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CASE REPORT

Endometrial Stromal Sarcoma Mimicking Benign Uterine Lesions: A Case Series

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Abstract

Introduction: Endometrial stromal sarcoma (ESS) is a rare malignant mesenchymal tumor of the uterus that accounts for a small proportion of uterine sarcomas and uterine malignancies. Because its clinical and radiological features may overlap with those of benign uterine lesions, particularly leiomyomas, preoperative diagnosis can be challenging. Delayed or incorrect diagnosis may result in inappropriate initial management and the need for additional surgical treatment. **Case Presentation:** We report three cases of ESS that were initially considered to represent benign uterine conditions. The patients presented with clinical and imaging findings suggestive of benign lesions, and the diagnosis was established only after histopathological examination of surgical specimens. Comprehensive pathological assessment, including evaluation of myometrial and vascular invasion and correlation with clinical findings, was essential for establishing the final diagnosis. **Conclusion:** These cases highlight the diagnostic challenges associated with ESS, particularly when clinical and radiological findings mimic benign uterine tumors. A high index of suspicion and thorough histopathological evaluation are essential for accurate diagnosis and appropriate management. Awareness of the possibility of ESS in patients with atypical or recurrent uterine lesions may facilitate earlier diagnosis and reduce the risk of inadequate initial treatment.

Keywords: Endometrial stromal sarcoma, low-grade endometrial stromal sarcoma, uterine sarcoma, uterine leiomyoma

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Introduction

Endometrial stromal sarcoma (ESS) is a rare malignant mesenchymal neoplasm of the uterus, accounting for approximately 10% of uterine sarcomas and a small proportion of all uterine malignancies [1]. ESS most commonly affects women in the peri- and postmenopausal age groups and may present with nonspecific symptoms, including abnormal uterine bleeding, pelvic pain, or an enlarged uterus. Because these clinical manifestations overlap considerably with those of common benign uterine disorders, particularly leiomyomas, ESS may not be suspected before surgery.

The distinction between an endometrial stromal nodule (ESN) and ESS is particularly important because the two entities may show similar histological features but differ substantially in malignant potential and management. The presence of infiltrative myometrial and/or vascular invasion is a major criterion supporting the diagnosis of ESS [2]. However, sampling limitations may make preoperative or limited biopsy-based diagnosis difficult, particularly when the tumor predominantly involves the myometrium. Consequently, some cases are diagnosed only after hysterectomy or other surgical procedures performed for a presumed benign uterine lesion.

The classification of uterine sarcomas has evolved with advances in morphological, immunohistochemical, and molecular characterization. Current classification systems recognize low-grade endometrial stromal sarcoma (LGESS) and high-grade endometrial stromal sarcoma (HGESS) as distinct entities, while undifferentiated uterine sarcoma (UUS) is considered a separate, diagnosis-of-exclusion category [3]. Molecular alterations, including characteristic gene fusions in subsets of ESS, have further improved the ability to distinguish these tumors from morphologically similar uterine neoplasms.

Despite these advances, ESS remains diagnostically challenging because its clinical presentation and imaging characteristics may resemble those of benign uterine lesions. In addition, endometrial biopsy or curettage may fail to adequately sample tumors with predominantly

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intramyometrial growth. Recognition of suspicious clinical, radiological, and pathological features is therefore essential to facilitate timely diagnosis and appropriate treatment.

In this report, we present three cases of ESS that were initially suspected to represent benign uterine lesions. These cases illustrate the difficulties encountered in the diagnosis of ESS and emphasize the importance of comprehensive histopathological evaluation and appropriate clinicopathological correlation.

Case Presentation

Case 1

A 28-year-old multiparous woman (P2L2) presented to our outpatient department with blood-stained vaginal discharge. One and a half months earlier, she had undergone total abdominal hysterectomy (TAH) with right salpingo-oophorectomy at another institution for abnormal uterine bleeding attributed to multiple uterine fibroids.

On examination, she was thin-built, with a healed transverse abdominal surgical scar. There was no abdominal mass, organomegaly, or ascites. Speculum examination showed a healthy vaginal vault, and bimanual and rectal examinations were unremarkable.

Review of the previous medical records revealed a histopathological diagnosis of high-grade endometrial stromal sarcoma (ESS) with a corpus luteal cyst in the right ovary, reported as FIGO stage IB. The case was discussed at the multidisciplinary tumor board (MDT). Positron emission tomography–computed tomography (PET/CT) showed no evidence of residual or metastatic disease. Histopathological review of the hysterectomy specimen at our institution confirmed the diagnosis of high-grade ESS (Figure 1).

Following MDT recommendations, completion staging surgery was advised. After obtaining informed consent, the patient underwent left salpingo-oophorectomy and thorough exploration of the abdominal and pelvic cavities. No macroscopic abnormalities were identified. The postoperative course was uneventful. During follow-up, she reported vaginal dryness, which was managed with a water-based vaginal lubricant. She remains under regular clinical surveillance.

Case 2

A 41-year-old multiparous woman (P3L3) with a history of seizure disorder was referred to our institution following abdominal hysterectomy performed elsewhere for abnormal uterine bleeding associated with uterine fibroids. Histopathological examination of the hysterectomy specimen revealed low-grade endometrial stromal sarcoma (LGESS).

The operative report did not document assessment of the ovaries; however, the uterus was described as corresponding to approximately 14 weeks of gestation. Histopathological review at our institution confirmed the diagnosis of LGESS.

The case was subsequently discussed at the MDT, which recommended completion staging surgery. The patient underwent bilateral salpingo-oophorectomy with comprehensive exploration of the abdominal and pelvic cavities. No macroscopic abnormalities were identified. The postoperative course was uneventful. Histopathological examination of the resected specimens showed normal bilateral ovaries and fallopian tubes.

Case 3

A 29-year-old multiparous woman (P2L2A1) presented with abnormal uterine bleeding that had initially been attributed to adenomyosis and an endometrial polyp. On examination, she had mild pallor. Abdominal examination revealed an enlarged uterus corresponding to approximately 18 weeks of gestation. Bimanual examination demonstrated a firm cervix and an enlarged, firm uterus measuring approximately 18–20 weeks in size, with free bilateral fornices.

The patient underwent abdominal hysterectomy with bilateral salpingectomy. Intraoperatively, the uterus was enlarged, both fallopian tubes were edematous, and both ovaries appeared grossly normal. The right ureter was adherent to a fibrotic area on the right side of the uterus. Following hysterectomy, the uterine specimen was sectioned and showed multiple fibroids within the uterine cavity. Intraoperative frozen-section examination suggested a leiomyomatous polyp (Figure 2). However, definitive histopathological examination revealed low-grade endometrial stromal sarcoma.

The case was reviewed at the MDT, and completion surgery with bilateral salpingo-oophorectomy was recommended. Histopathological examination of the resected ovaries and fallopian tubes showed no evidence of malignancy. The patient is currently under regular surveillance.

Discussion

Uterine sarcomas are rare and aggressive malignant tumors of mesenchymal origin and include leiomyosarcoma, endometrial stromal sarcoma (ESS), and other less common sarcoma subtypes. Although ESS accounts for a relatively small proportion of uterine malignancies, its diagnosis can be challenging because its clinical presentation frequently overlaps with that of

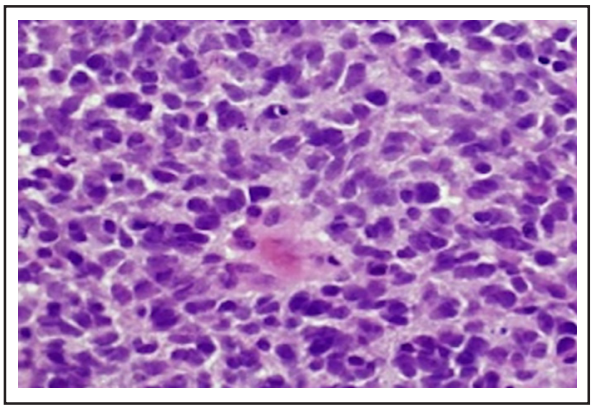


Figure 1. Histopathology of HGESS Showing Tumor Cells with Scanty Cytoplasm and Hyperchromatic Nuclei

Table 1. Key Differentiating Features of Low-Grade and High-Grade Endometrial Stromal Sarcoma

Feature	Low-grade endometrial stromal sarcoma (LGESS)	High-grade endometrial stromal sarcoma (HGESS)
Tumor cell morphology	Relatively uniform cells resembling proliferative-phase endometrial stromal cells	Marked cytologic atypia with round to spindle-shaped cells and more complex cellular morphology
Nuclear atypia	Mild or minimal	Moderate to marked
Mitotic activity	Usually low; a specific mitotic threshold is not required for diagnosis	Typically increased, although mitotic count alone is not diagnostic
Myometrial invasion	Characteristic infiltrative invasion with irregular tongue-like or worm-like projections	Frequently infiltrative and destructive
Lymphovascular invasion	May be present and can be extensive	May be prominent
Necrosis	Usually limited; extensive tumor necrosis is uncommon	Tumor necrosis may be prominent
CD10	Frequently positive	Variable; may be positive but is not specific
Estrogen receptor (ER)	Frequently positive	Usually negative or less consistently expressed
Progesterone receptor (PR)	Frequently positive	Usually negative or less consistently expressed
Cyclin D1	Usually negative or weak/focal	Often strongly and diffusely expressed in many cases
BCOR	Usually not diffusely overexpressed	May show strong nuclear BCOR expression in BCOR-altered tumors
Molecular alterations	Commonly associated with JAZF1-SUZ12 and related gene fusions	Commonly associated with *YWHAE-NUTM2* or BCOR alterations
Biological behavior	Generally indolent but capable of late recurrence and distant metastasis	More aggressive, with a greater risk of recurrence and metastatic disease
Hormonal sensitivity	Frequently hormone receptor-positive	Usually less hormone-responsive
Clinical implication	Requires long-term surveillance because recurrence may occur years after initial treatment	Requires management appropriate for a high-grade uterine sarcoma and careful assessment for metastatic disease

Abbreviations: BCOR, BCL6 corepressor; CD10, cluster of differentiation 10; ER, estrogen receptor; HGESS, high-grade endometrial stromal sarcoma; LGESS, low-grade endometrial stromal sarcoma; PR, progesterone receptor; *YWHAE-NUTM2, YWHAE-NUTM2* gene fusion; *JAZF1-SUZ12, JAZF1-SUZ12* gene fusion. Note: The diagnosis of LGESS or HGESS should not be based on a single immunohistochemical marker or a fixed mitotic-count threshold. Morphological findings should be integrated with immunohistochemical and, when indicated, molecular findings. Uterine sarcoma classification has evolved substantially with the incorporation of molecular characteristics.



Figure 2. Cut Open Specimen of High Grade Endometrial Stromal Sarcoma

common benign uterine disorders, particularly leiomyomas and adenomyosis. The three cases presented in this series illustrate this diagnostic difficulty, as all patients were initially managed for presumed benign uterine disease and the definitive diagnosis of ESS was established only after histopathological examination.

ESS most commonly occurs in peri- or postmenopausal women; however, the patients in our series were considerably younger, ranging from 28 to 41 years. This finding emphasizes that age alone should not exclude ESS from the differential diagnosis of an atypical uterine mass or abnormal uterine bleeding. The clinical presentation of ESS is generally nonspecific and may include abnormal uterine bleeding, pelvic pain, or uterine enlargement. These manifestations are also common in benign gynecological conditions, which can contribute to

diagnostic delay. In the present series, abnormal uterine bleeding was the principal presenting symptom and had initially been attributed to fibroids, adenomyosis, or an endometrial polyp.

The preoperative diagnosis of ESS remains particularly difficult. Imaging findings may overlap with those of leiomyomas and adenomyosis, and ultrasound may not reliably distinguish malignant stromal tumors from benign myometrial lesions. Moreover, endometrial biopsy or curettage may yield nondiagnostic tissue when the lesion has predominantly myometrial involvement. These limitations are clinically relevant because inadequate sampling may delay definitive diagnosis and allow patients to undergo surgery without appropriate oncologic planning. In our third case, for example, intraoperative frozen-section examination suggested a leiomyomatous polyp, whereas definitive histopathological examination subsequently established the diagnosis of LGESS. This case highlights the limitations of intraoperative sampling in tumors with heterogeneous morphology and the importance of thorough examination of the entire surgical specimen.

The distinction between ESS and other uterine mesenchymal tumors is primarily histopathological and increasingly supported by immunohistochemical and molecular findings. Gross examination may provide important clues. ESS can appear as a soft, tan-yellow or fleshy mass with an infiltrative interface with the surrounding myometrium, whereas conventional leiomyomas are typically well-circumscribed and firm with a characteristic whorled appearance. Microscopically, LGESS is characterized by cells resembling proliferative-phase endometrial stromal cells, often associated with infiltrative myometrial and/or lymphovascular invasion. In contrast, HGESS is characterized by more pronounced cytological atypia and aggressive biological behavior. Undifferentiated uterine sarcoma is a distinct entity characterized by marked pleomorphism and lack of specific differentiation.

Immunohistochemistry can be particularly useful when the morphological findings are equivocal. CD10 is commonly expressed in endometrial stromal tumors, while estrogen receptor (ER) and progesterone receptor (PR) expression is frequently observed in LGESS. Markers such as smooth muscle actin, desmin, and h-caldesmon may assist in differentiating stromal tumors from smooth-muscle neoplasms. However, no single immunohistochemical marker is sufficiently specific to establish the diagnosis in isolation. Immunohistochemical findings should therefore be interpreted in conjunction with morphology, clinical findings, and, when appropriate, molecular testing. The immunohistochemical profile of the tumors in our series, including positivity for CD10, ER, and PR in the tested cases, supported the histopathological diagnosis (Table 1).

The distinction between an endometrial stromal nodule and ESS is also clinically important. Unlike ESS, an endometrial stromal nodule is generally well circumscribed and lacks the infiltrative myometrial and vascular invasion characteristic of ESS. Careful assessment of the tumor–myometrium interface and lymphovascular spaces is therefore essential, particularly in hysterectomy specimens. Adequate gross examination, appropriate specimen sampling, and close clinicopathological correlation are critical when a uterine lesion initially considered benign shows atypical gross or microscopic features.

The management of ESS depends on histological subtype, tumor stage, hormone receptor status, and other clinicopathological and molecular characteristics. Surgery remains the primary treatment for localized disease. Total hysterectomy with appropriate assessment of the adnexa is generally considered the cornerstone of treatment. The role of bilateral salpingo-oophorectomy may differ according to menopausal status, histological subtype, hormone receptor expression, and individual clinical circumstances; therefore, it should not be presented as an obligatory procedure for every patient with ESS. In the present series, completion bilateral salpingo-oophorectomy was performed in Cases 2 and 3, while left salpingo-oophorectomy was performed in Case 1 as part of completion staging after previous surgery. No macroscopic or histopathological evidence of adnexal involvement was identified in these patients.

Similarly, systematic pelvic and para-aortic lymphadenectomy is not routinely required in all patients with ESS because lymphatic dissemination is relatively uncommon and the therapeutic benefit of routine lymphadenectomy remains uncertain. Surgical staging should therefore be individualized according to histological subtype, stage, imaging findings, and intraoperative assessment. Multidisciplinary discussion is particularly valuable in patients diagnosed unexpectedly after hysterectomy because the need for completion surgery, additional staging, adjuvant treatment, and surveillance must be considered on an individual basis.

The hormonal sensitivity of many ESSs, particularly LGESS, also has implications for postoperative management. ER and PR expression may provide a rationale for endocrine therapy in selected patients with advanced, recurrent, or residual hormone receptor-positive disease. Conversely, exogenous estrogen exposure should be approached cautiously in patients with hormone-sensitive ESS. The management of treatment-related genitourinary symptoms in young patients requires individualized consideration. In Case 1, vaginal dryness during follow-up was managed conservatively with a water-based lubricant. Importantly, management of menopausal or genitourinary symptoms should be individualized and coordinated with the treating oncology team, particularly when hormone-sensitive disease is present.

The three cases emphasize the consequences of an initial benign clinical impression. In Cases 1 and 2, ESS was diagnosed only after hysterectomy performed for presumed fibroids, whereas in Case 3, the definitive diagnosis was established after a frozen section suggested a benign leiomyomatous lesion. Although the patients underwent appropriate completion procedures after referral and multidisciplinary review, the need for

additional surgery illustrates the potential morbidity associated with an unexpected postoperative diagnosis. When ESS is suspected preoperatively, referral to a gynecologic oncology team and appropriate surgical planning may reduce the likelihood of incomplete initial management.

An important lesson from these cases is that a diagnosis of uterine fibroids should be reconsidered when clinical, imaging, or intraoperative findings are atypical. Rapid or disproportionate uterine enlargement, unusual tumor morphology, recurrent or persistent abnormal bleeding, intramyometrial or infiltrative growth, and discordance between imaging and operative findings should prompt careful evaluation. Nevertheless, these features are not specific for ESS, and benign uterine conditions remain considerably more common. Therefore, the objective should not be to label all atypical uterine lesions as malignant, but rather to maintain an appropriate level of clinical suspicion and ensure adequate pathological assessment when malignancy cannot be confidently excluded.

The principal limitation of this report is the small number of cases and its descriptive nature. As a three-case series, the findings cannot be generalized to all patients with ESS, and no conclusions regarding comparative treatment effectiveness or survival can be drawn. Nevertheless, the cases provide clinically relevant examples of diagnostic pitfalls that may be encountered when ESS mimics common benign uterine disorders. Further studies involving larger cohorts and long-term follow-up are required to better characterize the diagnostic, molecular, and therapeutic features of ESS, particularly in younger patients.

In conclusion, endometrial stromal sarcoma is a rare uterine malignancy that may closely mimic common benign gynecological conditions, resulting in unexpected postoperative diagnosis and, in some cases, the need for completion surgery. The three cases presented here demonstrate that ESS may occur in younger women and may be difficult to distinguish from leiomyoma, adenomyosis, or endometrial polyps on the basis of clinical and imaging findings alone. A high index of suspicion, careful gross examination, adequate tissue sampling, comprehensive histopathological evaluation, and appropriate immunohistochemical and molecular assessment are essential for accurate diagnosis. Multidisciplinary management is particularly important when ESS is diagnosed unexpectedly after surgery, allowing individualized decisions regarding completion surgery, adjuvant treatment, and surveillance. Earlier recognition and appropriate surgical planning may reduce the need for reoperation and improve the overall management of affected patients.

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Conflict of Interest

The authors declare no conflict of interest.

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