 2B) and necrotic foci (Fig. 2C) were also observed. Immunohistochemically, the tumor was positive for CD34 (Fig. 2D), CD99 (Fig. 2E), vimentin, and CD10, and was negative for Bcl-2, smooth muscle actin, and S100. The uterus, adnexa, and lymph nodes were negative for tumor cells. These results strongly supported a diagnosis of malignant SFT of the broad ligament of the uterus and Doege–Potter syndrome with R0 resection.

Six cycles of adjuvant chemotherapy with azithromycin, decarbonize, and ifosfamide were administered. Owing to the complete surgical resection, radiotherapy was not administered to this patient. Transvaginal ultrasonography was performed every 3 months and radiography was performed every 6 months for follow-up.

Forty-three months after surgery, CT scanning revealed a recurred right pelvic mass that was fundamentally different from the first. This was an intraperitoneal mass (7 × 6.5 × 4cm) with the right iliac vessels pushed to the left side; moreover, the peritoneum was separated from the pelvic cavity by the tumor (Fig. 3). The tumor was excised with 80mL of blood loss, and a recurrence of malignant SFT was confirmed.

Currently (67 months after the first surgery), the patient is alive and being followed; there have been no episodes of hypoglycemia and she has remained tumor-free 28 months after the second excision. (Table 1.)

2. Discussion

We searched the PubMed database using the search terms “solitary fibrous tumor,” “Doege–Potter syndrome,” “pelvic,” “uterus,” “cervix,” “fallopian tube,” “ovary,” “vagina,” and
Patients without recorded details were excluded. A total of 30 patients with SFT were found described in reports published between 1998 and 2017; their characteristics are listed in Table 2.

2.1. Clinical findings

The median age of female patients was 51 years (range, 14–78 years). The most common location was the vulva (11/30), followed by the vagina (6/30), uterine corpus (6/30), uterine cervix (4/30), fallopian tube (1/30), round ligament (1/30), and broad ligament (1/30). The maximum tumor diameter ranged from 1 to 23 cm (median, 6 cm).

The clinical presentations of SFTs vary according to the tumors’ locations, sizes, and features. There are usually no symptoms (14/30), especially at an early stage. Therefore, they tend to be large when discovered, and may also be found incidentally during imaging tests performed for other reasons. Large tumors may be accompanied by symptoms of regional pain.

Figure 2. Histochemical findings of the pelvic tumor (hematoxylin and eosin staining). (A) (×400): atypical spindle neoplastic cells (arrow d); (B) (×200): branching vessels (arrow e); (C) (×40): Necrotic foci (arrow f). Immunohistochemical findings using EnVision staining showed positivity for (D) (×400): CD34 and (E) (×400): CD99 (brown areas).
or abnormal vaginal bleeding (5/30). SFTs of the vulva and vagina always present with a palpable mass (3/30).[4,5] The paraneoplastic syndromes seborrheic keratosis (the Leser–Trelat sign), acromegaly (Pierre-Marie-Bamberger), and hypoglycemia (Doege–Potter) can rarely occur as a secondary effect of the tumor. Among the 30 patients investigated, only 1 was admitted to the hospital because of hypoglycemia with uterine corpus SFT; to our knowledge, ours is the first reported case of broad ligament SFT presenting with Doege–Potter syndrome.[6]

2.2. Clinical diagnosis

Laboratory findings of SFTs are always unremarkable. In previous reports, 5 patients were described as having undergone B ultrasonography examination, 7 underwent CT, and 2 underwent magnetic resonance imaging (MRI); 1 underwent both CT and MRI; imaging studies were not mentioned for 15 patients. However, imaging examination alone is insufficient for differential diagnosis, as it lacks the ability to detect certain features typical of SFTs. CT scanning and MRI show tumors with a clear boundary and heterogeneous density that push against surrounding organs, but never with invasion. On the other hand, imaging is very effective for assessing the links between tumors and adjacent organs, and for determining whether a distant metastasis is present. Thus, once the diagnosis is established, the patient is recommended for re-evaluation with imaging to rule out a concurrent tumor, especially in the chest.[7,8] Regular imaging examinations are also especially useful for follow-up examination.

Experienced pathologists are critical for the diagnosis of SFTs. Core needle biopsy of the superficial tumor is necessary for accurate disease diagnosis and prompt treatment; however, this has not been broadly applied in gynecological settings. Only 4 patients underwent fine-needle aspiration biopsy and were accurately diagnosed with SFTs preoperatively. A possible reason for the absence of fine-needle aspiration biopsy is that gynecologists do not consider this rare disease and instead assume uterine leiomyoma, ovarian cysts, cervical polyps, and even abscesses. Since the bulky lesion may have a rich blood supply (as was the case in our patient), the possibility of life-threatening hemorrhage ought to be considered. Additionally, the unpredictable biological behavior combined with the exceedingly rapid growth of these tumors may lead to needle-core biopsies and surgical specimens yielding discordant data.[9,10]

Grossly, the reported tumors ranged from 1 to 23 cm in maximum diameter (median: 6 cm) and generally comprised of firm lesions with well-demarcated margins and smooth surfaces. The cut face showed a mixture of solid and cystic components; some also exhibited mucinous areas. Microscopically, typical SFTs presented as both hypercellular and hypocellular lesions, with fibroblast-like cells in “patternless” patterns and “staghorn vascular cavity” formations. The definitive diagnosis required immunohistochemical analysis. In the 30 cases reviewed, all of the spindle cells (100%) expressed CD34; positivity for CD34 is reportedly a characteristic presentation observed in 90% to 95% of all SFTs.[11] Recently, Robinson et al.[12] proposed a genetic diagnosis criterion, reporting that the NAB2-STAT6 fusion gene is specific to SFTs and can lead to STAT6 immunexpression. Indeed, STAT6 is a biomarker with high sensitivity and specificity for distinguishing and diagnosing SFTs.

Diagnosing SFTs is a complex process; our patient serves as a reminder that, although extremely rare, Doege–Potter syndrome in the female reproductive organs should be quickly ruled out. If diagnosed, a multidisciplinary treatment effort is necessary.

**Table 1**
The milestones of diagnosis and interventions. ESS = endometrial stromal sarcoma, SFT = solitary fibrous tumors.

| Date          | Events                                |
|---------------|---------------------------------------|
| September, 2012 | Hypoglycemia occurred                 |
| October, 2012  | Surgery with frozen diagnoses as ESS   |
| December, 2012 | Pathological diagnosis was modified as SFT |
| December, 2012 | Adjuvant Chemotherapy                 |
| May, 2016      | Recurrence and surgery therapy        |
| May, 2018      | Follow-up every 6 months              |
2.3. Clinical treatment

All 30 patients retrieved in our study were treated with en bloc excision; additionally, 9 (30%) underwent hysterectomy, and 4 (13.3%) underwent pelvic lymphadenectomy. As for adjuvant therapy, 3 women (10%) received radiation therapy and 1 (3.3%) underwent pelvic lymphadenectomy. As for adjuvant therapy, 3 women (10%) received radiation therapy and 1 (3.3%) underwent pelvic lymphadenectomy. Complete surgical resection with a clear margin is currently the most effective treatment modality, and surgery remains the best option for recurred tumors.[7,13] Nevertheless, owing to these tumors' anatomical locations (e.g. the vagina, uterus, or cervix), adhesiveness and bulk present serious challenges to complete excision, therefore, the scope of surgery should be expanded appropriately to be manageable.

Discerning between benign and malignant SFTs is challenging, as their biological behaviors are difficult to predict. Hence, it is reasonable to treat all SFTs under the assumption that they are highly invasive. Mearini et al.[14] reported a patient with a renal SFT that was difficult to diagnose definitively during the surgery; therefore, lymphadenectomy was performed after which lymph node metastases were discovered after the operation. A 64-year-old patient underwent mass resection, hysterectomy, bilateral salpingo-oophorectomy, and supplementary surgery involving inguinal lymph node dissection for malignant vulval SFT; however, she died of cancer metastasis.[15] In our patient described herein, we extended the scope of surgery owing to her tumor status and her own family's wishes; despite this, she experienced a recurrence.

Furthermore, previous case studies strongly emphasize the importance of controlling intraoperative hemorrhaging instead of merely ensuring an adequate blood supply during surgery. In a patient with a 9.8 cm vulval SFT, 75 mL of blood was lost owing to a hysterectomy, while 500 mL was lost during tumor resection.[16] Noeakowski et al.[2] described an operation for a cervix SFT (16 × 10.9 × 9.8 cm) that caused 2200 mL of blood loss. Other reports also described failed surgeries in which preoperative evaluation was not adequately performed because of massive bleeding. Pelvic SFTs usually have multiple feeder vessels and always arise from the internal iliac and inferior gluteal arteries. Some cases even arise from the internal iliac arteries.[22] Therefore, pelvic SFTs usually require radical surgical procedures for treatment.

### Table 2

| References | Age (yr) | Location | Pathology | Adjuvant Treatments | Recurrence/Metastases | Follow-up (months) |
|------------|---------|----------|-----------|---------------------|-----------------------|-------------------|
| (Fukunaga, 2000) | 70 | Vulva | Benign | No | No | 9-mo, AWOD |
| (Biedrzycki, 2007) | 65 | Vulva | Benign | No | No | 6-mo, AWOD |
| (He, 2010) | 39 | Vulva | Benign | No | No | 10-mo, AWOD |
| (Lee, 2011) | 75 | Vulva | Benign | No | No | NA |
| (Vayssie, 2011) | 37 | Vulva | Malignant | No | No | 16-mo, AWOD |
| (Burnett, 2012) | 60 | Vulva | Malignant | No | No | 30-mo, AWOD |
| (Taki, 2012) | 56 | Vulva | Benign | No | No | 18-mo, AWOD |
| (Nag, 2015) | 57 | Vulva | NA | No | No | 24-mo, AWOD |
| (Pearre, 2017) | 64 | Vulva | Malignant | Radiotherapy | Pleura, bone | 5-mo, DOD |
| (Tardo, 2017) | 59 | Vulva | Benign | No | No | 44-mo, AWOD |
| (Tardo, 2017) | 25 | Vulva | Malignant | Radiotherapy | vulva | 23-mo, AWOD |
| (Wakami, 2005) | 78 | Uterine | Benign | No | No | 24-mo, AWOD |
| (Thaiyong, 2006) | 47 | Uterine | Benign | No | No | NA |
| (Chu, 2006) | 78 | Uterine | Benign | No | No | 12-mo, AWOD |
| (Casanova, 2012) | 39 | Uterine | Malignant | No | No | 50-mo, AWOD |
| (Dvorak, 2013) | 57 | Uterine | NA | No | NA | NA |
| (Strickland, 2016) | 81 | Uterine | Benign | No | Pleura | 6-mo, AWD |
| (Akiyama, 2000) | 34 | Vagina | Benign | No | No | NA |
| (Vadmal & Pellegrini, 2000) | 66 | Vagina | Benign | No | NA | NA |
| (Iyengar, 2007) | 52 | Vagina | Benign | No | vagina | 29-mo, AWOD |
| (Picci & Robert, 2012) | 48 | Vagina | Benign | No | No | 7-mo, AWD |
| (Reyhan, 2017) | 21 | Vagina | Malignant | No | No | 90-mo, AWOD |
| (Turkistani, 2002) | 37 | Paravaginal | Benign | No | NA | NA |
| (Hasegawa, 1998) | 78 | Cervix | Benign | No | No | 132-mo, AWOD |
| (Sidebotham, 2009) | 14 | Cervix | Benign | Radiotherapy, chemotherapy | NA | NA |
| (Rahimi, 2010) | 68 | Cervix | Benign | No | No | 8-mo, AWOD |
| (Nowakowski, 2014) | 45 | Cervix | Benign | NA | NA | NA |
| (Bezal-Camacho, 2005) | 32 | Fallopian pain | Benign | No | No | NA |
| (Porter, 2008) | 42 | Round ligament | Benign | No | No | 72-mo, AWD |
| (Gubor, 2007) | 50 | Broad ligament | Benign | No | No | NA |
| Present case | 37 | Broad ligament | Malignant | Chemotherapy | Peritoneum | 71-mo, AWOD |

*AWD = alive with disease, AWOD = indicates alive without disease, DOD = died of disease, NA = data not available.*
mucosal disease. 

4. Discussion

4.1. Pathological findings

Histopathological examination of the excised tissue showed a well-differentiated leiomyoma. The tumor was composed of spindled smooth muscle cells arranged in a fascicular pattern. Mitotic activity and atypical mitotic figures were not observed. Immunohistochemically, the tumor cells were positive for smooth muscle actin and negative for desmin. These findings were consistent with a diagnosis of leiomyoma.

4.2. Differential diagnosis

The differential diagnosis of the presented case included other causes of rectal bleeding, such as ulcerative colitis, Crohn's disease, and vascular anomalies. However, these conditions were unlikely based on the clinical presentation and endoscopic findings. Additionally, the absence of rectal polyps or masses in the colonoscopy further excluded the possibility of other gastrointestinal malignancies.

4.3. Clinical implications

The diagnosis of leiomyoma in the rectum is unusual and often presents as a non-specific symptom such as rectal bleeding. Поэтому, a high index of suspicion and thorough evaluation are crucial in the management of such cases. The follow-up of the patient is scheduled to monitor for any recurrence or progression of the disease.

References

[1] Sidebotham EL, DeLair D, Comerci JT, et al. Pediatric radical abdominal trachelectomy for solitary fibrous tumor of the uterine cervix. Gynecol Oncol 2009;115:302–5.

[2] Nowakowski A, Kozlowski W, Wlodarczyk D, et al. A case of a large solitary fibrous tumour of the uterine cervix. BMC Womens Health 2014;14.

[3] Han G, Zhang Z, Shen X, et al. Doege–Potter syndrome: a review of the literature including a new case report. Medicine (Baltimore) 2017;96: e7417.

[4] Placide N, Robert S. Solitary fibrous tumor of the vagina: a case report with review of the literature. Int J Surg Pathol 2012;20:101–4.

[5] Tardio JC, Machado I, Alemany I, et al. Solitary fibrous tumor of the vulva: report of 2 cases, including a de novo dedifferentiated solitary fibrous tumor diagnosed after molecular demonstration of NAB2–STAT6 gene fusion. Int J Gynecol Pathol 2017.

[6] Wakami K, Tateyama H, Kawashima H, et al. Solitary fibrous tumor of the uterus producing high-molecular-weight insulin-like growth factor II and associated with hypoglycemia. Int J Gynecol Pathol 2005;24:79–84.

[7] Reyhan A. Solitary fibrous tumor of the vagina with potentially malignant features: a case report and review of the literature. Turk Patoloji Derg 2017.

[8] Vassy C, Escourrou G, Motton S, et al. Solitary fibrous tumor of the vulva: a case report. Gynecol Obstet Fertil 2011;39:499–51.

[9] Ronchi A, La Mania E, Giguantino V, et al. A rare case of malignant solitary fibrous tumor in prostate with review of the literature. Diagn Pathol 2017;12:50.

[10] Ricciuti B, Metro G, Leonardi GC, et al. Malignant giant solitary fibrous tumor of the uterus producing high-molecular-weight insulin-like growth factor II and elevated serum alkaline phosphatase. Int J Gynecol Pathol 2017;35:25–9.

[11] Mearini E, Cojeti G, Barillaro F, et al. Malignant solitary fibrous tumor with single lymph node involvement: report of unusual metastasis and review of the literature. Onco Targets Ther 2014;7:879–83.

[12] Peare DC, Federspiel JJ, Grumbine FC. Solitary fibrous tumor of the vulva resulting in spinal metastasis: a case report. Gynecol Oncol Rep 2017;22:97–9.

[13] Ricciuti B, Metro G, Leonardi GC, et al. Malignant giant solitary fibrous tumor of the pleura metastatic to the thyroid gland. Tumori 2016;102 (suppl. 2):

[14] Ben-Gal-Cantafiole F, Montesinos-Carbonell M, Montesinos-Carbonell ML, et al. Solitary fibrous tumor arising in the fallopian tube. Gynecol Oncol 2017;156:880–2.

[15] Fukunaga M. Atypical solitary fibrous tumor of the vulva. Int J Gynecol Pathol 2000;19:164–8.

[16] Seda H, Kaimura O, Yamamoto H, et al. Giant intrapelvic solitary fibrous tumor arising from mesorectum. Clin J Gastroenterol 2010;3:136–9.

[17] Blechzycki O, Singh N, Habeeb F, et al. Renal malignant solitary fibrous tumor with single lymph node involvement: report of unusual metastasis and review of the literature. Oncology 2012;38:85–9.

[18] He Y, Yang KX, Yang F, et al. Primary solitary fibrous tumor of the vulva: a case report. J Reprod Med 2010;55:452–6.

[19] Lee JC, Fletcher CD. Malignant fat-forming solitary fibrous tumor of the pleura: a case report and review of the literature. Int J Gynecol Pathol 2011;30:155–61.

[20] Taki M, Baba T, Mandai M, et al. Solitary fibrous tumor arising in the mesorectum. Clin J Gastroenterol 2010;13:101–5.

[21] Casanova J, Vizcaino JR, Pinto F, et al. Abdominal mass mimicking a lipomatous hemangiopericytoma: a case report and literature review. Int J Gynecol Case Rep 2012;2:143–5.

[22] Dvorak O, Dvorakova E, Laco J, et al. Solitary fibrous tumor of endometrium—a case report. Ceska Gynekol 2013;78:302–5.

[23] Aoyama Y, Niibashima K, Kosta H, et al. Solitary fibrous tumor of the vagina. Pathol Int 2000;50:327–31.
[31] Vadmal MS, Pellegrini AE. Solitary fibrous tumor of the vagina. Am J Dermatopathol 2000;22:83–6.
[32] Turkistani I, Ghourab S, Al-Rikabi A, et al. Large paravaginal solitary fibrous tumor with secondary schistosoma hematobium infestation. Acta Obstet Gynecol Scand 2002;81:88–90.
[33] Iyengar P, Ismiil ND, Gerber D, et al. Vaginal solitary fibrous tumor: a case report with recurrence after incomplete excision. J Low Genit Tract Dis 2007;11:50–4.
[34] Hasegawa T, Matsuno Y, Shimoda T, et al. Frequent expression of bcl-2 protein in solitary fibrous tumors. Jpn J Clin Oncol 1998;28:86–91.
[35] Rahimi K, Shaw PA, Chetty R. Solitary fibrous tumor of the uterine cervix. Int J Gynecol Pathol 2010;29:189–92.
[36] Porter E, McGregor A, Brown L, et al. Solitary fibrous tumour of round ligament mimicking a leiomyoma. J Obstet Gynaecol 2008;28:463–4.