Successful Surgical Treatment of a Recurrent Pelvic Solitary Fibrous Tumor of Uterine Origin Accompanied by Doege-Potter Syndrome: A Case Report

Yasunori Deguchi
Wataru Komuta
Tomokazu Watanabe
Kazuho Saiga
Koki Kurahashi
Kazuo Otsuka
Koji Hirata
Masaki Mizumoto
Akihiro Kitaoka
Masazumi Zaima

Corresponding Author: Yasunori Deguchi, e-mail: ydeguchi@kuhp.kyoto-u.ac.jp

Financial support: None declared
Conflict of interest: None declared

Patient: Female, 70-year-old
Final Diagnosis: Solitary fibrous tumor
Symptoms: Hypoglycemia • urinary retention
Medication: —
Clinical Procedure: Surgical resection
Specialty: Laboratory Diagnostics • Obstetrics and Gynecology • Pathology • Surgery

Objective: Rare disease
Background: Solitary fibrous tumors (SFT), rare soft-tissue neoplasms, are usually found in the thoracic cavity, and a uterine origin is extremely rare. SFTs with insulin-like growth factor-II (IGF-II) production induce non-islet cell tumor-induced hypoglycemia (NICTH), referred to as Doege-Potter syndrome.

Case Report: A 70-year-old woman presented with urinary retention, and imaging revealed a huge mass occupying almost the entire pelvic space. She had a history of hysterectomy for leiomyoma of the uterus 7 years earlier. In her present course, she developed hypoglycemia, and NICTH was suspected. Her previous uterine specimen was reexamined, and immunohistochemistry (IHC) revealed the specimen to be CD34-positive and alpha-smooth muscle actin-negative, indicating that the uterine specimen was not leiomyoma but SFT. Therefore, the present pelvic tumor was considered to be a recurrence of SFT with NICTH, namely Doege-Potter syndrome. Surgical resection was performed, and the pathological examination showed the same histologic features as the previous uterine specimen, while IHC revealed the present specimen to be positive for CD34, signal transducers and activator of transcription 6, and IGF-II, consistent with the diagnosis of recurrent SFT with IGF-II production. The patient’s hypoglycemia improved after tumor resection. To confirm the IGF-II secretion from the SFT, we conducted immunoblotting of the patient’s perioperative serum, with results showing that the strong band of IGF-II in the preoperative serum disappeared after surgery.

Conclusions: Because SFTs, especially those with Doege-Potter syndrome, often recur, sometimes with a very long interval, long-term cautious surveillance is required, even after complete tumor resection.

Keywords: Hypoglycemia • Insulin-Like Growth Factor II • Solitary Fibrous Tumors • Uterus

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936806
Background

Solitary fibrous tumors (SFTs) are rare mesenchymal fibroblastic neoplasms that develop mostly in the thoracic cavity [1]. Although extra-thoracic SFTs have been increasingly reported, such as in the pelvic space [1-7], SFTs of a uterine corpus origin are extremely rare [8-13]. Ardighieri et al performed a systematic literature review, and found only 13 SFTs of a uterine corpus origin had been reported in the English-language literature [11]. They noted that most patients presented with local symptoms related to a leiomyoma-like mass, such as abnormal uterine bleeding, abdominal fullness, or a palpable mass; furthermore, all patients underwent surgical resection, and 10 patients who had data available were all alive at 6 to 56 months of follow-up, while 2 patients had developed metastases or local recurrence.

Approximately 4% to 11.5% of patients with SFT develop non-islet cell tumor-induced hypoglycemia (NICTH) by secreting high-molecular-weight (HMW) insulin-like growth factor-II (IGF-II), which is referred to as Doege-Potter syndrome. The predominant symptom of Doege-Potter syndrome is severe and refractory hypoglycemia, and hypoglycemic symptoms can sometimes be the initial indicator that leads to the detection of a large tumor by imaging studies and ultimately the diagnosis of an SFT [14,15].

We report a case of recurrent SFT of uterine origin accompanied by Doege-Potter syndrome that was successfully treated with surgical resection.

Case Report

The patient was a 70-year-old woman who had a history of total hysterectomy with bilateral salpingo-oophorectomy for uterine leiomyoma 7 years earlier. She presented to our hospital with a concern of urinary retention. Contrast-enhanced computed tomography (CT) revealed a huge hypervascular tumor occupying most of the pelvic space, compressing the bladder and rectum (Figure 1), and she was admitted to our hospital. She was on medication for hypertension and osteoporosis and had no other relevant medical history. About 1 month after her presentation, she felt nocturnal weakness and fatigue every night that lasted until early in the morning, symptoms that were found to be indicative of hypoglycemia.

At admission, her abdomen was slightly swollen, but she had no abdominal pain or tenderness. A laboratory examination at admission showed hypoglycemia (39 mg/dL) and suppressed serum insulin (<2.0 μU/mL) and C-peptide (0.09 mg/mL), but no anti-insulin antibody. A CT scan showed an almost 12-cm-diameter solid mass with heterogenous enhancement in the pelvic space that was compressing the bladder and rectum to the right (Figure 1A). Magnetic resonance imaging (MRI) showed that the mass was composed of a low-intensity area on T1-weighted imaging (Figure 1B) and a heterogenous iso-to high-intensity area on T2-weighted imaging (Figure 1C).

Because she developed hypoglycemic symptoms at night despite a low insulin level, NICTH was suspected and the uterus specimen of 7 years ago was reexamined. Grossly, the tumor was well circumscribed and elastic and firm, and the cut surfaces were yellow to brown in color. Microscopically, the tumor cells were spindle-shaped and had a patternless arrangement, with collagenous stroma and irregularly dilated vasculature. The tumor cells showed moderate atypia, and the mitosis index was 1 mitosis per 10 high-power fields (HPFs) (Figure 2A).

Immunohistochemistry (IHC) revealed that the specimen was CD34-positive but negative for alpha-smooth muscle actin (SMA), c-kit, S100, and myoglobin, findings that led to the correct diagnosis of the uterus tumor as SFT instead of leiomyoma (Figure 2B, 2C). Therefore, the present pelvic tumor was considered to be the recurrent tumor of the uterus SFT producing IGF-II, resulting in hypoglycemia.

It took time to conduct preoperative investigations and to prepare for the operation because of the COVID-19 pandemic; therefore, about 1.5 months after her first presentation, tumor resection was scheduled following continuous glucose infusion. During laparotomy, disseminated tumors were found, and the main pelvic tumor had severely adhered to the rectum and left ureter. Tumor resection, including excision of all visible disseminated tumors with combined resection of the rectum (low anterior resection) and left ureter (accompanied with ureteroneocystostomy), was performed. The operation time was 567 min, intraoperative blood loss was 2925 g, and 1560 mL of blood transfusion was performed. The main tumor measured 19 cm in maximum diameter and weighed 1050 g (Figure 3A). The tumors were solid and elastic soft, and their cut surfaces were yellowish- to grayish-white in color (Figure 3B). Pathologically, similar to the previous uterine specimen, the tumor was mainly composed of haphazardly arranged spindle cells with dilated and staghorn-shaped vasculature and partially necrotic lesions. Tumor cells were denser than in the previous uterine specimen, showing moderate atypia, and the mitosis index was 1 mitosis per 10 HPFs (Figure 4A, 4B). IHC revealed the tumor cells to be positive for CD34 (Figure 4C), signal transducers and activator of transcription 6 (STAT6) (Figure 4D), and IGF-II (Figure 4E) and negative for alpha-SMA, c-kit, and S100, consistent with the diagnosis of recurrent SFT with IGF-II production. The Ki67 index was 17% in the main tumor and 3% to 10% in the disseminated tumors (Figure 4F).

To support the diagnosis of Doege-Potter syndrome, we conducted an immunoblotting analysis of the patient’s
perioperative serum along with homogenized tumor tissue. Clear bands of HMW IGF-II (around 15 kDa) were detected in both the preoperative serum and tumor tissue, but they disappeared in the postoperative serum (Figure 5). The patient no longer had hypoglycemia after surgery.

A follow-up CT at 5 months after surgery showed a supposedly residual disseminated tumor at the bottom of the pelvis. As she refused re-operation because of her mental illness, which had developed due to postoperative stress disorder, cautious follow-up was conducted. The tumor size did not change during the follow-up; however, she ultimately died of a cause other than SFT 2 years after the surgery.

Discussion

We encountered a very rare case of “malignant” SFT of uterine corpus origin, which had been misdiagnosed as a leiomyoma. Ardighieri et al reported only 13 cases of SFTs of the uterine corpus in their systematic review, 2 of which had distant metastases or pelvic recurrence at over 6 to 56 months of follow-up [11]. Furthermore, only 1 of the 13 cases presented with hypoglycemia, making our case the first uterine corpus SFT case to recur after 7 years of follow-up, accompanied by Doege-Potter syndrome.

SFTs are histologically composed of spindled to ovoid cells with indistinct, pale eosinophilic cytoplasm within a variably collagenous stroma [16] and can mimic many unrelated mesenchymal and non-mesenchymal tumor entities [10,17]. CD34 is one of the most characteristic conventional IHC markers in SFTs, although gastrointestinal stromal tumors are also positive for CD34 and should be excluded [1,18]. Recently, strong nuclear STAT6 expression due to a NAB2-STAT6 gene fusion was identified as the most consistent and specific IHC marker of SFTs [19-21]. The 2020 WHO Classification of Soft Tissue Tumours describes that, in addition to the reported histological features, CD34 and/or STAT6 expression by IHC is essential for a diagnosis [16]. In addition to CD34 and STAT6, bcl2 and vimentin are usually immunoreactive in SFTs, whereas...
SMA and desmin (myocyte marker), or S-100 and synaptophysin (perineural tissue marker), or c-kit (gastrointestinal stromal tumor marker) are negative [10,12,14]. Other histological differential diagnoses are synovial sarcoma or deep fibrous histiocytoma (which are both negative for CD34), or myopericytoma (which usually develops in the extremities and is positive for SMA). We probably would have detected the pelvic tumor much earlier at a much smaller size with close follow-up if the uterine tumor 7 years earlier had been precisely diagnosed as an SFT by IHC. The pathologist at that time most likely overlooked other possibilities in the differential diagnosis because leiomyomas are predominantly identified to be non-epithelial uterine tumors. As a result, the pathologist may have not considered IHCs to be required.

Doege-Potter syndrome is a paraneoplastic syndrome associated with SFTs, and its predominant symptom is severe and refractory hypoglycemia. Large SFTs (>20 cm) tend to present with this uncommon syndrome [14]. In patients with Doege-Potter syndrome.
syndrome, neoplastic cells of SFTs overexpress and secret HMW-IGF-II, which is insufficiently processed into IGF-II protein, resulting in NICTH [14,22]. The IHC of IGF-II is helpful for the diagnosis of Doege-Potter syndrome, while IGF-II overexpression does not always induce clinical hypoglycemia [14]. Several studies have confirmed the secretion of HMW-IGF-II using immunoblotting analyses of perioperative serum [15,22,23]. In the present case, an immunoblotting analysis revealed that the strong band of HMW-IGF-II in the preoperative serum had disappeared after tumor resection, which is compatible with

![Figure 4. Pathological findings of the resected specimens. (A, B) Hematoxylin and eosin staining with a (A) low-power view and a (B) high-power view. (C-E) Immunohistochemistry (IHC) showed positive staining for CD34 (C), STAT6 (D), and IGF-II (E). (F) IHC study of Ki67 (Scale bars: 100 µm).](image-url)
the clinical improvement of hypoglycemia after surgery. The tumor size is reportedly related to IGF-II production, and over 90% of tumors greater than 9 cm in size have IGF-II overexpression [14]. In our case, the patient had not developed hypoglycemia until the recurrent tumor had grown to occupy the whole pelvic space.

Surgical resection has been the mainstay of SFT treatment. As SFTs are typically well-circumscribed masses and grow expansively, not invasively, complete tumor resection is usually possible. En bloc resection is not always required, and even piecemeal resection is acceptable for achieving good local control, resulting in a favorable prognosis [24]. However, repeated surgeries for recurrent SFTs or too-large tumors can cause distressful adhesion, and complete surgical resection is considerably challenging [15]. To avoid a positive surgical margin and reduce operative blood loss, several studies have reported the utility of preoperative transcatheter arterial embolization, as SFTs are usually hypervascular tumors [5,25]. In our case, the main pelvic tumor had grown so large that the tumor had severe adhesion to the rectum and the left ureter, so it might have been wise to consider preoperative transcatheter arterial embolization followed by surgery. Limited studies have additionally reported that systemic chemotherapy and radiotherapy are effective for SFT treatment. Further studies concerning the molecular pathways involved with SFTs are expected to highlight promising molecular targets [1].

For predicting the recurrence or metastasis of surgically resected SFTs, England’s pathologic criteria are well reported: size over 10 cm, increased cellularity, over 4 mitoses per 10 HPFs, nuclear pleomorphism, and tumor necrosis or hemorrhaging [26]. Even “benign” SFTs that do not meet England’s criteria are often reported to recur, and recently several risk factors in addition to England’s criteria have been proposed, such as an extrathoracic location [27,28]. Furthermore, SFTs with Doege-Potter syndrome are known to be much more malignant than those without Doege-Potter syndrome, and indeed, Han et al reported that as many as 60% of SFTs with Doege-Potter syndrome were malignant, compared with only 5% to 10.4% of those without the syndrome [14]. In addition, it should be noted that SFTs sometimes recur many years after the initial surgery [15,29]. In our present case, because the patient had a huge SFT tumor over 10 cm in size accompanied by Doege-Potter syndrome and already had disseminating tumors, the risk of recurrence was considered very high, so we intended to cautiously conduct follow-up, but she unfortunately died of a cause other than SFT recurrence.

Conclusions

We reported a very rare case of recurrent SFT of uterine origin with Doege-Potter syndrome. We confirmed that the tumor cells had produced and secreted IGF-II and that the serum IGF-II had dramatically decreased after tumor resection. Because SFTs, especially those with Doege-Potter syndrome, often recur, sometimes with a very long interval, long-term cautious surveillance is required, even after complete tumor resection.

Acknowledgements

We are thankful to the patient, her family, and the medical staff who cared for her. We are grateful to Prof. I. Fukuda (Department of Endocrinology, Diabetes and Metabolism, Graduate School of Medicine, Nippon Medical School) for the immunoblotting of IGF-II and to Dr. N. Satoh-Asahara (Department of Endocrinology, Metabolism and Hypertension Research, Clinical Research Institute, National Hospital Organization Kyoto Medical Center) for her very constructive advice and help. We would like to thank Japan Medical Communication (www.japan-mc.co.jp) for the English language editing.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.
References:

1. Davanzo B, Emerson RE, Lisy M, et al. Solitary fibrous tumor. Transl Gastroenterol Hepatol. 2018;3:94
2. Gold JS, Antonescu CR, Hajdu C, et al. Clinicopathologic correlates of solitary fibrous tumors. Cancer. 2002;94(4):1057-68
3. Hasegawa T, Matsuno Y, Shimoda T, et al. Extrathoracic solitary fibrous tumors: Their histological variability and potentially aggressive behavior. Hum Pathol. 1999;30(12):1464-73
4. Wada Y, Okano K, Ando Y, et al. A solitary fibrous tumor in the pelvic cavity of a patient with Doege-Potter syndrome: A case report. Surg Case Rep. 2019;5(1):60
5. Yuza K, Sakata I, Nagao H, et al. A giant pelvic solitary fibrous tumor with Doege-Potter syndrome successfully treated with transcatheter arterial embolization followed by surgical resection: A case report. Surg Case Rep. 2020;6(1):299
6. Gholami S, Cassidy MR, Kirane A, et al. Size and location are the most important risk factors for malignant behavior in resected solitary fibrous tumors. Ann Surg Oncol. 2017;24(13):3865-71
7. Morimitsu Y, Nakajima M, Hisaoka M, Hashimoto H. Extrapleural solitary fibrous tumor: Clinicopathologic study of 17 cases and molecular analysis of the p53 pathway. APMS. 2000;108(9):617-25
8. Yang EL, Howitt BE, Fletcher CD, Nucci MR. Solitary fibrous tumour of the female genital tract: A clinicopathological analysis of 25 cases. Histopathology. 2018;72(5):749-59
9. Strickland KC, Nucci MR, Esselen KM, et al. Solitary fibrous tumor of the uterus presenting with lung metastases: A case report. Int J Gynecol Pathol. 2016;35(1):25-29
10. Casanova J, Vizcalno JR, Pinto F, et al. Abdominal mass mimicking a leiomyoma: Malignant uterine solitary fibrous tumor. Gynecol Onkol Case Rep. 2012;2(4):143-45
11. Ardighieri L, Palicelli A, Ferrari F, et al. Risk assessment in solitary fibrous tumor of the uterine corpus: Report of a case and systematic review of the literature. Int J Surg Pathol. 2022;30(2):177-83
12. Chu PW, Liu JY, Peng YI, Yu MH. Solitary fibrous tumor of the uterus. Taiwan J Obstet Gynecol. 2006;45(4):350-52
13. 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(1):79-84
14. 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(27):e7417
15. Ishihara H, Omae K, Iizuka J, et al. Late recurrence of a malignant hypoglycemia-inducing pelvic solitary fibrous tumor secreting high-molecular-weight insulin-like growth factor-II: A case report with protein analysis. Oncol Lett. 2016;12(1):479-84
16. Demicco EG, Frithchie KJ, Han A. Solitary fibrous tumour. In: WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Soft tissue and bone tumours. 5th ed., 104-8
17. Skaraglia A, Bellan E, Dei Tos AP. The 2020 WHO Classification of soft tissue tumours: News and perspectives. Pathologica. 2021;113(2):70-84
18. Flint A, Weiss SW. CD-34 and keratin expression distinguishes solitary fibrous tumor (fibrous mesothelioma) of pleura from desmoplastic mesothelioma. Hum Pathol. 1995;26(4):428-31
19. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet. 2013;45(2):180-85
20. Doyle IA, Vierre M, Fletcher CD, et al. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mod Pathol. 2014;27(3):390-95
21. Yamada Y, Kohashi K, Kinoshita I, et al. Clinicopathological review of solitary fibrous tumors: dedifferentiation is a major cause of patient death. Virchows Arch. 2019;475(4):467-77
22. Tominaga N, Kawarasaki C, Kanemoto K, et al. Recurrent solitary fibrous tumor of the pleura with malignant transformation and non-islet cell tumor-induced hypoglycemia due to paraneoplastic overexpression and secretion of high-molecular-weight insulin-like growth factor II. Intern Med. 2012;51(23):3267-72
23. Hata T, Tsuruta Y, Takamori S, Shishikura Y. Non-islet cell tumor hypoglycemia at the second recurrence of malignant solitary fibrous tumor in the retropertitoneum and pelvis: A case report. Case Rep Oncol. 2012;5(2):420-27
24. Wang Y, Wei R, Ji T, et al. Surgical treatment of primary solitary fibrous tumors involving the pelvic ring. PLoS One. 2018;13(11):e0207581
25. Takahashi A, Nishimura H, Amano T, et al. An abdominal-sacral approach with preoperative embolisation for vulvar solitary fibrous tumour: A case report. World J Surg Oncol. 2021;19(1):92
26. England DM, Hochholzer L, McCarthy MI. Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. Am J Surg Pathol. 1989;13(8):640-58
27. Ronchi A, Cozzolino I, Zito Marino F, et al. Extrapleural solitary fibrous tumor: A distinct entity from pleural solitary fibrous tumor. An update on clinical, molecular and diagnostic features. Ann Diagn Pathol. 2018;34:142-50
28. Demicco EG, Wagner MJ, Makri RG, et al. Risk assessment in solitary fibrous tumors: Validation and refinement of a risk stratification model. Mod Pathol. 2016;35(1):25-29
29. Baldi GG, Stacchiotti S, Mauro V, et al. Solitary fibrous tumor of all sites: Outcome of late recurrences in 14 patients. Clin Sarcoma Res. 2013;3:4

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)
Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]