EJGO European Journal of Gynaecological Oncology

Primary vaginal endometrial stromal sarcoma associated with endometriosis: a case report with a review of the literature

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Summary

Extrauterine endometrial stromal sarcomas (ESSs) are quite rare tumors, and vagina is an unusual site for these tumors. This paper presents a very rare pathological entity of primary vaginal ESS. A 46-year-old woman with a complaint of postcoital vaginal bleeding, low abdominal pain, and constipation was admitted to the clinic. She had a mass of seven cm in size, located in the posterior fornix detected on physical examination. The preoperative biopsy showed ESS, surgical material, and evaluation of an endometrium confirmed the diagnosis of primary vaginal ESS. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial vaginectomy. The diagnosis of ESS performed by pathologic and immunohistochemical evaluation was: caldesmon (-), actin (-), desmin (-). CD10 (+), ER (+), PR (+), and vimentin (+). There was no ESS lesion in the endometrium. The patient was free of tumor for 22 months after the surgery without any additional therapy. In this study, the authors report the sixth case of primary vaginal ESS in the literature and aim to discuss diagnostic criteria and management protocols in the light of the literature.

Key words: Endometrial stromal sarcoma; Extrauterine; Extragonadal; Vaginal tumors; Uterine sarcoma.

Introduction

Endometrial stromal sarcomas (ESS) are rare malignant tumors of the uterus and constitute 0.2% of all uterine malignancies. ESS are slow progressing tumors and may show recurrence even years after the initial diagnosis [1]. The correct histological diagnosis plays a significant role in the subsequent follow-up and management of such cases. The WHO defines ESS in three categories: endometrial stromal nodule (ESN), low grade endometrial stromal carcinomas (LGESS), and undifferentiated endometrial sarcoma (UES). The differentiation between low-grade and undifferentiated tumors depends on nuclear pleomorphism and necrosis, rather than the number of mitoses [2].

Although the pathogenesis of ESS is unknown, hormonal factors such as unopposed estrogens are accused in the pathogenesis of uterine ESSs. However, foci of endometriosis are found in the vicinity of the neoplasm in extrauterine ESS cases [3]. Primary extrauterine ESS are quite rare tumors, and about 80 cases have been reported, until now, in literature [3, 4]. The largest series was reported by MD Anderson Cancer Center, Texas, in 2013 [3]. According to this series, abdominal peritoneum, bowel wall, ovaries, and pelvis were extrauterine sites and about half of the cases were associated with foci of endometriosis [3]. Of these primary extrauterine ESS locations, vagina is quite rare. Literature up to date has shown only five cases of extrauterine ESS with vaginal origin [5-9]. Due to the small number of instances, there is insufficient data on the pathogenesis, risk factors, outcome, and treatment modalities. This paper presents the sixth case of primary vaginal ESS and discusses diagnostic criteria and management protocols in light of the data from the prior cases in the literature.

Case Report

A 46-year-old woman presented to a gynecology clinic for intermittent vaginal bleeding, especially after intercourse, low abdominal pain, and constipation. There was no history of hormone treatment, surgery, radiotherapy, chemotherapy, medical problems, alcohol or smoking habits. Patient had no gynecological follow-up previously. She had two prior parturitions with vaginal delivery, no curettage, or spontaneous abortion.

Preoperative Findings

The bimanual examination of the uterus was about eight weeks of gestation size with irregular surface. There was a mass of seven cm in diameter in the posterior fornix protruding through the vagina. The rectal examination showed that Douglas was filled by the mass without roughening of the rectal mucosa. Rectal mucosa was seen intact by colonoscopy.

A gray scale pelvic ultrasonography and pelvic magnetic resonance imaging demonstrated solitary mass (70×60 mm in size) in the Douglas protruding into the vagina. The uterus was multiple myomatous in appearance. Routine hematology and biochemistry analysis results, including serum AFP, CA19.9, CEA, and hCG

Revised manuscript accepted for publication April 28, 2015

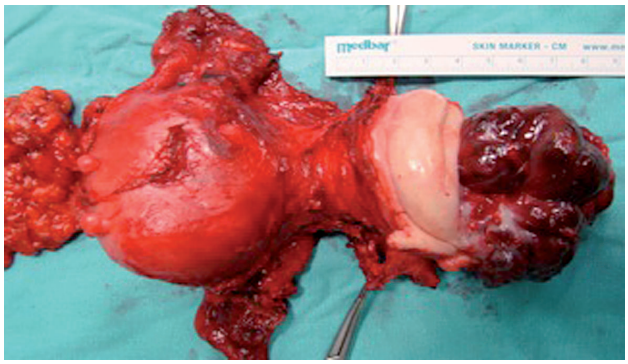

Figure 1. — Macroscopic view of uterus, adnexa, and vaginal mass.

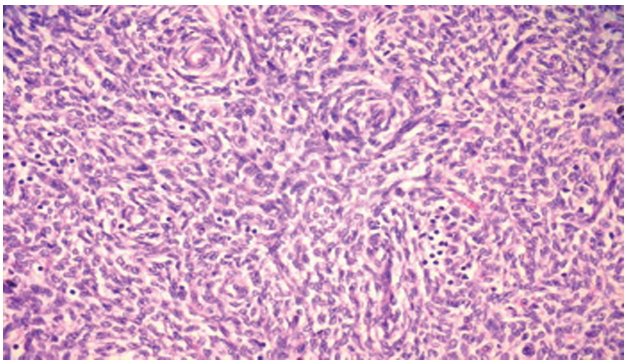

Figure 2. — Hematoxylin and Eosin stain (H&E ×200). The neoplasm is composed of cells that resemble the stromal cells in proliferative endometrium. The tumor cells have minimal cytologic atypia, and mitotic index is 2-3 per 10 high-power fields; necrosis is absent.

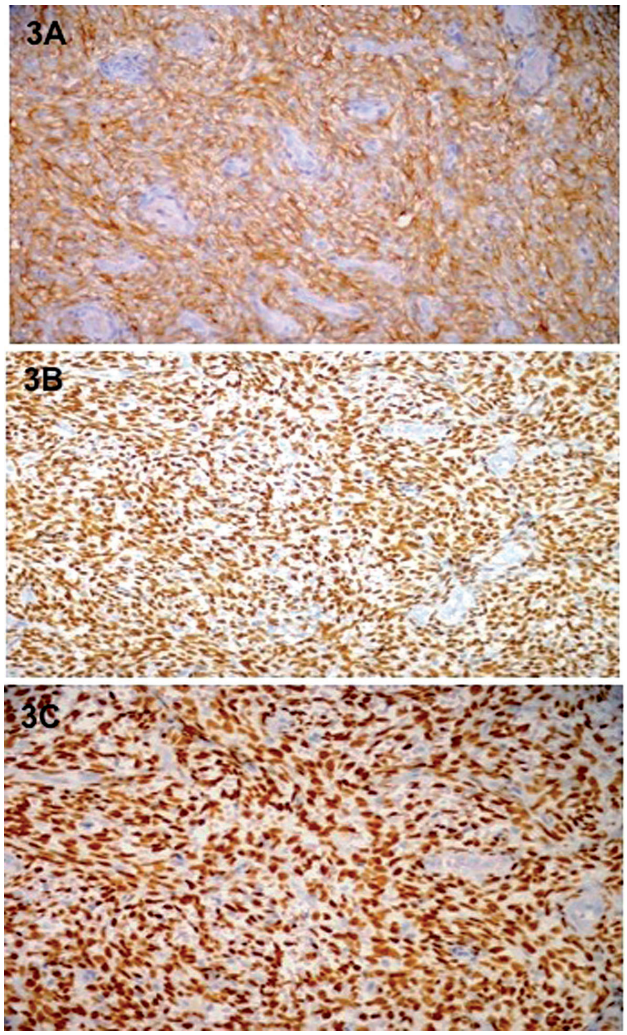

Figure 3. — Immunohistochemical staining tumor cells for CD10, estrogen receptor, progesterone receptor, and vimentin (×200). The tumor cells are positive for CD10 (A), estrogen receptor (B), progesterone receptor (C), and vimentin (D).

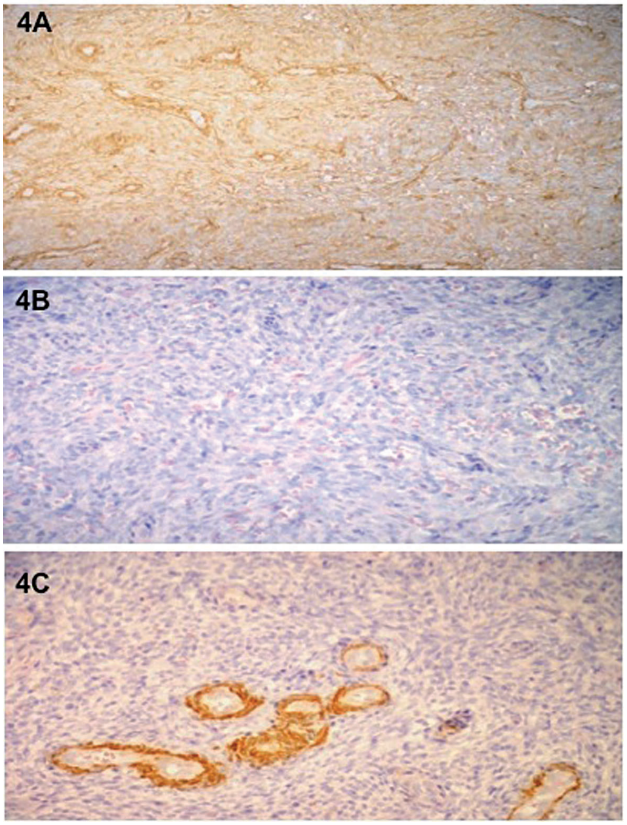

Figure 4. — Immunohistochemical staining tumor cells for smooth muscle actin, desmin, and caldesmon (×200) The tumor cells are negative for actin (A) and desmin (B). Tumor cells are negative for caldesmon, but muscle of blood vessels are positive (C).

levels were all in reference ranges, except serum CA12.5 level which was elevated (75 IU/ml).

Preoperative histopathologic evaluation was performed by fractional dilatation and curettage, pap smear, and the punch biopsy was carried out from vaginal mass. The histopathologic evaluation of endocervical and endometrial curettage materials was usual (proliferative endometrium and endometrial polyp). The punch biopsy from vaginal mass showed the endometriosis and endometrial stromal sarcoma with mitosis 2-3/10 HPF with mild atypia and no necrosis. The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial vaginectomy.

Pathologic evaluation

Macroscopic findings: The cervix, ovaries, and bilateral fallopian tubes were normal. Uterus was larger in size with multiple myomas. Omental tissue was infiltrated by tumor attached to uterus fundal serosa. There was a 70×65 mm, red colored mass with hard consistency (Figure 1), located in the posterior fornix of the vagina. The mass was not infiltrated into the uterus, parametrial tissue, or the cervix. The margins of tumor excision appeared to be free of tumor.

Microscopic findings: There was no ESS lesion in endometrium, myometrium, cervix, bilateral tubes or ovaries. Peritoneal part of the uterus and the iliac part of peritoneal biopsy results and omental tissue showed endometrial stromal sarcoma metastasis. The pathological examination of vaginal mass was low-grade endometrial stromal sarcoma and lymphovascular space invasion was observed.

The neoplasm was composed of cells that resembled the stromal cells in proliferative endometrium. The tumor cells had minimal cytologic atypia, and mitotic index was 2-3 per 10 high-power fields, and there was no necrosis. Figure 2 shows Hematoxylin and Eosin stain. (H&E ×200). Immunohistochemical staining of tumor cells for CD10, estrogen receptor, progesterone receptor, and vimentin (×200) are shown in Figure 3.

The tumor cells were positive for CD10 (A), estrogen receptor (B), progesterone receptor (C), and vimentin (D). Immunohistochemical staining of tumor cells for smooth muscle actin, desmin, and caldesmon (×200) can bee seen in Figure 4. The tumor cells were negative for actin (A), and desmin (B), while tumor cells were negative for caldesmon and muscle of blood vessels were positive (C).

Discussion

ESS is a rare type of cancer which develops in the endometrial supporting connective tissue [2]. Vagina is an unusual site for extrauterine ESS [9]. This paper presents a very rare pathological entity of primary vaginal ESS. To the present authors' knowledge, this is the sixth case published.

Endometrial stromal tumors are defined by stromal differentiation and tumor invasiveness with respect to their margins as low or high grade (undifferentiated). However, heterogeneous morphologic features may necessitate further research for precise diagnosis via immunohistochemical markers. The differential diagnosis of ESS from normal endometrial stroma, cellular myoma, and leiomyosarcoma need further evaluation with these markers. Diffuse CD10 immunoreactivity is a useful positive predictive marker of ESS while it is negative in cellular myomas. ER staining and CD34 non-staining are other informative markers for diagnosis [10]. There is also estrogen and progesterone receptor positivity in ESS. In this case the results were: ER(+), PR(+), CD10(+), desmin (-), and caldesmon (-).

About half of the cases of extrauterine ESSs are associated with endometriosis. The association between endometriosis and malignancy has been suggested in previous studies. There is still no definite data whether this a cause-effect relationship or the sharing of common risk factors. Nevertheless endometriosis is a common gynecologic pathology with proven increased likelihood of malignancy, but it is still a quiet rare condition, affecting 0.7-1% of all endometriosis cases [11]. The diagnosis of 'malignancy associated endometriosis' is defined by Sampson and the following three criteria are required for the diagnose: 1) presence of both neoplastic and benign endometrial tissue in the neoplasm, 2) histologic tumor is endometrial origin, and, 3) no identifiable primary tumor site [12]. Scott added the fourth criteria which is cytological or structural atypia in the endometrial glands [13]. Likewise in the present case, both neoplastic tissue and endometriosis were demonstrated in the same specimen. The most common sites of malign transformation of endometriosis foci are the ovaries, but 20% of the cases are observed in extragonadal sites such as rectovaginal septum, colon, and vagina. Although the majority of the neoplasms related to endometriosis are epithelial in origin, stromal neoplasms occur in 20.8% of the cases. Among the six vaginal primary ESS cases, three of them including the present case are associated with endometriosis. ESSs occur at younger ages (40 and 55 years), as noted in the present report. Thus, similar to other extrauterine ESS tumors, half of the cases were related to endometriosis and they were presented at younger ages compared to other uterine sarcomas

Surgery is the treatment of choice in ESS, but the final decision for optimal treatment is controversial and in order to form a consensus, the collection of case reports would be beneficial [14]. Since ESS is a hormone-sensitive tumor, salpingo-oophorectomy is recommended even in premenopausal women. In addition, the impact of routine lymph node dissection has not proved to be beneficial on survival rates.

For this reason, the treatment of ESS is hysterectomy with salpingo-oophorectomy and lymph node dissection of enlarged nodes and cytoreduction. Radiotherapy, chemotherapy, and hormonal therapy are the treatment options after surgery [11, 14-18]. However, optimal treatment strategies for ESS need further evaluation and clinical trials.

This primary vaginal ESS case is the sixth one reported in the literature. The prior reports show different surgical and postoperative management of the cases from varying from local excision of tumors to hysterectomy with salpingo-oophorectomy and radiotherapy or chemotherapy [5-9].

Only two of the prior cases had received the neoplasm excision with full healthy margins. No hysterectomy and no further treatment was performed. One of the patients was

Table 1. — *Summary of all six ESS cases reported in chronological order.*

Author	Surgical therapy	Additional therapy	Follow up-Outcome
Berkowitz *et al.* (1978)	Exploratory laparotomy + partial vaginectomy (including the parametrial tissue) + (hysterectomy + left salpingo-oophorectomy in history)	Pelvic irradiation	>18 months free of tumor
Kondhi-Paphtis *et al.* (1998)	Local tumor excision	None	38 months free of tumor
Chang *et al.* (2000)	Local tumor excision + hysterectomy + bilateral salphingo-oophorectomy + lymph node dissection	Vaginal irradiation	18 months free of tumor
Corpa *et al.* (2004)	Local tumor excision	None	36 months free of tumor
Liu *et al.* (2013)	Hysterectomy + unilateral salpingo-oophorectomy + partial vaginectomy.	Chemotherapy	18 months free of tumor
Sanverdi *et al.* (2015)	Hysterectomy + BSO + partial vaginectomy	None	22 months free of tumor

free of tumor three years after the surgery and the other patient was free of tumor 38 months after diagnosis. Another case who had a previous history of hysterectomy and left salpingo-oophorectomy for endometriosis was reported by Berkowitz *et al.* [5]. They performed an exploratory laparotomy and partial vaginectomy including the parametrial tissue. There was no intra-abdominal metastasis. Postoperatively, the patient received external irradiation to whole pelvis and internal irradiation to the vaginal cuff. The other case was reported by Chang *et al.*, and they first performed the tumor excision, then hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection [7]. In addition she received whole vaginal irradiation therapy. After one and a half years of follow up there was no tumor recurrence. Liu *et al.* reported the fifth vaginal ESS. They performed hysterectomy with unilateral salpingo-oophorectomy including partial vaginectomy. In addition the patient received six courses of platinum-containing combination chemotherapy (PAC regimen) as an adjuvant therapy after surgery. The follow ups showed that there was no recurrence or metastasis after 18 months of follow-up. The present is the sixth case of primary vaginal ESS. Similar to the case of Liu *et al.*, the present patient underwent TAH-BSO and partial vaginectomy. The patient was safe and free of tumor after 22 months and showed no tumor recurrence after surgery without additional chemo- or radiotherapy.

ESSs are indolent tumors with favorable prognosis and five-year survival rate is 98% for Stage I tumors. However, late recurrences may occur even in early stage tumors. The outcome of ESSs depends on the stage of the tumor at the presentation. For this reason, long-term follow-up is mandatory. In addition, there is not enough data regarding the long-term survival rates and optimal treatment modalities in extrauterine ESSs. In summary, two of the prior ESS cases published the patients underwent only local neoplasm excision [6, 8], in four other reports including the present, hysterectomy with uni- or bilateral salpingo-oophorectomy was performed, two of these patients received pelvic irradiation [5, 7] and one of them received chemotherapy in addition [9]. Follow ups showed that all patients were disease free for at least 18 months (Table 1).

In conclusion, primary vaginal ESS is a quite rare tumor and pathological diagnosis needs to be confirmed with immunohistochemical markers. In the present case, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial vaginectomy was the choice of treatment with no other additional therapies. The outcome of the disease is satisfactory as the patient is safe and free of tumor, 22 months after surgery. Although surgery is the treatment of choice with ESS cases, more reports are needed to finally conclude whether hysterectomy with/without oophorectomy or partial/full excision would be the most convenient choice. The present authors' experience with the current case and the data collected and summarised from prior cases suggest the questionability of adjuvant radiotherapy in ESS treatment, as most cases had no recurrence of the tumor for a significant period without any adjuvant therapy following the surgery. Further data from cases like this one will make it easier to have final judgement on the absolute role of adjuvant radiotherapy or chemotherapy on survival rates and forming future treatment strategies.

Acknowledgements

The authors thank to Assoc. Prof. Tetikkurt for her collaboration.

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