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Case Report

Endometrial stromal sarcoma arising in vagina

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Abstract: Endometrial stromal sarcoma (ESS) arising in the vagina is an extremely rare extrauterine endometrial stroma sarcoma, with only 4 cases reported in the literature up to date. Here we report a case of neoplasm originating from vagina. A 32-year-old woman complained of intermittent vaginal bleeding especially after intercourse. A mass with a diameter of 1.0 cm was found in the middle and upper segments of the right posterior vaginal wall. Biopsy showed ESS. Total abdominal hysterectomy, unilateral salpingo-oophorectomy (right) and partial vaginectomy were performed. No ESS lesion was found in endometrium. The patient received six courses of platinum-containing combination chemotherapy after surgery and was free of tumor 18 months after the diagnosis of ESS. The diagnosis of ESS relies on pathologic examination. CD10 is the most useful immunohistochemical marker for the diagnosis of this tumor. The mainstay treatment of ESS is surgery. Local excision and ovarian retaining may be considered in premenopausal women.

Keywords: Extrauterine sarcoma, endometrial stromal, vagina, immunohistochemistry

Introduction

Endometrial stromal sarcoma (ESS) is a rare tumor, comprising less than 1% of uterine malignancies. Most tumors of this kind occur in the uterus. Occasionally, it arises primarily in extrauterine sites, such as pelvic cavity, ovary, abdominal cavity, fallopian tube, retroperitoneum, vagina, and vulva [1]. Of these extrauterine sites, the vagina is an extremely rare site. To our knowledge, current literature has shown that only 4 cases of extra uterine ESS were of vaginal origin. In the majority of the extrauterine ESS cases, foci of endometriosis are found in the vicinity of the neoplasm. Now we present a case of primary vaginal ESS, which is the fourth case without detectable association of endometriosis. Clinical and pathologic features of this neoplasm will be reviewed and therapeutic consideration will be discussed.

Case report

A 32-year-old G2P2 woman was admitted to our hospital on September 26th, 2011 because of intermittent vaginal bleeding especially after intercourse. A mass had been subsequently detected in the posterior wall of her vaginal tract for 2 months. She started to have an occasional stabbing pain in her posterior vaginal wall 2 years ago without vaginal bleeding or other abnormal feelings. Her past medical history was unremarkable. There was no history of hormone usage. Physical examination showed a smooth hard broad-based grayish-red mass with a diameter of 1.0 cm, which was located in the middle and upper segments of the right posterior vaginal wall. No abnormalities had been found in the uterus and the adnexal region. A digital rectal examination revealed that there were no thickening or roughening of the rectal mucous and no blood at the gloved fingertip. Subsequent biopsy of the vaginal mass confirmed that it was endometrial stromal sarcoma.

Metastatic workup, including CT scan, ultrasonography, gastroscopy, sigmoidoscopy, colposcopy, and chest x-ray did not find any evidence of metastatic disease. Routine hematology and

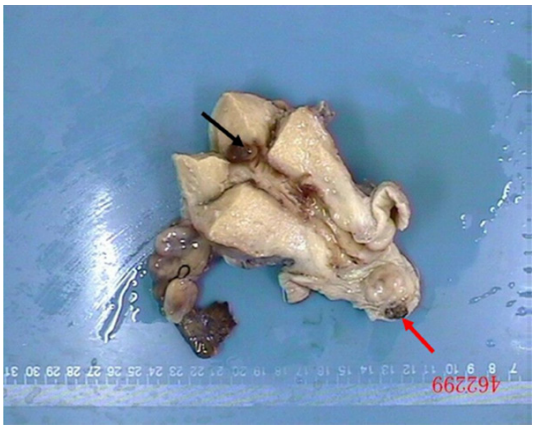

Figure 1. Total abdominal hysterectomy, unilateral salpingo-oophorectomy (right) and partial vaginectomy specimen. A polyp (black arrow) locates on the uterine fundus and a grayish-red nodule (red arrow) locates on the posterior vaginal wall.

chemistries, including serum AFP, CA125, CA199, CEA, HCG were all negative. Since the patient was young and desired to preserve ovarian function, she then underwent total abdominal hysterectomy, unilateral salpingo-oophorectomy (right) and partial vaginectomy. No metastatic disease was found during surgical exploration. The patient received six courses of platinum-containing combination chemotherapy (PAC regimen) as an adjuvant therapy after surgery.

The uterine endometrium was in the proliferative phase and had a polyp of 1.2×1.2×0.5 cm. There was a follicular cyst with a diameter of 2 cm in the right ovary. The right tube had a mesonephric duct cyst measuring 1 cm in diameter. There was a circumscribed tumor, measuring 1.0×0.8×0.2 cm with hard consistency and grayish-red color, arising from the posterior vaginal wall and 2.5 cm away from external cervical os (**Figure 1**). The margins of tumor excision appeared free of tumor. Microscopical examination showed a stromal sarcoma, consisting of small oval to fusiform cells resembling the cells of endometrial stroma during the proliferative phase of the cycle. The tumor cells grew diffusively and formed nodular or irregular clusters with vaginal muscular invasion. No lymphovascular invasion was found. Cytologic atypia was unremarkable, necrosis was absent, and mitotic index was 5-6 per 10 high-power fields (HPF) (**Figure 2A**, **2B**). Immunohistochemical examination demonstrated a positive staining of CD10, ER, PR and Vimentin (**Figure 3A-D**) and a negative staining of desmin, muscle actin, S-100 protein stains (**Figure 4A-C**).

Discussion

Endometrial stromal sarcoma (ESS) is a rare, malignant mesenchymal tumor of the uterus, accounting for about 0.5% of all uterine malignancies and 10% of all uterine sarcomas [2]. According to the latest World Health Organization Classification, ESS can be classified into low-grade ESS (LGESS) and undifferentiated endometrial sarcoma (UES). LGESS are low malignant tumors, typically composed of uniform, oval to fusiform cells reminiscent of endometrial stromal cells in proliferative-phase, with numerous small plexiform arterioles, which invade the myometrium as well as the intramyometrial or parametrial vessels. There is usually little cytological atypia or pleomorphism. The mitotic rate is usually lower than 10 mitosis/10HPF. Necrosis is rarely seen in LGESS. In contrast, UES are malignant and lack overt endometrial stromal differentiation. It often exhibits myometrial invasion, hemorrhage and necrosis, as well as marked nuclear pleomorphism and high mitotic activity with 10 mitosis/10HPF or higher. Current classification limits the diagnosis of ESS to low-grade ESS. The most important feature that distinguishes ESS from UES is the resemblance of the neoplastic cells to proliferative endometrial stroma. Our case belongs to ESS according to pathological examination.

Cases of primary ESS in extrauterine locations have been widely reported. The sites of occurrence include pelvic cavity, ovary, abdominal cavity, fallopian tube, retroperitoneum, vulva, and vagina [1]. However, of these extrauterine sites, the vagina is an extremely rare site. Only 4 cases of extrauterine ESS arising in vagina were reported in the literature up to date. Three of them had no detectable association of endometriosis. Therefore, our case is the fourth one without presence of endometriosis. The origin of the extrauterine ESS tumor cells is not yet known. The foci of endometriosis were found in the vicinity of the neoplasm in the majority of extrauterine ESS cases, and the presence of endometriosis could explain the occurrence of these tumors in extrauterine sites such as ovaries, fallopian tube, and pelvic peritoneum,

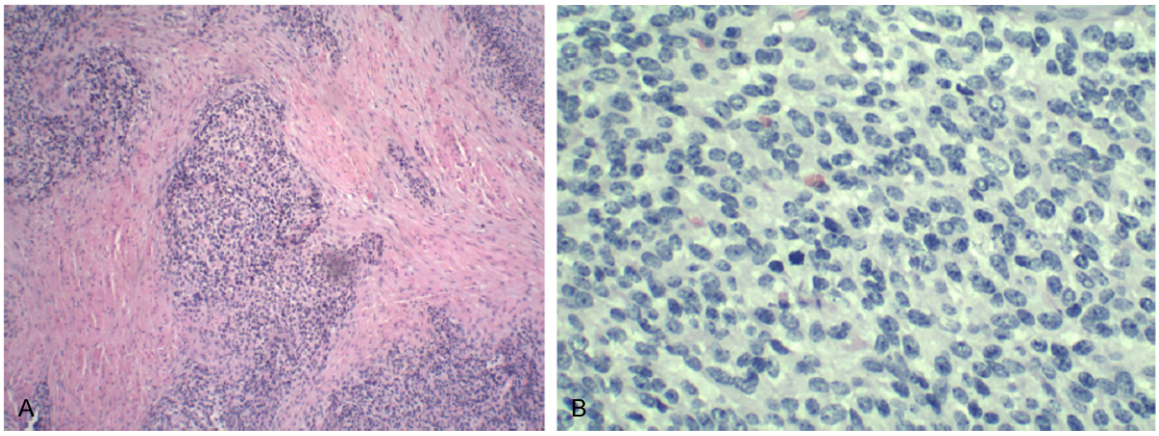

Figure 2. Hematoxylin and Eosin Stain. A. H&E stain at ×100 reveals that the neoplasm is composed of spindle cells forming nodular or irregular clusters and disposed in an infiltrative fashion. B. H&E stain at ×400 Cytologic atypia was unremarkable, necrosis was absent, and mitotic index was 5-6 per 10 high-power fields.

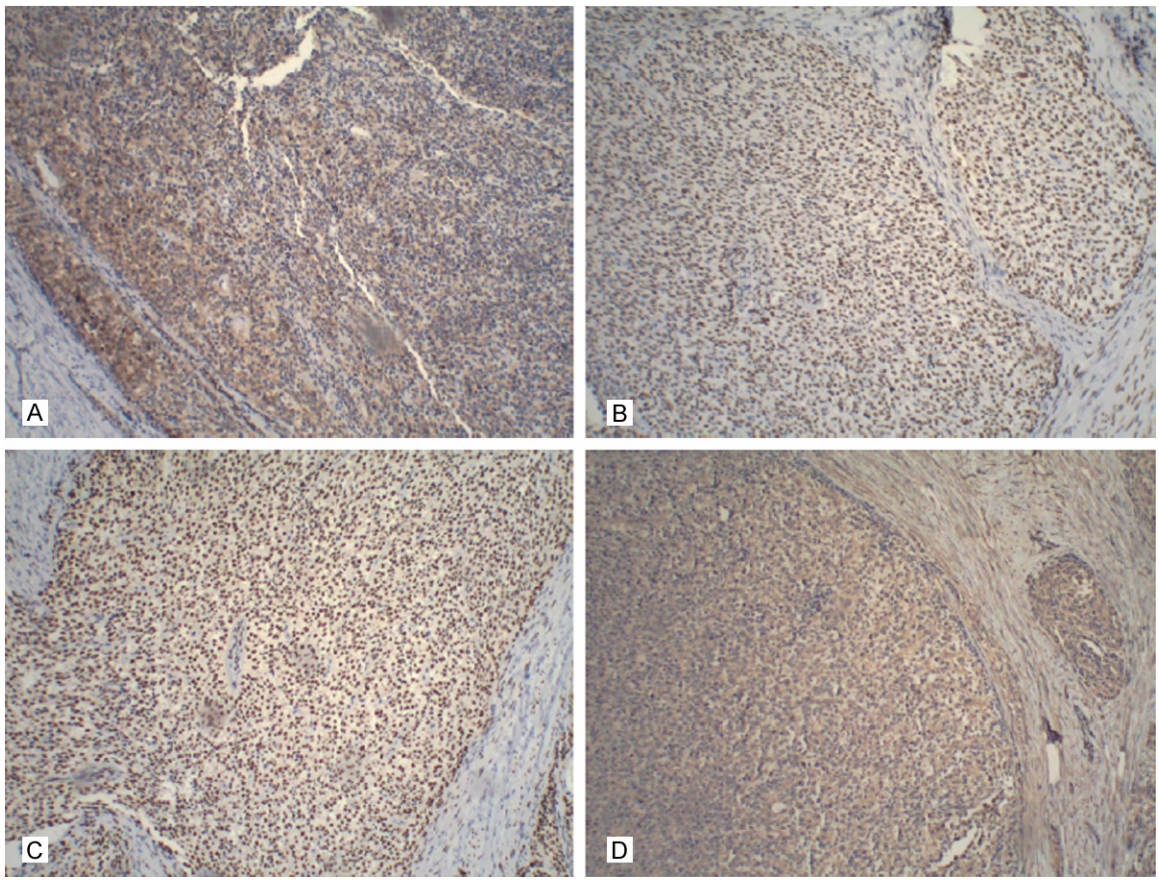

Figure 3. Immunohistochemical Staining Tumor Cells for CD10, Estrogen Receptor, Progesterone Receptor and Vimentin. After immunohistochemical staining (×100), the tumor cells were positive for CD10 (A), estrogen receptor (B), progesterone receptor (C) and Vimentin (D).

according to the hypothesis of secondary müllerian system [3]. This hypothesis suggests that the mesenchymal cells present in tissues derived from the celomic epithelium have the potential to differentiate into müllerian-type epithelium and stroma such as endometriosis

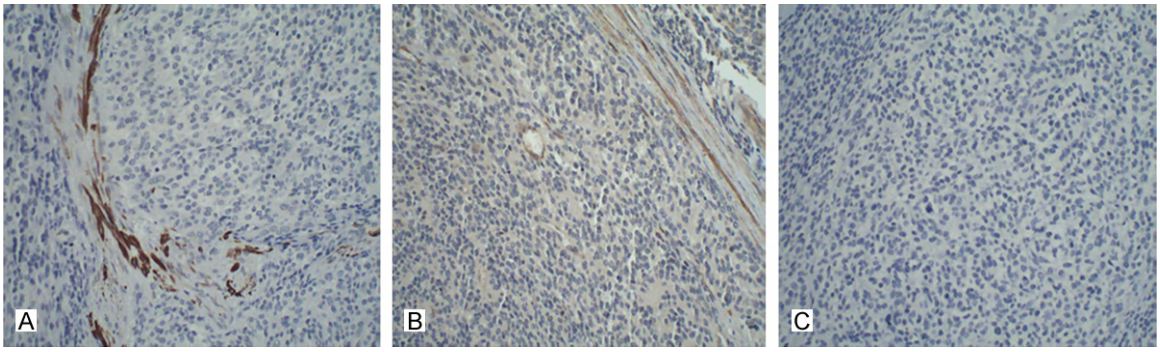

Figure 4. Immunohistochemical Staining Tumors Cells for Desmin, Muscle Actin and S-100 Protein. After immunohistochemical staining (×200), the tumor cells were negative for Desmin (A), muscle actin (B), S-100 protein (C).

tissue. On the other hand, primitive cells of the pelvis and retroperitoneum are an alternative possible origin for the tumor if endometriosis is not present [4]. However, both of them cannot be applied to cases occurring in sites such as vulva and vagina without foci of endometriosis. Including our case, 4 out of 5 cases of vaginal ESS aren't associated with endometriosis. Hence, the pathogenesis of vaginal ESS needs to be further explored.

The symptoms of vaginal ESS are usually nonspecific, including irregular vaginal bleeding, especially after intercourse, increasing abdominal girth and abdominal discomfort. Therefore, the diagnosis of ESS relied on pathologic examination. Immunohistochemistry is most often used to differentiate it from other extrauterine tumors. Although none of the immunohistochemical markers is specific for the diagnosis of ESS, CD10 staining is consistently positive in most ESS cases, as demonstrated in a recent study, which included 17 ESS cases, 94% of them had a positive CD10 staining [5]. Others have also demonstrated the usefulness of this marker for the diagnosis of this tumor. Furthermore, other stromal sarcomas should be excluded. Cellular leiomyomas which are desmin-actin positive, mixed müllerian tumor with their usually distinct morphology, hemangiopericytomas which are factor VIII positive, small cell carcinomas which are EMA positive, and lymphomas which are LCA positive must be considered. However, ESS present a distinctive immunohistochemical profile, in which all the above markers are negative, while CD10 and Vimentin staining are usually intensely positive and expression of ER, PR is variable. Immunohistochemical stain results in our case clearly showed positive staining of CD10, Vimentin, ER, PR, and negative staining of Desmin, muscle actin, S-100 protein, which is in agreement with the diagnosis of ESS.

General treatment recommendations or guidelines based on prospective studies are not available and information is only available from case reports, due to the rarity of these tumors. The mainstay of treatment of ESS is surgery. Total hysterectomy in combination with BSO and carefully abdominal exploration is commonly accepted as treatment of choice for early-stage cases confined to the uterus (stage I-II) [6]. Because ESS is a hormone-sensitive malignancy, bilateral salpingo-oophorectomy has been recommended even in premenopausal patients with early-stage disease. But recent larger studies suggested that ovarian preservation did not affect the outcome of premenopausal patients with early-stage disease [7, 8]. Although lymph node involvement was found at early stages in approximately 6-9% of patients, a routine systematic pelvic and periaortic lymph node dissection does not appear to provide a survival benefit; thus, only suspicious or enlarged nodes should be removed under the aspect of cytoreduction [9, 10]. After surgery, treatment options may include radiation therapy, hormone therapy and chemotherapy. Although radiotherapy may reduce local failure, its effect on long-term survival is not clear. Low-grade ESS is typically positive for progesterone receptor. Therefore, hormonal therapy, particularly progestin therapy, is an option for consideration in women who present with advanced-stage or recurrent disease. Because of the rarity of the disease, only a few clinical trials of chemotherapy for advanced or recurrent ESS

have been reported, and most of the results were disappointing [11].

Primary vaginal ESS is extremely rare. There are only five cases of primary vaginal ESS including ours. Two of the 5 patients [1, 12] only received neoplasm excision with wide healthy margin. Hysterectomy was not performed and no further treatment was given. One patient recovered well 3 years after surgery. Another patient was alive and well, free of tumor 38 months after the diagnosis. Another case reported by Berkowitz et al [13], who had a history of total abdominal hysterectomy and left salpingo-oophorectomy for endometriosis many years before, underwent exploratory laparotomy and partial vaginectomy encompassing paracolpos and parametrial tissue. Thorough review of the abdominal cavity and viscera demonstrated no metastatic disease in this patient. Postoperatively, the patient received 4400 rads of external irradiation to the whole pelvis and 3000 rads to the vaginal cuff via a radium vaginal cylinder. The fourth case reported by Chang YC et al was a 34-year-old woman presenting with endometrial stromal sarcoma arising in the vagina without coexistent endometriosis [4]. This patient underwent neoplasm excision first, followed by abdominal total hysterectomy and bilateral salpingo-oophorectomy with lymph node dissection when vaginal ESS was confirmed. After surgery she received whole vaginal irradiation with a dose of 500-cGy RAL per course for eight courses subsequently. After one- and -a-half years of follow-up, neither tumor recurrence nor distant metastasis was found. The fifth patient, reported herein, underwent total abdominal hysterectomy, unilateral salpingo-oophorectomy (right) and partial vaginectomy, then received six courses platinum-containing combination chemotherapy (PAC regimen) as an adjuvant therapy after surgery. The patient was alive, well and free of tumor 18 months after the diagnosis. In summary of the treatment, two of them only underwent local excision, three of them preserved uni- or bilateral ovary and no recurrence during follow-up. More studies are needed to confirm whether local excision is sufficient and preserving ovarian function is feasible for vaginal ESS without metastasis and no further treatment after surgery.

There are limited and heterogeneous data published to date as clinical guidelines for originally vaginal ESS. Further research is needed to define the optimal management of this disease as well as the prognostic and therapeutic implications of lymph node dissection, total abdominal hysterectomy and salpingo-oophorectomy, given the limited and retrospective nature of the available data. Treatment decisions should be individualized and based on appropriate patient counseling.

Disclosure of conflict of interest

None.

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