Endometrial Stromal Sarcoma Arising from Endometriosis: A Clinicopathological Study and Literature Review

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Key Words

Endometrial stromal sarcoma • Endometriosis • Dissemination • Complete resection

Abstract

Objectives: We aimed to investigate the nature of endometrial stromal sarcoma (ESS) arising from endometriosis. **Methods:** The clinical data of 5 patients with ESS arising from endometriosis were reviewed retrospectively. The expression of CD117, HER2/neu, EGFR, VEGF, and PDGFR was analyzed by immunohistochemical staining. **Results:** The median age of the 5 patients was 45 years. The primary tumor sites were the ovary in 2, the pelvis in 2, and the cervical canal in 1 patient. Three patients had disseminated disease at diagnosis. Four patients underwent complete tumor resection. All of the 5 cases received adjuvant chemotherapy and 2 received progesterone therapy, while none were treated with radiotherapy. No recurrence occurred in the 4 cases who had complete tumor resection, and the only patient who progressed was the patient in whom the tumor was unresectable. Tumor cells in all cases exhibited positive staining for PDGFR and were negative for CD117 and HER2/neu. The expression of EGFR and VEGF was observed in 2 and 4 cases, respectively. **Conclusion:** ESS arising from endometriosis is rare. Complete tumor resection in ESS arising from endometriosis may reduce the recurrence rate.

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Introduction

Endometriosis is one of the most common benign gynecologic disorders, affecting up to 10% of women of reproductive age [1]. Malignant transformation in endometriosis is considered to be an unusual event, only occurring in 0.7–0.1% of cases [2]. In 1925, Sampson [3] reported the first case series of malignancy arising from endometriosis and recommended three criteria for its diagnosis: (1) examples of endometriosis in close proximity to the tumor; (2) no other primary site of malignancy, and (3) histological appearance compatible with the origin from endometriosis. Theoretically, any histological type of tumor found in the endometrium might also occur in endometriosis [4]. As reported, most of the malignant tumors that originate from endometriosis are endometrioid adenocarcinoma and clear cell types, and endometrial stromal sarcoma (ESS) is extremely unusual.

ESS, which is characterized by cells that resemble those of the endometrial stroma during the proliferative phase, usually originates from the uterine corpus, although it may arise in extra-uterine locations [5]. ESS has

C.L. and X.H. contributed equally to the study.

Table 1. Primary antibodies, dilutions, and sources

Antibodies	Clone	Dilution	Vendor
Desmin	mouse monoclonal	ready-to-use	ZSGB-BIO, Beijing, China
HHF35	mouse monoclonal	ready-to-use	ZSGB-BIO, Beijing, China
CK	mouse monoclonal	ready-to-use	ZSGB-BIO, Beijing, China
S-100 protein	mouse monoclonal	ready-to-use	ZSGB-BIO, Beijing, China
CD34	mouse monoclonal	ready-to-use	ZSGB-BIO, Beijing, China
CD10	mouse monoclonal	1:50	ZSGB-BIO, Beijing, China
ER	rabbit monoclonal	1:100	ZSGB-BIO, Beijing, China
PR	rabbit monoclonal	1:100	ZSGB-BIO, Beijing, China
CD117	rabbit polyclonal	ready-to-use	ZSGB-BIO, Beijing, China
HER2/neu	mouse monoclonal	ready-to-use	ZSGB-BIO, Beijing, China
EGFR	mouse monoclonal	1:50	Novocastra Laboratories, UK
VEGF	rabbit monoclonal	ready-to-use	ZSGB-BIO, Beijing, China
PDGFR	rabbit monoclonal	1:50	ZSGB-BIO, Beijing, China

traditionally been divided into two categories, low-grade ESS (LGESS) and high-grade ESS (HGESS). However, the term ESS is now restricted to neoplasms that were formally referred to as LGESS [6], with typically morphologic features of proliferative-phase endometrial stroma and an indolent clinical course. The category of HGESS, in which there is no recognizable evidence of a definite endometrial stromal phenotype, is now designated as poorly differentiated or undifferentiated endometrial sarcoma; most of these may not originate from the endometrial stroma and carry a poorer prognosis [6, 7].

ESS arising from endometriosis is considered to be an indolent tumor with an excellent prognosis. However, late recurrence and distant metastases may occur. Recurrence and deaths have been documented as occurring more than 25 years after the initial diagnosis [8]. The treatment for disseminated disease is particularly problematic. There is a need to develop novel therapeutic strategies for this unusual neoplasm. Targeted therapy has gained impressive success in the treatment of some human malignancies. However, it is unclear whether there is any target for targeted therapy in ESS arising from endometriosis. Thus, it is essential to identify potential target molecules in such cases.

We therefore reported 5 cases of ESS that arose from endometriosis in order to better understand the nature of this disease. Moreover, we investigated the expression of several molecules and receptors on the tumors to gather biological information for the development of targeted therapy for ESS arising from endometriosis.

Patients and Methods

In accordance with the three widely accepted criteria formulated by Sampson [3], as well as the 2003 WHO classification system [9], 5 patients with ESS originating from endometriosis were identified from the database of the Sun Yat-sen University Cancer Center from September 1995 to May 2010. Only LGESS arising from endometriosis was included; poorly differentiated or undifferentiated endometrial sarcomas were excluded from the present study. Approval was granted from the institutional review board of Sun Yat-sen University Cancer Center. The hospital records of the 5 patients were reviewed to obtain demographic details, clinicopathological variables, treatment, disease recurrence and outcome.

All slides of the 5 cases were re-examined by 2 pathologists at our center to confirm the diagnosis. Selected representative formalin-fixed, paraffin-embedded sections were used in immunohistochemical study, which was performed using a standard two-step technique. The tissue slides were dewaxed in xylene, rehydrated through graded alcohol, and immersed in 3% hydrogen peroxide for 10 min to block endogenous peroxidase activity. An antigen retrieval process was also employed in a microwave oven with 10 mM citrate buffer, pH 6, for 15 min. The slides were pre-incubated with 10% normal goat serum at room temperature for 20 min to reduce nonspecific reaction. Subsequently, the slides were incubated overnight at 4°C in a moist chamber with antibodies against desmin, muscle actin (HHF35), cytokeratin (CK), S-100 protein, CD34, CD10, estrogen receptor (ER), progesterone receptor (PR), CD117, HER2/neu, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and platelet-derived growth factor receptor (PDGFR) (the primary antibodies applied in the study are showed in table 1). After 5 times of rinsing with 0.01 M phosphate-buffered saline (pH = 7.4) for 10 min, the detection of the primary antibody was achieved with a secondary antibody (ZSGB-BIO, Beijing, China) for 1 h at room temperature, and stained with 3,3'-diaminobenzidine after a further wash in phosphate-buffered saline. Finally, the sections were counterstained with Mayer's hematoxylin, dehydrated, and mounted. A negative control was obtained by replacing the primary antibody with a normal rabbit or mouse IgG. The result was assessed with the semiquantitative evaluation of the

Table 2. Clinicopathological features of the 5 patients with ESS arising from endometriosis

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, years	22	53	45	37	46
GP	G0P0	G4P3	G3P2	G3P2	G1P1
History of gynecologic surgery	No	TAH for leiomyoma 8 years ago	SAH for leiomyoma 2 years ago	SAH and LSO for leiomyoma 3 years ago	Bilateral ovarian cystectomy for EM 9 years ago
Symptoms	Vaginal bleeding	Abd pain	Abd distention	Vaginal bleeding	Abd pain, pelvic mass
CA125 level, U/ml	25	22	19	15	1,788
Site of tumor	Cervical canal	Pelvis	Left ovary	Pelvis	Right ovary
Dissemination at diagnosis	No	Pelvic wall, bladder, upper 1/3 of vagina	Pelvis, cervix	No	Right tube, anterior cul-de-sac, anterior Abd wall
Initial treatment	D&C, Piver II RH, PLA, Chemo	Chemo	Radical resection of the cervix, BSO, Chemo, progesterone therapy	Cervix resection, RSO, Oment, tumor resection, Chemo	TAH and BSO, Oment, appendectomy, tumor resection, adhesiolysis, Chemo, progesterone therapy
Recurrence/progression	No	Yes	No	No	No
Recurrence/progression site	No	Pelvis	No	No	No
Recurrence/progression treatment	No	Enterostomy	No	No	No
Status	NED 7 years	DOD 24 months	NED 9 years	NED 6 years	NED 8 months

G = Gravidity; P = parity; TAH = total abdominal hysterectomy; SAH = subtotal abdominal hysterectomy; LSO = left salpingo-oophorectomy; EM = endometriosis; Abd = abdominal; D&C = dilation and curettage; RH = radical hysterectomy; PLA = pelvic lymphadenectomy; Chemo = chemotherapy; BSO = bilateral salpingo-oophorectomy; RSO = right salpingo-oophorectomy; Oment = omentectomy; NED = no evidence of disease; DOD = died of disease.

number of positively stained cells as follows: – = no staining; + = weakly positive (1–25% of cells stained); ++ = positive (26–50% of cells stained); +++ = strongly positive (51–100% of cells stained).

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 software. Frequency data was analyzed using χ^2 tests. Statistical significance was defined as $p < 0.05$.

Results

Clinical Features

Table 2 summarizes the clinical and histopathological features of the 5 patients. The median age was 45 years (range 22–53). One patient was postmenopausal, and 1

was 22 years old with no previous sexual activity. Only 1 nullipara was observed with no sexual experience. The others had gravidity 1–4 as well as parity 1–3. Only 1 patient had a previous history of endometriosis. Two patients presented with abdominal pain. Symptoms of vaginal bleeding, abdominal distention, and pelvic mass were also observed in 2, 1, and 1 patient, respectively. The primary tumor sites were considered to be the ovary in 2 patients, the pelvis in 2, and the cervical canal in 1. One patient presented with preoperative CA125 levels that were remarkably raised (1,788 U/ml); the other 4 patients had CA125 levels within normal limits. Three patients had disseminated disease at diagnosis, including 2 with pelvic extension and 1 with abdominal extension. No patient had a distant metastasis at the time of diagnosis.

Fig. 1. Histological characteristic of ESS arising from endometriosis. **a** The tumor composed of sheets of small packed cells in continuity with a focus of endometriosis (HE, $\times 40$). **b** Whorled arrangement of tumor cells around small arterioles (HE, $\times 200$). **c** A focus of endometriosis, containing benign glands (HE, $\times 200$).

Histopathology

The microscopic features of the 5 cases were virtually identical. All of the tumors were typically composed of sheets of small packed cells resembling the stroma of the proliferative endometrium, with scant cytoplasm and round to oval nuclei. The tumors exhibited prominent stromal vascularity, few mitotic figures, and absent or only mild cellular atypia. Tumor cell necrosis was absent. Foci of endometriosis were observed in all of the cases (fig. 1).

The immunohistochemical results are shown in figure 2. Tumor cells in all 5 cases were CD10 positive, while no immunoreactivity for desmin, HHF35, CK, S-100 protein, CD34, CD117, and HER2/neu were detected. A weakly positive ER reaction was present in 1 case, and positive ER expression was observed in 2 cases. All 5 cases exhibited PR immunostaining, including weak staining in 4 cases and positive staining in 1. Notably, PDGFR expression was observed in all 5 cases, including PDGFR (+) in 1, PDGFR (++) in 2, and PDGFR (+++) in 2. Tumor cells were EGFR (++) in 2 out of 5 cases. The expression of VEGF was weakly positive in 1, positive in 2, and strongly positive in 1 patient.

Treatment and Outcome

Case 1, who presented with a tumor originating from the cervical canal, underwent a radical hysterectomy with ovarian preservation and pelvic lymphadenectomy. The histopathological examination of the surgical specimens confirmed that the disease was in the cervical canal and the endometrium was normal. Postoperatively, she received 4 cycles of adjuvant chemotherapy with a regimen of ifosfamide, doxorubicin, and carboplatin. There has been no sign of recurrence after 7 years of follow-up.

Case 2 had a tumor that originated from the pelvis infiltrating the left side of the pelvic wall as well as the upper third of the vagina. A magnetic resonance imaging scan showed a pelvic mass which measured $10 \times 12 \times 12 \text{ cm}^3$, extended to the bladder and left pelvic wall, and had induced left ureteral obstruction as well as severe hydronephrosis. The serum creatinine was $304 \mu\text{M}$. A biopsy was taken transvaginally and a percutaneous nephrostomy was performed; the creatinine level then decreased to $122 \mu\text{M}$. Since the mass could not be widely resected, chemotherapy consisting of cyclophosphamide, doxorubicin, and carboplatin was administered. The disease progressed after 4 courses were completed. The patient refused further treatment and was discharged. One year later, she was readmitted as a result of intestinal obstruction. At exploratory laparotomy, a partial bowel resection and enterostomy were performed. One cycle of chemotherapy was administered, which consisted of doxorubicin, ifosfamide, and dacarbazine. She died of the disease 24 months after the initial diagnosis.

Case 3 had a past history of subtotal abdominal hysterectomy. The patient developed a tumor arising from the left ovary which was adherent to the surrounding tissues and the cervix. She received a complete surgical resection and had 6 cycles of chemotherapy with a regimen of paclitaxel and oxaliplatin. A progesterone agent was also delivered for 6 months. The patient remains well without any tumor recurrence for 9 years.

Case 4, who had a previous history of subtotal hysterectomy and left salpingo-oophorectomy, underwent the excision of the cervix, a right salpingo-oophorectomy, and omentectomy. Four courses of chemotherapy with cyclophosphamide, doxorubicin, and carboplatin were delivered. She has remained well during the 6 years of follow-up.

Fig. 2. Immunoreactivity in ESS arising from endometriosis. **a** Negative expression of HHF35. **b** Negative expression of CK. **c** Negative expression of S-100 protein. **d** Positive staining for CD10. **e** Positive staining for ER. **f** Positive staining for PR. **g** Negative expression of CD117. **h** Negative expression of HER2/neu. **i** Positive staining for EGFR. **j** Positive staining for VEGF. **k** Positive staining for PDGFR.

Case 5 presented with a primary tumor involving the right ovary. She underwent an optimal surgery with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, tumor debulking, and adhesiolysis. Four courses of adjuvant chemotherapy were administered with a regimen of ifosfamide, doxorubicin, and dacarbazine. She remains free of disease and has been maintained on progesterone therapy for 8 months.

Discussion

ESS is a rare tumor, only accounting for approximately 0.2% of all malignant uterine tumors [10]. However, ESS arising from endometriosis is a rarer disease with an incompletely understood etiology. Previous studies have usually been based on case reports, and no more than 50 cases of ESS arising in endometriosis have been reported in the English literature (table 3) [2, 4, 11–37]. In the cur-

Table 3. Summary of the patients with ESS arising from endometriosis

References	Age years	Parity	Site of tumor	Dissemination at diagnosis	Initial treatment	Complete resection	Recurrence/ progression	Status
1 Nylander et al. (1938) [4] [†]	36	0	Rectum	NA	Resection	NA	NA	NED 10 months
2 Philipp and Huber (1939) [4, 11, 15] ^{†,‡}	26	NA	Pelvis	Vagina	NA	NA	Yes	DOD 3 years
3 Ober and Black (1955) [4] [†]	63	0	Pelvis	NA	TAH and BSO	NA	NA	NED 18 months
4 Ferraro et al. (1956) [11]	44	0	Pelvis	Ileum	Tumor and partial ileum resection, RT	NA	Yes	DOD 9 months
5 Ginzler and Herkera (1957) [4] [†]	64	0	Omentum	NA	TAH and BSO, resection	NA	NA	NA
6 Koller and Rygh (1960) [12]	56	0	Left ovary	Ureter, colon, pelvis	Tumor biopsy, TAH and BSO, debulking, RT	Yes	No	NED 15 months
7 Benjamin and Campbell (1960) [13]	37	6	Bilateral ovaries	Omentum	BSO, Oment	No	No	NED 5 weeks
8 Kanevskaya and Slarin (1960) [4] [†]	58	2	Rectovaginal	NA	NA	NA	NA	DOD 1 month
9 Scully et al. (1966) [14]	64	NA	Sigmoid colon	No	Sigmoid colon resection	Yes	No	DWOD 18 years
10 Palladino and Trousdell (1969) [15]	42	2	Bilateral ovaries	No	BSO	No	Yes	DOD 16.5 years
11 Gruskin et al. (1970) [16]	47	3	Left ovary	No	TAH and BSO, partial sigmoid resection	Yes	No	NED 1 year
12 Azoury and Woodruff (1971) [17]	41	2	Left ovary	Liver	Left oophorectomy, X-ray therapy	NA	NA	DOD 2 years
13 Azoury and Woodruff (1971) [17]	41	2	Right ovary	No	RSO, X-ray therapy	NA	No	NED 24 years
14 Labay and Feiner (1971) [18]	20	0	Right pleura and omentum	Peritoneum	Partial pleurectomy, diaphragmatic biopsy, omentum biopsy, RT	No	Yes	DOD 3 years
15 Persaud and Anderson (1977) [19]	63	4	Right broad Lig	Pelvis	TAH and BSO, tumor resection	Yes	Yes	DOD 14 months
16 Tuguchi et al. (1977) [4] [†]	21	0	Urinary tract	NA	Resection	NA	NA	DOD 3 months
17 Berkowitz et al. (1978) [20]	57	3	Vagina	No	Partial vaginectomy, RT	Yes	NA	NA
18 Crum et al. (1981) [21]	49	2	Pelvis	Midabdomen	Tumor resection	No	NA	NA
19 Silverberg and Fernandez (1981) [22]	52	0	Left ovary	Mesentery	TAH and BSO, mesenteric mass resection	Yes	No	NED 1 year
20 Silverberg and Fernandez (1981) [22]	43	4	Right ovary	Appendix, mesentery, omentum	TAH and BSO, sigmoid resection, Oment, Chemo, megestrol acetate	Yes	No	NED 1 year
21 Baiocchi et al. (1990) [4]	38	0	Transverse and ascending colon	Ileum, gastrocolic Lig, mesentery, plevis	Partial ileal and colon resection, Chemo, progesterone therapy	No	No	NED 5 months
22 Baiocchi et al. (1990) [4]	50	0	Left ovary	Omentum, colon	LSO, Oment, megestrol acetate	NA	No	NED 10 months
23 McCluggage et al. (1996) [23]	62	NA	Pelvis	Both ovaries, omentum	Partial vaginectomy, bilateral oophorectomy, Oment	Yes	No	NED 3 months

Table 3 (continued)

References	Age years	Parity	Site of tumor	Dissemination at diagnosis	Initial treatment	Complete resection	Recurrence/ progression	Status
24 Fukunaga et al. (1998) [24]	40	4	Bilateral ovaries	Tubes, omentum	TAH and BSO, Oment, Chemo	Yes	No	NED 16 months
25 Fukunaga et al. (1998) [24]	43	2	Pelvis	Bladder, rectum	TAH and BSO, partial rectum resection, tumorectomy	NA	No	NED 39 months
26 Yantiss et al. (2000) [25]	63	NA	Rectum	No	Resection, RT	NA	Yes	AWD 3 years
27 Mourra et al. (2001) [2]	61	1	Sigmoid colon	No	Rectosigmoid colon resection, D&C	Yes	No	NED 30 months
28 Bosincu et al. (2001) [26]	42	NA	Rectum	Omentum, uterine,	TAH and BSO, appendectomy, Oment, colorectal resection, Chemo	NA	No	NED 20 months
29 Cho et al. (2002) [27]	48	NA	Sigmoid colon	Bladder, ureter, mesentery	Segmental sigmoid colon resection, RLND	NA	No	NED 4 months
30 Khan et al. (2002) [28]	59	NA	Mesentery	No	Tumor resection, TAH and BSO	Yes	Yes	NED 4 years
30 Khan et al. (2002) [28]	59	NA	Mesentery	No	Tumor resection, TAH and BSO	Yes	Yes	NED 4 years
31 Mourad et al. (2003) [29]	45	2	Pelvis	Omentum, bilateral adnexa	TAH and BSO, debulking surgery, progesterone therapy	NA	NA	NA
32 Mitchard et al. (2004) [30]	35	NA	Right ovary	Omentum, appendix	TAH and BSO, appendectomy, Oment	NA	NA	NA
33 Geas et al. (2004) [31]	45	0	Bilateral ovaries	Omentum, colon, spleen, stomach, pancreas	TAH and BSO, debulking surgery, megestrol acetate	Yes	No	NED 36 months
34 Lacroix-Triki et al. (2004) [32]	50	NA	Left sciatic nerve	Bladder, sigmoid colon	TAH and BSO, left buttock mass biopsy, Chemo, GnRH agonist therapy	No	Yes	DOD not long afterward
35–37 Kondi-Pafiti et al. (2004) (3 cases) [33]	46–48	NA	Uterine wall	No	TAH and BSO	Yes	No	NED 2–3 years
38 Kondi-Pafiti et al. (2004) [33]	45	NA	Vaginal wall	No	Resection	Yes	No	NED 2 years
39 Kondi-Pafiti et al. (2004) [33]	50	NA	Pelvis	No	TAH and BSO	Yes	No	NED 1 year
40 Kovac et al. (2005) [34]	46	NA	Sigmoid colon	Mesentery, adnexa	LSO, Oment, colon and tumor resection	NA	No	NED 11 months
41 Hasiakos et al. (2007) [35]	44	NA	Cervix	Peritoneal cytology positive	Excision of the cervical mass, D&C,	Yes	No	NED 1 year
42 Budäus et al. (2008) [36]	46	0	Terminal ileum	No	Partial ileal resection, Oment, Chemo	Yes	No	NED 12 months
43 Kim et al. (2009) [37]	50	3	Bilateral ovaries	Omentum, para-aortic LNs, posterior cul-de-sac	BSO, appendectomy, omentum biopsy, RT, Chemo, progestins	No	No	AWD the 5th cycle of Chemo

NA = Not available; NED = no evidence of disease; DOD = died of disease; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; RT = radiotherapy; Oment = omentectomy; DWOD = died without disease; RSO = right salpingo-oophorectomy; Lig = ligament; Chemo = chemotherapy; LSO = left salpingo-oophorectomy; AWD = alive with disease;

D&C = dilation and curettage; RLND = regional lymph node dissection; GnRH = gonadotropin-releasing hormone; RH = radical hysterectomy; LN = lymph node. [†] Since the original article could not be found, the data were quoted from the report of Baiocchi et al. [4]. [‡] The data were quoted from the report of Ferraro et al. [11] and Palladino and Trousdell [15].

rent study, we reported the clinicopathological features of a series of 5 cases treated in our center, including the results of expression analyses for several possible markers for targeted therapy.

In 1990, a literature review by Baiocchi et al. [4] summarized the clinical features of 22 cases of ESS arising from endometriosis. They found that approximately half of the patients were nulliparous [4]. The authors hypothesized that this might be explained by the fact that 30–40% of patients with endometriosis were infertile. However, only 1 patient (1/5, 20%) in our series was nulliparous and had no sexual activity. Despite this controversial result observed in our data, the small number of patients limited our ability to find the actual incidence of nulliparity in patients with this disease. Additionally, the data of gravidity were not available in many case reports [23, 25–28, 30, 32, 33, 35]. Therefore, the association between nulliparity and ESS arising from endometriosis needs to be studied in more detail.

Examination of the level of CA125 has been widely used for detection of endometriosis [38, 39]. As reported, the elevation of serum CA125 in endometriosis is usually <1,000 mM [38, 40]. Clinically, a level of CA125 >1,000 mM accompanied by a pelvic or adnexal mass would suggest ovarian epithelial carcinoma. However, 1 case in our study, as well as 1 in the report by Kim et al. [37], who both had tumors of ovarian origin and exhibited multiple metastases, presented with CA125 levels >1,000 mM. It is interesting to note that the patient in our series presented with the highest level ever reported of 1,788 mM. Therefore, it is reasonable to suggest that ESS arising from endometriosis should be considered in the differential diagnosis of a pelvic mass in patients with highly elevated CA125 levels together with a history of endometriosis. Nevertheless, data with regard to serum CA125 levels in patients with ESS arising from endometriosis are limited and are currently only available in 7 published case reports [2, 24, 29–31, 35, 37]. More studies to estimate the value of the CA125 level in ESS arising from endometriosis are warranted.

Malignant tumors arising from endometriosis can be of uterine wall origin as well as extra-uterine origin. With respect to ESS arising from endometriosis, as shown in published studies (table 3), the ovary was the most common primary site of tumor origin, accounting for 30.2% (13/43) of cases. The intestine (20.9%, 9/43) was the second most common site of involvement, followed by the pelvis (18.6%, 8/43). In our data, the same number (40%, 2/5) of cases had tumors arising from the ovary and the pelvis. Previously, only 1 case had been reported who had

disease originating from the cervix, so the patient in our cohort was the second reported to have a tumor of cervical origin.

A distinct feature of our 5 cases was that 60% (3/5) of the patients, including all with tumors originating from the ovary, presented with disseminated disease at the time of diagnosis. In previous studies (table 3), 76.9% (10/13) of patients with tumors arising from the ovary had disease extension, including 61.5% (8/13) with abdominal extension and 15.4% (2/13) with distant extension. High frequencies of disease dissemination were also found in patients with tumors arising from the pelvis (75%, 6/8) as well as the intestine (44.4%, 4/9). With regard to the patients with tumors involving other uncommon sites, including the broad ligament, sciatic nerve, and pleura, all of them presented with initial pelvic or abdominal metastases. However, in the review of Leath et al. [5], including 72 primary uterine LGESS, only 31% of the cases had disseminated disease at diagnosis. A similar result was also reported by D'Angelo and Prat [10], where extra-uterine pelvic extensions were only found in 1 of 3 of the patients with uterine ESS. Thus, we speculate that ESS arising from endometriosis might be more prone to disseminate beyond its site of origin at diagnosis. Nevertheless, more information on this issue is necessary.

Total abdominal hysterectomy with bilateral salpingo-oophorectomy is considered to be the standard management for uterine ESS. However, the treatment for extra-uterine ESS as well as disseminated disease is controversial. Several authors postulated that a primary surgical procedure with complete tumor resection should be attempted [31, 37, 41, 42]. Organ resection (e.g. splenectomy or partial bowel resection) can be considered, especially if it contributes to an absence of the residual tumor [41, 42]. As shown in table 3, the detailed surgical data together with information on recurrence were available in 24 patients. Among these 24 cases (χ^2 tests, data not shown), patients who did not undergo complete tumor resection had a significantly higher recurrence rate (50.0%, 3/6) than the patients who did (11.1%, 2/18; $p = 0.042$). The survival rate was not compared due to the rather small number of patients, as well as the limited follow-up data. In our series, no recurrence occurred in the 4 (4/5, 80%) cases who had complete tumor resection, and the only patient who progressed had unresectable disease at presentation. Therefore, the surgical debulking of as much tumor as possible may reduce recurrence rate, and more studies are needed to determine this issue.

The optimal choice of adjuvant therapy for ESS remains unknown at the present time. The response of ESS

to chemotherapy is limited [5, 43], and radiotherapy does not appear to affect overall survival [44]. Similarly, there have been no definitive recommendations for hormonal therapy in patients with ESS [5]. Thus, novel therapeutic strategies for this disease are needed. Targeted therapy has been a great success in other solid tumors, which provides an interesting approach for future investigations in the treatment of ESS. In our study, tumor cells in all 5 cases with ESS arising from endometriosis lacked CD117 and Her-2/neu expression, which was consistent with previous studies on ESS [45, 46].

Of interest, all of the cases with ESS arising from endometriosis in our series exhibited PDGFR expression, which was identical to several reports that included tumor specimens of ESS [46, 47]. The strong expression of PDGFR in our data provided the theoretical basis for using imatinib mesylate in ESS originating from endometriosis. In the report by Moinfar et al. [48], a high rate (70%) of ESS tumors demonstrated positive staining for

EGFR. Similarly, positive staining for EGFR was observed in 2 of the 5 patients in our study. With respect to VEGF, positive staining was found in 80% of cases in our data. To the best of our knowledge, this is the first study about the possible target markers of ESS arising from endometriosis. Our results suggested that biological agents targeting PDGFR, EGFR, and VEGF might be effective against ESS arising from endometriosis. However, further investigations are necessary to confirm these findings.

In conclusion, ESS arising from endometriosis is rare. Complete tumor resection in ESS arising from endometriosis may reduce the recurrence rate.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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