Case Report

From Diagnosis to Management: A Rare Case of Disseminated Low-Grade Endometrial Stromal Sarcoma with Extensive Extrauterine Spread

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Abstract
Objective: To report a rare case of low-grade endometrial stromal sarcoma; which was found not only in the uterus but also in several extrauterine sites, such as the ovary, omentum, and jejuno-ileum. In this article, we provided the management performed, based on appropriate literatures.
Methods: Case report.
Case: A 44-year old para 2 complained of abdominal enlargement since 3 months. Patient also complained of pelvic pain. The patient has never received treatment before and has never been diagnosed with endometriosis. Abdominal examination revealed a 20-cm mass in the lower to umbilical region and positive shifting dullness. Bimanual pelvic examination revealed immobile and smooth masses in both sides of adnexa, with pain during palpation. Computerized tomography (CT) scan of the abdomen revealed complex cystic masses suspected for right and left ovaries-origin (±11 & 15 cm respectively) Surgical resection and staging, frozen section, cytology examination, and immunohistochemistry (IHC) test were performed, revealing consistent result of endometrioid stromal sarcoma, low grade. Five-months postoperative follow-up through abdominal CT-scan in the patient revealing no abnormalities.
Conclusion: We know that LG-ESS is one of the rare types of endometrial stromal sarcoma. Moreover in this case extrauterine manifestations make it more challenging in clinical management. Risk factors and history of endometriosis are important to explore when meeting ESS cases. Further research needs to be done regarding the exact mechanism and the association between endometriosis or other risk factors and the development of ESS, especially the EESS type to allow intervention.

Keywords: endometrial stromal sarcoma, management, uterine sarcoma

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INTRODUCTION

Endometrial stromal sarcoma (ESS) is a type of mesenchymal tumor, which accounts for about 0.2% of uterine malignancies and approximately 15% of uterine sarcomas.[1] ESS is studied to be the second most common type of uterine mesenchymal neoplasia, after uterine leiomyosarcoma. This type of sarcoma is typically found in the uterus, but also can be found in some extrauterine sites, including in the bowel wall, pelvic structures, peritoneum, vagina, and the ovary.[2,3] However, greater number of extra-uterine endometrial stromal sarcoma (EESS) cases presented are confined to the ovaries. Some references are also conventionally using the term “endometrioid stromal sarcoma” to define extrauterine endometrial stromal sarcoma.[3,4]

Patients with endometrial stromal sarcoma typically complain with enlargement of the abdomen, vaginal bleeding, or even pelvic pain.[3] The World Health Organization (WHO) simply classifies endometrial stromal neoplasms as benign endometrial stromal

nodule (ESN) and ESS. The main difference in this classification is that in ESN, there is no infiltration of myometrium, whereas in ESS it's the other way around. ESS itself is classified into low-grade endometrial stromal sarcoma (LG-ESS) or high-grade endometrial stromal sarcoma (HG-ESS) based on cell morphology and mitotic count.[5]

In the past decade, endometrial stromal sarcomas of the uterus are quite notable and some related guidelines have been made. However, clinical and scientific experience with ESS with primary lesions in the ovary is limited since they are quite rare. We report a case of a patient with low-grade endometrial stromal sarcoma that was found in both uterus and several extrauterine sites (primarily arising from both ovaries) managed with surgical resection.

CASE

A 44-year old Asian para 2 came to the obstetrics and gynecology outpatient clinic with the chief complaint of abdominal enlargement since 3 months prior to admission. The patient also complained of pelvic pain with numerical pain rating scale (NPRS) 5. The pain was felt both during and outside the menstrual cycle and had gotten worse in the last 2 weeks. The patient has never received treatment for this complaint and has never been diagnosed with endometriosis before. Weight loss, abnormal bleeding, abnormal vaginal discharge, dyschezia, painful urination, bloody stool, difficulty in defecating, and other complaints were all denied. History of hepatitis, hepatic cirrhosis, irritable bowel syndrome, malignancy, or other systemic diseases were also denied.

On physical examination, the general condition and vital signs were within normal range. The patient's anthropometric measurement was also considered to be normal. On abdominal examination, the percussion revealed dullness and a mass was palpable in the lower region up to the umbilical region, with positive shifting dullness and a diameter of approximately 20 cm. There was pain and tenderness during deep palpation of the mass. Enlargement of lymph nodes in the neck, axillary, or inguinal was not found in this patient. Clinical gynecologic examination revealed normal condition of vulvovaginal and portio. There was no fluor albus, blood or active bleeding, abnormal vaginal discharge, mass, inflammation, or erosion found during examination. Bimanual pelvic examination revealed masses in both sides of adnexa, immobile, with smooth surface, and pain on palpation

Laboratory examination parameters were all within the normal limit. Abdominal computerized tomography (CT) scan with contrast was performed, revealing complex cystic masses suspected for right and left ovaries-origin (±11 & 15 cm respectively) that extend into the abdominal cavity, pushing the intestinal cisterns cranially, and pressing the uterus inferiorly (highly suspicious of malignancy). Infiltration to the anterosuperior wall of the urinary bladder and left distal ureter was suspected. Ascites and multiple peritoneal seeding nodules were also found. CT scan also revealed some findings such as mild bilateral pleural effusion especially on the right, signs of adhesion, mesenteric mass and adenopathy (suspected of metastasis), mild hepatosplenomegaly, suspected intramural uterine myoma, and thickening of left aspect mesentery with fat stranding suspected of metastasis. No abnormality was found in the pancreas, aorta, bilateral kidney, psoas muscles, or rectum. Tumor marker CA-125 result on this patient was about 348.1 U/mL, highly increased from the normal limit of <35 U/mL.

Multidisciplinary surgical resection and staging were performed on this patient by gynecologic oncologist and digestive surgeon, with estimated operation duration for about 3 hours. Incision was performed in the midline up to approximately 2 cm above the umbilicus. Ascites as much as 1000 cc was found and about 20 cc was taken for cytological examination. A 20 cm cystic mass from the left ovary was found attached to the rectosigmoid; adhesiolysis was carried out. The cyst ruptured and came out as much as

700 cc of brown fluid; adhesiolysis was continued. Left salpingo-oophorectomy was performed and tissue specimen was sent for frozen section. The uterus enlarged to a size of 15 x10 x 10 cm and total hysterectomy and right salpingo oophorectomy were performed. During exploration, impression of an omental cake was found, so a total omentectomy was performed. No enlarged pelvic and paraaortic lymph nodes were found. The peritoneum, liver, and spleen are smooth. Further exploration revealed a mass in the mesentery and ileum. Digestive surgeons identified that the small intestine was occluded by a mass in the mesojejunoileal approximately 50 cm from the ligament of Treitz to the oral and 100 cm distal to the ileocecal valve. Resection was performed at 40 cm from the Treiz ligament and 90 cm from the ileocecal valve and then a side-to-side jejunoileal anastomosis was performed. Bleeding during the surgical procedure was approximately 400 cc.

Frozen section examination revealed the cyst was lined with granulation tissue (hemosiderophages). On the solid part, endometrial stroma and glands were partially separated by fibrotic connective tissue. Conclusion of the frozen section diagnosis in the form of endometrial cyst with stromal hyperplasia. Cytology examination from ascites specimens revealed reactive mesothelial cells, leukocytes, macrophages, and glandular structures lined with simple thoracic epithelium with minimal nuclear atypia. Conclusion of the cytology examination compatible with endometriosis.

Immunohistochemistry (IHC) examination was performed, revealing positive CD10, positive CD34 on connective tissue and vascular vessel walls, and 5% positive KI67. Estrogen receptors (ER) and progesterone receptors (PR) were also positive, while CD117 and DOG1 were both negative. IHC examination is consistent with an endometrioid stromal sarcoma, low grade.

Follow-up examination in this patient through abdominal CT scan was performed 5 months after surgery. No residual mass, pleural effusion, ascites, or enlarged lymph nodes were found. No mesenteric mass or ileus sign was seen anymore. Other structures were found to appear normal.

DISCUSSION

As mentioned above, uterine sarcoma is a diverse group of rare tumors in the uterine connective tissue and musculature. According to the current World Health Organization (WHO) classification, they are distinguished from malignant mixed epithelial-mesenchymal tumors and malignant mesenchymal tumors. It classified uterine sarcomas into leiomyosarcoma, low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), undifferentiated uterine sarcoma (UUS), rhabdomyosarcoma, adenosarcoma, and malignant-type perivascular epithelioid cell tumor 6,7. In the latest WHO classification published in 2014, LG-ESS is classified as an endometrial stromal tumor along with benign endometrial stromal nodule (ESN), HG-ESS, and UUS. ESS is staged along with uterine leiomyosarcoma according to the FIGO and TNM classifications.[7,8]

Symptoms of a patient with ESS are unspecific, with abnormal uterine bleeding being one of the most common symptoms related. Other symptoms include abdominal or pelvic mass, pain, and gastrointestinal symptoms. Some of them may be asymptomatic.[9–11] Most frequent manifestations of EESS are abdominal or pelvic pain, mass, gastrointestinal symptoms and vaginal bleeding.[4] In this case, the patient only complained of abdominal enlargement and pelvic pain, while other symptoms were denied. ESS occurs primarily in premenopausal and perimenopausal women, ranging between 45 to 55 years of age. Compared to HG-ESS, the age group of LG-ESS is typically younger.[9] Our patient presented at 44 years, which is similar to the common age group. The exact pathogenesis of these tumors is yet to be determined, but some identified risk factors for ESS are long-term tamoxifen use, unopposed estrogen use, and past exposure

to pelvic radiation therapy. However, those were not found in this patient. But again, the patient is suspected to have a history of endometriosis based on the cytology examination, which has not been previously diagnosed. This condition could be related to her current condition, as 30 out of the 63 EESS cases in one series had endometriosis.[4] Extrauterine low-grade endometrial stromal sarcoma is supposed to derive from endometriosis, as most reported cases of EESS were associated with foci of endometriosis. [1,11]

In this patient, extreme and unexplained weight loss in the past months was not found. Ascites that were suspected from positive shifting dullness during physical examination, could also be confirmed from abdominal CT scan. CT findings showed that the masses were large enough, suspected for the ovaries-origin, extending into the abdominal cavity, and pushing other structures nearby. Metastasis was also suspected in this patient considering there was mesenteric mass and adenopathy, thickening of left aspect mesentery with fat stranding, and also multiple peritoneal seeding nodules. Regardless of these findings during abdominal CT scan examination, no gastrointestinal or EESS symptoms were found in this patient. In contrast to carcinomas of the endometrium, a diagnosis of LG-ESS cannot be securely determined using hysteroscopy and fractional curettage. Moreover, a clear distinction from benign ESN can only be reliably determined after histological analysis of the tumor's entire interface with the neighboring myometrium.[12,13] Analysis of the patient's specimens in this case was performed through frozen section, cytology, and IHC examination. Immunohistochemistry test results showed a matched and consistent findings of endometrioid stromal sarcoma, low grade. This can be seen on positive CD10, ER and PR, which is usually negative in high-grade ESS cases and is typically varied/heterogeneous in undifferentiated uterine sarcoma. Differences of the low-grade ESS, high-grade ESS, and undifferentiated uterine sarcoma can be seen in the figure below.[14]

Preoperative tumor marker CA-125 level in this patient was extremely high, which was 348.1 U/mL from the normal range of less than 35 U/mL. CA-125 is an antigenic tumor marker which is commonly expressed by the epithelial ovarian neoplasms and other tissues such as cells lining the endometrium, fallopian tubes, pleura, peritoneum, and pericardium. It is carried out when suspecting ovarian neoplasm and is also used in monitoring patients that have already been diagnosed with epithelial ovarian cancer. CA-125 level in this patient was markedly increased probably because the sites of the ESS involved the ovaries and other extrauterine sites that expressed this marker. It was not measured anymore after the surgery in this patient since it is not a specific marker for endometrioid stromal sarcoma. This test has limited utility in diagnosing the early stage of ovarian cancer, owing to its low sensitivity. The specificity is particularly low in premenopausal women; thus, it is most useful in postmenopausal women.[15,16]

Based on the recommendation of the German guideline Sarcoma of the Uterus (DGGG and OEGG, 2019), the treatment of choice for LG-ESS must consist of complete resection of the uterus (total hysterectomy) without morcellation but with complete bilateral resection of the adnexa.[14] In this patient, surgical resection and staging have been done, including total hysterectomy and complete removal of bilateral adnexa, which has been done in accordance with the latest guideline.

There is much evidence regarding the endocrine dependence of LG-ESS. A retrospective study of 153 patients with LG-ESS found a significantly increased rate of recurrence when the ovaries of premenopausal patients were not removed.[17–19] In this patient, bilateral adnexa

were removed considering the risk and higher probability of recurrence. About the oncological safety of hormone replacement therapy after previous primary treatment of a low-grade ESS, there are currently no data. Since the tumor biology of LG-ESS is highly estrogen-dependent, patients should be dissuaded from starting hormone replacement therapy.[20] Prognosis of the patient with LG-ESS is mainly based on the tumor stage. The disease-specific 5-year survival rate for LG-ESS is 80-90% and the 10-year survival rate is approximately 70%. If the tumor is limited only to the uterus at the time of diagnosis, thus the rates are even higher; about 100% and 90%, respectively. The rate drops to 40% for higher stage disease. Positive hormone receptors are a favorable prognostic factor with regard to overall survival. When compared to the high-grade ESS and undifferentiated uterine sarcoma (UES), low-grade ESS has a favorable prognosis. [4,21,22] In this case, tumor sites at the time of diagnosis were already located at several extrauterine sites. Nevertheless, 2 years and 6 months following the surgical procedure there was no complaint or relapse, and overall favorable outcomes could be seen in this patient. However, it is important to keep routine monitoring and follow-up on the patient if signs of recurrence or metastasis appear at any time.

Emerging evidence highlights that adjuvant hormonal therapy can play a pivotal role in preventing recurrence in LG-ESS cases, particularly in hormone receptor-positive tumors.[9, 20] Progestins, such as medroxyprogesterone acetate, and aromatase inhibitors like letrozole, have been shown to stabilize residual disease and improve outcomes.[23] Additionally, multidisciplinary approaches to managing extensive extrauterine involvement—such as combining cytoreductive surgery with targeted therapies—have demonstrated potential for improved survival rates.[24]

CONCLUSION

We know that LG-ESS is one of the rare types of endometrial stromal sarcoma. Moreover, in this case, extrauterine manifestations make it more challenging in clinical management. Risk factors and history of endometriosis are important to explore when meeting ESS cases. Further research needs to be done regarding the exact mechanism and the association between endometriosis or other risk factors and the development of ESS, especially the type of EESS to allow medical intervention. So far, guidelines on ESS management are available, but to the best of the author's knowledge there are no guidelines that specifically address specific management related to EESS, so the management principles are basically still the same. Early diagnosis and increased awareness are important because the patient's prognosis depends on the stage, or the extent to which the disease progresses. In addition, it is also important for clinicians to educate patients diagnosed with ESS about the possibilities that can occur if left untreated, complications, relapse rates, death and survival rates.

REFERENCES

1. Back, J.A., Choi, M.G., Ju, U.C., et al., A Case of Advanced-stage Endometrial Stromal Sarcoma of the Ovary Arising from Endometriosis.2019;59: 323–7.
2. Heaps, J.M., Nieberg, R.K., Berek, J.S., Malignant neoplasms arising in endometriosis. Obstet. Gynecol. 1990; 75:1023–8.
3. Masand, R.P., Euscher, E.D., Deavers, M.T., et al.,Endometrioid stromal sarcoma: a clinicopathologic study of 63 cases. Am. J. Surg. Pathol.2013;37:1635–47.
4. Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary extrauterine endometrial stromal neoplasms: a clinicopathologic study of 20 cases and a review of the literature. Int J Gynecol Pathol. 1993;12:282-96.
5. Leung F, Terzibachian JJ, Aouar Z, Govyadovskiy A, Lassabe C. Uterine Sarcomas: clinical and histopathological

aspects. Report on 15 cases. Gynecol Obstet Fertil. 2008;36:628-35.
6. Conklin CM, Longacre TA: Endometrial stromal tumors: the new WHO classification. Adv Anat Pathol. 2014;21:383–93.
7. Oliva E, Carcangiu ML, Carinelli SG, et al. Mesenchymal tumors of the uterus; in Kurman RJ, Carcangiu ML, Herrington CS, Young RH (eds): WHO Classification of Tumours of Female Reproductive Organs. Lyon, IARC Press. 2014: 135–47.
8. Wittekind C, Meyer HJ: TNM-Klassifikation Maligner Tumoren. Weinheim, Wiley-VHC Verlag. 2010.
9. Fekete PS, Vellios F. The clinical and histologic spectrum of endometrial stromal neoplasm: a report of 41 cases. Int J Gynecol Pathol. 1984;3:198-212.
10. Young RH, Prat J, Scully RE. Endometrioid stromal sarcomas of the ovary. A clinicopathologic analysis of 23 cases. Cancer. 1984;53:1143-55.
11. Oliva E, Egger JF, Young RH. Primary endometrioid stromal sarcoma of the ovary: a clinicopathologic study of 27 cases with morphologic and behavioral features similar to those of uterine low-grade endometrial stromal sarcoma. Am J Surg Pathol. 2014;38:305-15.
12. Hoang L, Chiang S, Lee CH: Endometrial stromal sarcomas and related neoplasms: new developments and diagnostic considerations. Pathol. 2018;50:162–77.
13. Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I: Clinical management of uterine sarcomas. Lancet. Oncol. 2009;10:1188–98.
14. Denschlag D, Ackermann S, Battista MJ, Cremer W, Egerer G, Follmann M, et al. Sarcoma of the uterus. guideline of the DGGG and OEGGG (S2K level, AWMF Register number 015/074, February 2019). Geburtshilfe und Frauenheilkunde. 2019;79(10):1043–60.
15. Scholler N, Urban N. CA125 in ovarian cancer. Biomark Med. 2007 Dec;1(4):513-23.
16. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. Obstet Gynecol. 2016 Nov;128(5):e210-e226.
17. Chan JK, Kawar NM, Shin JY et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer. 2008; 99: 1210–5.
18. Bai H, Yang J, Cao D et al. Ovary and uterus-sparing procedures for low-grade endometrial stromal sarcoma: a retrospective study of 153 cases. Gynecol Oncol. 2014;132:654–60.
19. Shah JP, Bryant CS, Kumar S et al. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. Obstet Gynecol. 2008;112:1102–8.
20. Chu MC, Mor G, Lim C et al. Low-grade endometrial stromal sarcoma: hormonal aspects. Gynecol Oncol. 2003; 90:170–6
21. Chew I, Oliva E. Endometrial stromal sarcomas: a review of potential prognostic factors. Adv Anat Pathol. 2010;17:113–21
22. Seagle BL, Sobecki-Rausch J, Strohl AE et al. Prognosis and treatment of uterine leiomyosarcoma: A National Cancer Database study. Gynecol Oncol. 2017;145:61–70.
23. Garavaglia E, Pella F, Montoli S, Voci C, Taccagni G, Mangili G. Treatment of Recurrent or Metastatic Low-Grade Endometrial Stromal Sarcoma. International Journal of Gynecological Cancer. 2010;20(7):1197-1200. doi:10.1111/igc.0b013e3181ef6d87
24. Leath CA, Huh WK, Hyde J, et al. A multi-institutional review of outcomes of endometrial stromal sarcoma. Gynecologic Oncology. 2007;105(3):630-634. doi:10.1016/j.ygyno.2007.01.031

Figure 1. FIGO and TNM stages for leiomyosarcomas and endometrial stromal sarcomas* of the uterus.[9]

FIGO/TNM stage		Definition
I/T1		Tumor limited to the uterus
	IA/T1a	Tumor 5 cm or less in greatest dimension
	IB/T1b	Tumor larger than 5 cm in greatest dimension
II/T2		Tumor extends beyond the uterus, within the pelvis
	IIA/T2a	Involvement of the adnexa (unilateral or bilateral)
	IIB/T2b	Tumor has spread to extrauterine pelvic tissue excluding the adnexa
III/T3		Tumor has infiltrated abdominal tissue
N1	IIIA/T3a	One site
	IIIB/T3b	More than one site
	IIIC	Metastasis of pelvic and/or para-aortic lymph nodes
IV/T4	IVA/T4	Tumor has infiltrated bladder and/or rectum
	IVB	Distant metastasis

*Tumors simultaneously present in the corpus uteri and the ovary/pelvis accompanied by ovarian/pelvic endometriosis must be classified as independent primary tumors.

Figure 2. Summary of the morphology, IHC, and molecular pathology of ESS and UES.[9]