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Case Report

# Advanced-stage Endometrial Stromal Sarcoma Presenting as Primary Infertility in a Young Nulligravida: A Case Report

## *Genç Bir Nulligravida'da Primer İnfertilite Olarak Ortaya Çıkan İleri Evre Endometriyal Stromal Sarkom: Bir Olgu Sunumu*

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**ABSTRACT**

Endometrial stromal sarcoma (ESS) rarely causes infertility in young women. We report a nulligravida in her 30s who presented with primary infertility of 15 years. Hysteroscopy revealed a submucosal necrotic fibroid polyp. Ultrasonography detected multiple intramural fibroids. Open myomectomy with polypectomy was performed. Histopathology revealed low-grade ESS (LGESS) within the fibroid polyp. Subsequently, the patient underwent completion surgery. Her final diagnosis was estrogen-receptor positive LGESS stage IIIB, and she was suggested anastrozole adjuvant therapy and long-term surveillance. ESS with abnormal perimenopausal bleeding, though the most common presentation, may not always observed. Hence, a high index of suspicion of ESS should always be kept as a differential diagnosis in uterine fibroid polyp, though rare. Considering the scarcity of more extensive studies on ESS, reporting of cases will aid in formulating management protocols.

**Keywords:** Uterine sarcoma, endometrial stromal sarcoma, low-grade endometrial stromal sarcoma, bilateral salpingo-oophorectomy, adjuvant radiation hormonal therapy

**ÖZ**

Endometriyal stromal sarkom (ESS) genç kadınlarda nadiren infertiliteye neden olmaktadır. Çalışmamızda 15 yıllık primer infertilite ile başvuran 30'lu yaşlarında bir nulligravida sunmaktayız. Histeroskopisinde submukozal nekrotik fibroid polip saptandı. Ultrasonografi birden fazla intramural fibroid olduğunu ortaya koydu. Polipektomi ile açık myomektomi yapıldı. Histopatoloji, fibroid polip içinde düşük dereceli ESS (LGESS) ortaya çıkardı. Ardından hastaya tamamlayıcı cerrahi uygulandı. Nihai tanısı östrojen reseptörü pozitif LGESS evre IIIB idi ve hastaya anastrozol adjuvan tedavisi ve uzun süreli gözetim önerildi. Anormal perimenopozal kanamalı ESS, en yaygın semptom olmasına rağmen her zaman gözlenmeyebilir. Bu nedenle, nadir de olsa uterin fibroid polipinde ESS şüphesi yüksek bir ayırıcı tanı olarak daima akılda tutulmalıdır. ESS ile ilgili daha kapsamlı çalışmaların azlığı göz önüne alındığında, olguların raporlanması yönetim protokollerinin formüle edilmesine yardımcı olacaktır.

**Anahtar kelimeler:** Uterin sarkom, endometriyal stromal sarkom, düşük dereceli endometriyal stromal sarkom, bilateral salpingo-ooferektomi, adjuvan radyasyon hormonal tedavisi

## INTRODUCTION

Uterine sarcomas represent only 8% of primary uterine malignancies in the most recent analysis of the Surveillance, Epidemiology, and End Results database, and endometrial stromal sarcoma (ESS) contributes to 33% of all sarcomas[1]. It primarily occurs in perimenopausal women aged 45-50 years, with one-third of cases occurring in post-menopausal women. Our current understanding of ESS depends on individual case reports and a few retrospective case series. Considering the variety of ways that ESS can present and the lack of consensus on the management protocol, every case report adds to our understanding of this rare entity and various management modalities. We feel obligated to report this case because of the younger age at presentation, uncommon presenting complaint of primary infertility, and advanced-stage low-grade ESS (LGESS) at diagnosis. Through this case report, we strive

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to emphasize the need for a high index of suspicion for diagnosing the uncommon presentations of ESS and detailed histopathology of all surgical specimens for diagnosis and timely management. The patient provided informed consent for the report of this case.

## CASE REPORT

A 30-year-old nulligravida presented to our institution with complaints of heavy menstrual bleeding and irregular menstrual cycle for the last three years, dysmenorrhea for one year, and primary subfertility of 15 years. On general examination, she was pale. Abdominal examination revealed a firm, nontender, mass of 18 weeks gestation, with side to side mobility. On bimanual palpation, the mass was firm and nontender with a smooth surface and regular margins. It was mobile from side to side, and the cervix moved with the mass. Her past and family histories were not remarkable.

Her blood parameters were normal, except for hemoglobin of 8 gm/dL. Her endocrine parameters for subfertility workup and her husband's seminal analysis were within normal limits. Transabdominal and transvaginal ultrasonography detected multiple intramural fibroids in the fundus and anterior myometrium, with the largest measuring 7.8×7.75 cm, and another hypoechoic lesion of 3.2×1.2 cm distending the endometrial cavity, which was likely to be a submucosal fibroid polyp. Diagnostic hysteroscopy revealed a submucosal fibroid polyp measuring 2×2 cm that arose from the fundus near the left cornual region, obscuring the left ostium, and the surface of the polyp showed necrotic slough (Figure 1). Based on ultrasonography and hysteroscopic findings, the provisional diagnosis was abnormal uterine bleeding (AUB) caused by multiple uterine fibroids with a submucosal fibroid polyp. After correction of anemia by preoperative packed cell transfusion, she underwent open myomectomy of all three fibroids; through the same uterine incision, the uterine cavity was entered and the submucosal fibroid polyp measuring 2×2 cm was removed and sent for histopathological examination. The patient had an uneventful postoperative recovery and was discharged on postoperative day 4 with the advice to review with histopathology report.

Histopathological examination of the submucosal fibroid polyp revealed multiple tumor nodules, partly circumscribed and focally infiltrative, dispersed within the endometrium with infiltration around the endometrial glands. Individual tumor cells were monomorphic, simulating the endometrial stromal cells with hyperchromatic nuclei, inconspicuous nucleoli, and scanty cytoplasm. The nodules were composed of predominantly hyalinized stroma with some cellularity and some areas of serpiginous sexcord stromal-like pattern (Figure 2). There were 1-2 mitoses/10 high-power

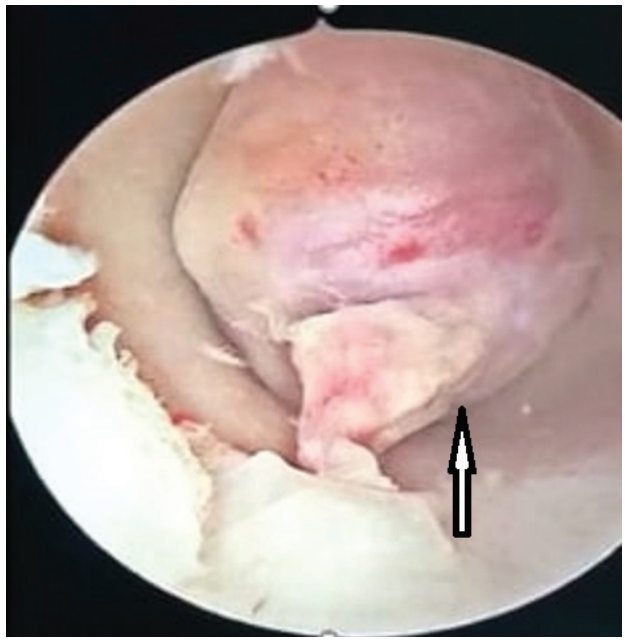

**Figure 1.** Hysteroscopy image of the uterine cavity with a submucosal fibroid polyp marked by white arrow.

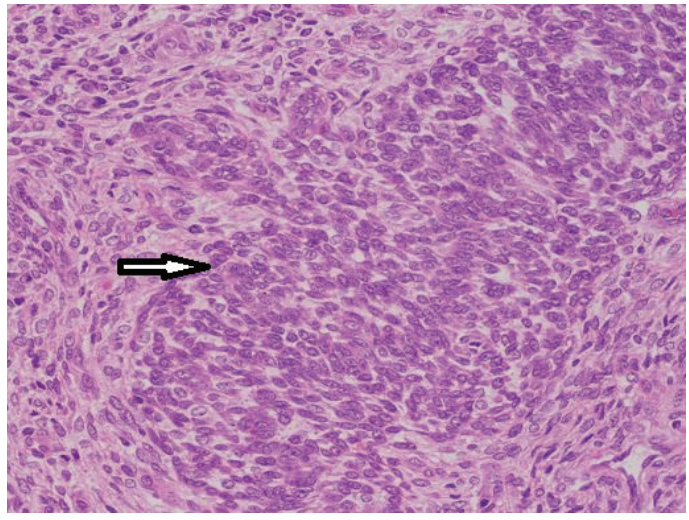

**Figure 2.** Hematoxylin and eosin staining ×40. The stained section of the submucosal fibroid polyp revealed multiple tumor nodules, simulating endometrial stromal cells with atypical changes, few mitoses (1-2 mitoses per10 high-power fields) marked by white arrow. Nodules were composed of predominantly hyalinized stroma with some cellularity. Some areas of serpiginous sexcord stromal-like pattern invaded into the myometrium.

fields. Immunohistochemistry revealed diffuse and strong positivity for smooth muscle actin (cytoplasmic) and CD10 (membranocytoplasmic), patchy and variable intensity positivity for desmin, and diffuse strong nuclear positivity for estrogen receptor (ER) and progesterone receptor (PR). Androgen receptor showed patchy and strong nuclear positivity (Figure 3a-c). C-kit was negative. The overall features were suggestive of LGESS with smooth muscle differentiation in the submucosal polyp, and other specimens had the classical histopathology of benign leiomyomata.

Before surgery, metastatic workup and surgical oncology consultation were obtained. The preoperative contrast-enhanced computed tomography (CT) of the abdominopelvic region showed neither evidence of spread to adjacent organs nor any lymph node enlargement. Thus, she was planned for total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO).

As final operative findings, the omentum and large bowel were adherent to the previous myomectomy scar, which was released by sharp dissection, and a dissected portion of the omentum was sent for histopathological study. The microscopic analysis revealed multiple tumor deposits in the omental specimen, with the largest measuring 2 cm in diameter, and showed metastasis by the same uterine tumor. On the macroscopic view, the uterus measured 12×10×7 cm, with multiple small seedling fibroids, posterior intramural myoma, and polypoidal mass at the top of the endometrial cavity (Figure 4). Microscopic findings included spindle-shaped tumor cells with scanty eosinophilic cytoplasm, elongated nuclei, vesicular chromatin, and inconspicuous nucleoli arranged in diffuse sheets and intersecting fascicles with an infiltrating pattern and tumor cells arranged in whorls around small vessels. Thus, the diagnosis of LGESS was confirmed. With these findings, the final diagnosis of LGESS stage IIIB was made, and the patient had an uneventful postoperative clinical course.

With the final diagnosis of LGESS stage IIIB, and considering the ER and PR status, the patient was planned for adjuvant therapy with aromatase inhibitor (anastrozole 1 mg per day) and close follow-up with clinical examination and CT surveillance. Surveillance was scheduled at once every three months for the first year, followed by once every six months for the next four years. Then, the annual follow-up for a lifetime was planned.

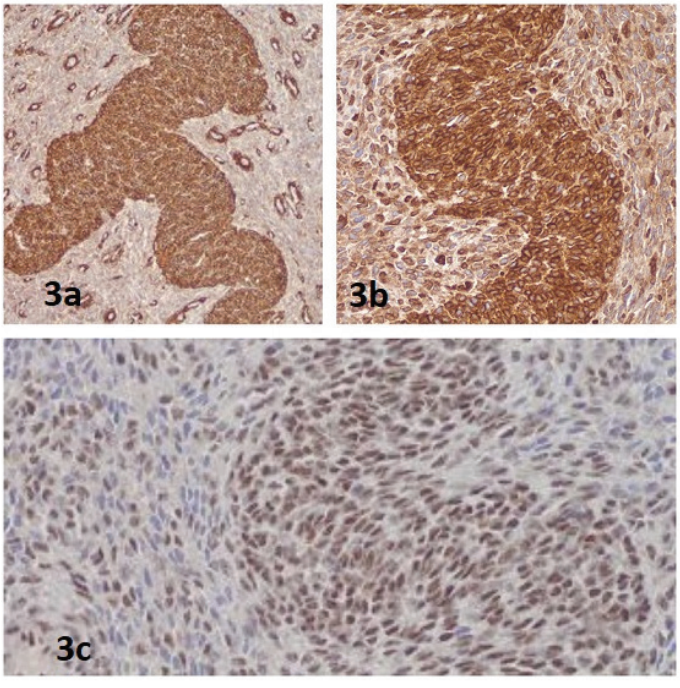


**Figure 3. (3a).** Immunohistochemistry revealed diffuse and strong positivity for smooth muscle actin (cytoplasmic), **(3b)** strong positivity of CD10 in tumor cells (membranocytoplasmic), **(3c)** diffuse strong nuclear positivity for estrogen receptor and progesterone receptor and patchy strong positivity for androgen receptor.

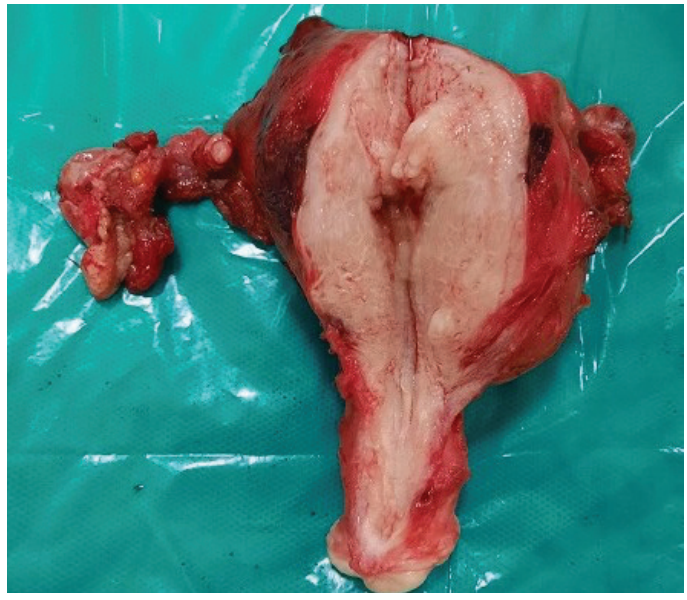

**Figure 4.** Cut section of the uterus showing irregular polypoidal growth arising from the endometrium near the fundus. The myometrium was thickened, with multiple seeding of intramural fibroids. Bilateral ovaries and fallopian tubes are normal.

## DISCUSSION

Uterine sarcomas are uncommon tumors of mesenchymal elements that arise from either uterine muscles or endometrial stroma. Depending on the presence and nature of the epithelial component, malignancies of endometrial stromal origin are classified into carcinosarcoma, adenosarcoma, and ESS.

ESS results from malignant transformation of endometrial mesenchymal tissues with no epithelial component. The World Health Organization has classified endometrial stromal tumors based on histopathological features, molecular genetics, and prognostic differences into endometrial stromal nodule, LGESS, and high-grade ESS, and undifferentiated ESS[2]. LGESS is characterized by the invasion of the myometrium and vascular channels and little or no cellular atypia. Usually, they have <10 mitotic figures per 10 high-power fields.

The pathophysiology of ESS is not clearly established. The unopposed estrogen exposure, as in polycystic ovarian syndrome, is a contributing factor among young subfertile women[3]. This could be a plausible factor in our case. ESS may present with AUB, asymptomatic rapid uterine enlargement, or pelvic pain. They have a protracted clinical course. In 40% of cases, ESS extends beyond the uterus at the time of diagnosis. In the presented case, the disease was diagnosed as stage IIIB at presentation with omental metastasis, which is a rare occurrence[4].

The diagnosis of ESS remains challenging as the symptoms are nonspecific, and endometrial biopsy fails to identify the lesion in many cases. No specific radiological identifying features are established. A characteristic nodule-in-nodule appearance on magnetic resonance imaging (MRI) has been described in an isolated case report[5]. However, the sensitivity and specificity of MRI in the diagnosis of ESS are yet to be established. Thus, the usual preoperative diagnosis is leiomyoma, and ESS is predominantly a histopathological diagnosis.

LGESS confined to the uterus can be adequately managed with TAH and BSO with good long-term survival. LGESS has a 5-year survival rate of >90%, with late recurrence in 40-50% of cases, 20 years after the initial therapy. In the present case, BSO was performed given the increased risk of recurrence in the preserved ovaries and to eliminate the possible risk of stimulation by ovarian estrogens[6].

Leath et al.[7] observed in a large multi-institutional series of 72 ESS cases that cytoreductive surgery had no effects on survival in patients with LGESS. Thus, complete omentectomy was not performed on our patient to reduce the postoperative morbidities of prolonged surgery and allow for early initiation of adjuvant treatment.

Case reports and case series presented results of hormonal therapy using letrozole, leuprolide acetate, medroxyprogesterone acetate, and megesterol, showing favorable outcomes depending on the concentration and relative expression of sex steroid receptors[3,7-10]. No single standardized adjuvant therapy protocol has been established. As per the National Comprehensive Cancer Network (NCCN) guidelines of 2016, adjuvant hormonal therapy is "appropriate" for LGESS. It is used in the adjuvant setting to prevent recurrence or control recurrent or metastatic sarcomas. These hormonal therapies reduce the levels or activities of endogenous estrogen and provide a noncytotoxic alternative systemic therapy for treating hormone-sensitive uterine sarcomas. The NCCN also recommends postoperative hormone therapy for LGESS stages I-IV[11]. Multiple single-institution retrospective analyses have supported the efficacy of aromatase inhibitors, progestins, or gonadotropin-releasing hormone analog in the treatment of LGESS, and few available data suggested a 67% overall response rate of ESS to aromatase inhibitors[11-13]. According to the guidelines of the European Society for Medical Oncology European Reference Network for Rare Adult Solid Cancers, adjuvant hormonal therapy is deemed an appropriate alternative for higher-stage ER/PR-positive LGESS[14,15].

In advanced-stage diseases, brachytherapy with or without pelvic radiation may be considered to control local recurrences[9,15]. Chemotherapy with gemcitabine and docetaxel is used in recurrent, advanced high-grade ESS and undifferentiated ESS[16,17]. Taking into account the protracted clinical course and the propensity of late recurrence, close long-term surveillance is advocated[3].

A high index of suspicion is essential in diagnosing this rare form of sarcoma whose symptoms mimic benign conditions, and the nonavailability of definitive radiological modalities or tumor markers makes the diagnosis even more evasive. MRI may be performed in cases with recent sudden enlargement of fibroids. The surgical management of LGESS immediately after histopathological diagnosis goes a long way in improving survival. BSO is a more preferred option than fertility-sparing surgeries even in nulliparous young women. Individualized adjuvant therapy should be planned. Moreover, no consensus or standard guidelines are available for the optimum management of this relatively less known entity. Considering the scarcity of case reports and studies about ESS, every experience with ESS should

be reported for a better understanding of the disease presentation and management.

### Ethics

**Informed Consent:** The patient provided informed consent for the report of this case.

**Peer-review:** Externally and internally peer-reviewed.

### Author Contributions

Concept: A.P., J.B., Design: J.B., Data Collection and/or Processing: A.P., D.B., Analysis and/or Interpretation: S.M., S.S., Literature Search: A.P., Writing: A.P., J.B.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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