



Case report

Endometrial stromal sarcoma occurring 20 years after total hysterectomy for myomas



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ABSTRACT

Extrauterine and extraovarian endometrial stromal sarcomas (ESSs) without endometriosis are extremely rare. A 57-year-old woman had a pelvic mass. Twenty years previously, she had undergone total hysterectomy and left salpingo-oophorectomy for uterine myomas. A series of examinations, including upper and lower gastrointestinal evaluations, and tumor markers such as cancer antigen (CA)-125, CA 19-9, and carcinoembryonic antigen were all unremarkable; however, an 18-cm heterogeneous mass with strong enhancement and many surrounding engorged vessels was present in the pelvic computed tomography image. Exploratory laparotomy showed a 20-cm gray firm mass. A complete tumor excision was performed. Microscopic features showed abundant spindle cells and epithelioid-like cells with increased cellularity. Immunohistochemistry was strongly positive for CD10, FLI-1, and vimentin; weakly positive for estrogen and progesterone receptors; and negative for CD117, CD34, HMB45, alpha-inhibin, SMA, and S-100. This favored the diagnosis of ESS. The right ovary and fallopian tube, omentum, and pelvic lymph nodes were unremarkable. The patient was treated with 2-year hormone therapy (oral megestrol, 160 mg, taken daily) and radiation therapy (50.4 Gy, separated by 28 fractions). She has been disease-free for 3 years. Active management, including complete resection and hormone therapy with/without radiation is beneficial for women with extrauterine and extraovarian ESS.

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Introduction

Endometrial stromal sarcoma (ESS) is a rare neoplasm that comprises approximately 0.2% of all uterine malignancies and approximately 10–15% of all uterine sarcomas.¹ Endometrial stromal sarcoma histologically resembles stromal cells during the proliferative phase of the menstrual cycle and displays a characteristic pattern of myometrial infiltration and a rich network of small

arterioles resembling the spiral arterioles of the secretory endometrium.² Because endometrial stromal cells are a key component of ESS, extrauterine and extraovarian ESSs are extremely rare, especially in women without endometriosis, although ESS is supposed to share some similarities with endometriosis. In this report, we present a case of extrauterine and extraovarian ESS of the pelvis. The case was unusual because of the history of total hysterectomy and absence of associated endometriosis.

Case report

A 57-year-old woman, gravida 2, para 2, had noticed a palpable mass in the left lower quadrant of the abdomen for months, and also had complained of frequency and nocturia during this period. Her past history was unremarkable, except that she had undergone

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abdominal hysterectomy and left salpingo-oophorectomy for uterine myomas 20 years previously. A series of examinations, which included upper and lower gastrointestinal tract evaluations, and measurement of the levels of tumor markers such as cancer antigen (CA)-125 (10.70 U/mL; normal range, <35 U/mL), CA 19-9 (2.54 U/mL; normal range, <35 U/mL), carcinoembryonic antigen (1.31 ng/mL; normal range, <15 ng/mL) were all unremarkable. However, magnetic resonance image findings were positive for an 18-cm heterogeneous solid mass with strong enhancement that was surrounded by many engorged vessels (Fig. 1). Exploratory laparotomy was performed with complete removal of the tumor (a 20-cm gray firm mass) after delicate dissection of the surrounding tissue, including the omentum and the small intestines. Frozen pathology favored malignancy. A thorough staging surgery (which included lymph node sampling) and multiple random biopsies were performed. The tumor was grossly 20 cm, gray, and firm. The cut surface showed multiple yellow necrotic parts (Fig. 2). Microscopic features showed abundant spindle cells and epithelioid-like cells with increased cellularity. The immunohistochemistry study (Fig. 3) was strongly positive for CD10, FLI-1, and vimentin; weakly positive for the estrogen receptor (ER) and progesterone receptor (PR); and negative for CD117, CD34, HMB45, alpha-inhibin, smooth muscle actin (SMA), and S-100. Because the other excisions—which included the right ovary and fallopian tube, omentum, and pelvic lymph nodes—were all free of tumor, the final surgicopathologic diagnosis was ESS, 2009 International Federation of Gynecology and Obstetrics (FIGO) stage IIIA. The patient was treated with 2-year hormone therapy (oral megestrol, 160 mg, taken daily) and radiation therapy (50.4 Gy, separated by 28 fractions). She has been disease-free for 3 years.

Discussion

Endometrial stromal sarcomas are the second most common uterine sarcoma and are classified as low-grade ESS or undifferentiated endometrial sarcoma.³ Because ESSs are exclusively composed of cells resembling those of the endometrial stroma in its



Fig. 2. A 20 cm × 13 cm × 11 cm gray firm tumor with several yellowish necrotic parts.

proliferative phase,⁴ extrauterine ESSs are rare. In addition, the ovary is the primary site in 76% of extrauterine ESS cases, and extraovarian sites account for the remaining 24%.^{5,6} This suggests that our reported case was unusual. In fact, extrauterine and extraovarian ESSs have been found in many abdominal or pelvic organs, including the Fallopian tubes, pelvic cavity, colon, appendix, and retroperitoneum.⁶ Many ESSs are associated with endometriosis or may be associated with prolonged estrogenic stimulation, tamoxifen treatment, or a history of pelvic irradiation.⁷ In our patient, endometriosis could not be identified in the pathological review after complete surgical staging, which further demonstrates the uniqueness of our case.

It is sometimes difficult to make an accurate diagnosis of low-grade ESS, especially the extrauterine type. Most ESSs of the uterus are low-grade and display overt endometrial stromal differentiation and bland nuclear features.³ However, the gross appearance of low-grade ESS can vary, and it is typically soft, fleshy, bulging, and tan to yellow without prominent necrosis. By contrast, in our ESS case, the gross picture showed a gray firm mass with multiple yellow necrotic parts. In the microscopic view, low-grade ESSs are typically cellular and composed of uniform, oval, fusiform to spindle cells that resemble proliferative endometrial stromal cells with mild nuclear atypia. The mitotic rate of low-grade ESS is low, often less than 3 mitotic figures (MF)/10 high-power field (HPF), as seen in our patient.

An immunohistochemistry evaluation is often used in the diagnosis of low-grade ESS. Low-grade ESS is typically positive for CD10, which is the most useful marker.³ However, some studies have found only focal and weak CD10 positivity in up to 40% of low-grade ESS, and rare cases have been completely negative for this marker.⁸ Desmin, h-caldesmon, and histone deacetylase 8 are typically negative in pure ESS, although focal staining for desmin has been found in some patients; this suggests that in the differential diagnosis between ESS and smooth muscle tumors, h-caldesmon and histone deacetylase 8 are more specific and sensitive, compared to desmin.⁷ Because no single marker is entirely sensitive or specific, a panel of immunostains is of the most value in making an accurate diagnosis, as shown in our ESS case.

Most ESSs express hormone receptors, including the ER and PR and possibly the androgen receptor (AR); however, these hormone receptors seem to be heterogeneous among tumors, ranging from a weak and focal pattern to a strong and diffuse pattern and from 0% to 95%.⁷ In general, low-grade ESSs express a high percentage of positivity for the ER and PR, and different subtypes of ERs and PRs seem to be valuable in ESSs. Approximately 80% of ESSs express ER-

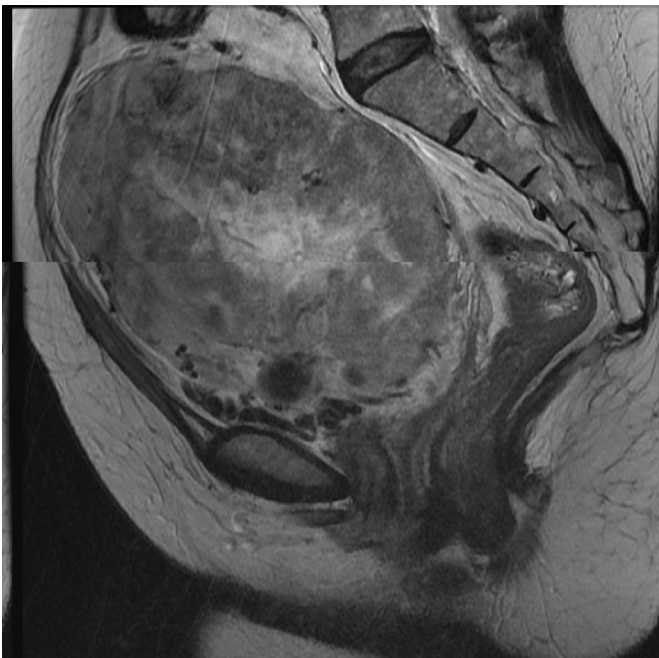


Fig. 1. The sagittal T2-weighted fat-suppressed image (4800/110; slice thickness, 5 mm; 256 × 256) shows a large heterogeneously enhanced mass.

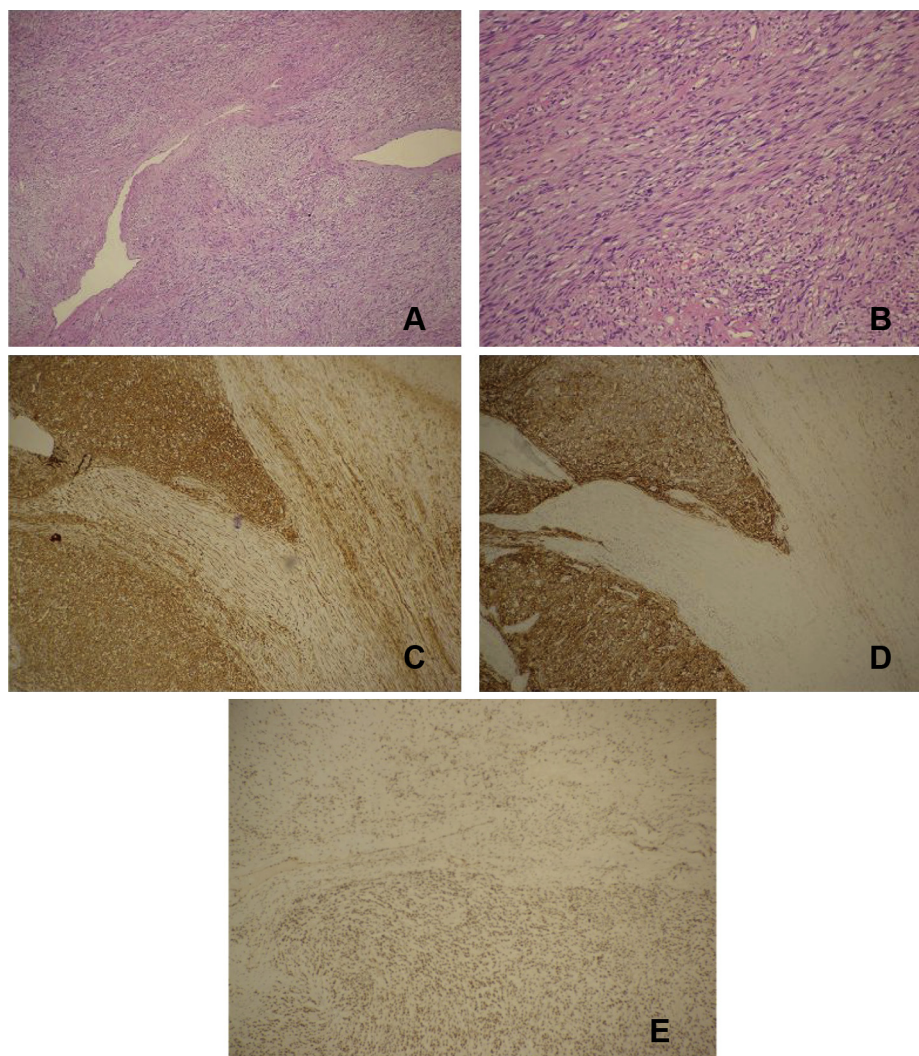


Fig. 3. Microscopic findings of the tumor. The sections show spindle and epithelioid features: (A) hematoxylin-eosin stain, $\times 200$ magnification; (B) hematoxylin-eosin stain, $\times 400$. Immunohistochemical staining analyses reveal that the neoplastic cells are immunoreactive to (C) vimentin, $\times 400$; (D) CD10, $\times 400$; and weakly stain for (E) estrogen receptor (ER), $\times 400$.

alpha (which is involved in cell proliferation), but not ER-beta (which is involved in apoptosis).⁹ By contrast, PR-alpha is the dominant isoform in ESSs; however, in recurrent ESSs, PR-alpha levels are reduced and PR-beta levels are increased.¹⁰

In the management of our patient, some controversial issues were present. First, it was difficult to provide the 2009 FIGO stage for this patient because 2009 FIGO stage IIA or IIIA were both acceptable. The definition of 2009 FIGO stage II and stage III of uterine sarcomas is that the tumor extends to the pelvis and invades abdominal tissues, respectively.¹¹ However, the tumor in the current patient who had a history of total hysterectomy, and the main tumor grew from the pelvic cavity to the abdominal cavity (not just protruding into the abdomen) because the infracolic omentum covered the tumor and the small intestine adhered to the abdominal part of the tumor. The final pathology failed to detect seeding or tumor invasion of the omentum or other organs. Second, many prognostic factors in ESSs have been reported previously, including clinical and pathological factors such as age, race, parity, menopausal status, stage, tumor size, nuclear atypia, mitotic index, tumor necrosis, lymphatic space invasion, status of surgical resection margins, DNA ploidy/proliferation index, and ER, PR, and AR expression.⁷ However, all of these factors are based on uterine type-ESSs. Therefore, the prognostic factors of extrauterine and

extraovarian ESS are unknown. We believe that surgery may be the most important component of treatment for ESSs because the absence of primary surgery and incomplete cytoreduction have indeed been shown to be independent prognostic factors.¹² As with uterine ESSs, postoperative adjuvant therapy is debated. Until recently, evidence of the role of adjuvant radiotherapy in uterine ESSs had been limited to retrospective noncomparative case series because no case series has been sufficiently large to quantify the potential benefit of radiotherapy. For example, the European Organization for Research and Treatment of Cancer Gynaecological Cancer Group (EORTC CGC) conducted a prospective, randomized Phase III study to evaluate the effect of postoperative radiation in FIGO stage I and stage II diseases; the group spent 13 years on the study and only 30 cases of ESS were included.¹³ In addition, recent data from the National Cancer Institute (Bethesda, MD, USA) Surveillance, Epidemiology, and End Results program (SEER) showed no improvement in overall survival with the addition of radiotherapy to surgery, although the impact on local tumor control was not mentioned.¹⁴

The role of adjuvant chemotherapy is also conflicted because chemotherapy is used for metastatic disease. The acceptable first-line regimen is a combination of doxorubicin with or without ifosfamide, although gemcitabine and docetaxel look promising in

the first-line setting. However, this information is based on a study of leiomyosarcoma with very little information available on the role of chemotherapy in ESS.⁷ Therefore, no chemotherapy was prescribed for this patient.

Third, because most low-grade ESSs are positive for the ER and PR, hormone therapy may be an alternative with clear evidence of ESS responsiveness to hormone therapy; responses to progestins, aromatase inhibitors, and gonadotropin releasing hormone agonists have been reported.^{15–17} In this ESS case, we treated the patient with 2-year megestrol (160 mg) on a daily basis; this protocol was based on two small studies^{15,18} that showed the benefits of using adjuvant medroxyprogesterone (250 mg) or megestrol (160 mg) on a daily basis for 2 years. However, patients should be informed of the potential side effects of progestins, including thrombosis and weight gain.^{19,20}

In conclusion, extrauterine and extraovarian ESSs are extremely rare; therefore, treatment is often based on experience in managing uterine ESSs. Complete surgical resection is the main component of a good outcome.²¹ The use of postoperative radiotherapy and/or hormone therapy can be guided by the history and condition of the patient.

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