Radical tumor resection of a relapsed high-grade endometrial stromal sarcoma with an extremely rare mutation: a case report

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Background: Endometrial stromal sarcomas (ESS) are rare uterine mesenchymal tumors that histologically resemble endometrial stroma of functioning endometrium. The key characteristic of those tumors is the difficulty to diagnose preoperatively that leads to high rate of misdiagnosis. The aim of this case report is to present an extremely rare mutation of these already rare tumors and urge for more personalized therapies in the future.

Case Description: We present a case of a 62-year-old postmenopausal patient initially diagnosed with high-grade ESS (HG-ESS). In her routine follow-up, her computerized tomography (CT) and positron emission tomography-CT (PET-CT) scan showed a relapse in the vaginal vault and enlarged left iliac lymph nodes. The patient did not respond to chemotherapy and suffered from severe abdominal pain and her quality of life severely deteriorated. A cytoreduction laparotomic surgery was decided with complete resection (R0) of the tumor in the pelvis with no visible residual disease. Chemosensitivity and gene expression analysis report showed a high tumor mutation burden with 11 mutations/Mb and the detection of *COL1A1-PDGFβ* fusion. *COL1A1-PDGFβ* fusion is an extremely rare mutation observed in ESS with only a handful of cases in the literature and is suggestive of potential therapeutic benefit from imatinib administration. HG-ESS have frequent recurrences and intermediate prognosis.

Conclusions: Recurrent or advanced tumors should be treated aggressively with chemotherapy and radiation. Effort for complete resection and targeted therapy should be offered to the patients. Discovery of rare mutations might offer better personalized therapies in the future. Despite its radicality, cytoreductive surgery is a valid option in cases where life quality has severely deteriorated, offering a few qualitative months of life to the patient.

Keywords: Endometrial stromal sarcoma (ESS); high-grade ESS (HG-ESS); mesenchymal tumors; cytoreductive surgery; case report

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Introduction

Endometrial stromal sarcomas (ESS) are rare uterine mesenchymal tumors which histologically resemble endometrial stroma of functioning endometrium (1). Their annual incidence is estimated in approximately 3 cases per million women and has remained constant over the last few decades (2). Endometrial stromal tumors represent less than one percent of the uterine tumors (1).

Regarding classification, in the 2020 classification system, the World Health Organization (WHO) included ESS in the category "endometrial stromal and related tumors". ESS are classified as endometrial stromal nodule (ESN), low-grade ESS (LG-ESS), high-grade ESS (HG-ESS) and undifferentiated uterine sarcomas (USS) (3). The classification and terminology of these tumors has changed many times in the past. The histopathology of these neoplasms is based on the invasion to surrounding myometrium, their mitotic rate and nuclear atypia (1). However, heterogenous histological characteristics such as myxoid, rhabdoid, smooth-muscle etc., can make their classification even more challenging (4). HG-ESS is a more aggressive and undifferentiated stage of LG-ESS with a high-grade nuclear atypia, extensive myometrial invasion and higher mitotic activity with more than 10 mitoses per 10 high power fields (5).

The onset of ESS has been associated with distinct nonrandom chromosomal translocations and rearrangements. For instance, the most common translocation for LG-ESS involves chromosomes 7 and 17 (6). In HG-ESS, translocations of chromosomes 10 and 17 lead to gene fusions that are associated with the oncogenic transformation (7). HG-ESS have strong cyclin D1 and BCL6 corepressor (BCOR) positive expression (8).

Regarding their diagnosis and presentation, ESS tumors have mild symptoms with abnormal uterine bleeding being the most frequently observed. The sonographic findings are nonspecific with an enlarged uterus and a hypoechoic endometrial mass with or without myometrial involvement (9). Risk factors for developing ESS include long-term tamoxifen administration, pelvic radiation, hereditary and environmental factors (10-12). The key characteristic of those tumors is the difficulty in providing a preoperative diagnosis leading to a high rate of misdiagnosis. Even endometrial biopsies are not sufficient and until today there is no single examination to offer valid preoperative diagnosis (13). Definite diagnosis of ESS is frequently made postoperatively, often after hysterectomy or myomectomy performed for presumed benign conditions. Given the rarity of these tumors, a high index of suspicion is crucial, particularly in patients presenting with abnormal uterine bleeding or a palpable pelvic mass, to ensure timely and appropriate management. Molecular and genomic profiling may also aid in distinguishing ESS from other uterine tumors, particularly in complex cases where histological features are ambiguous (14). This work has been reported in line with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-177/rc).

Highlight box

Key findings

- We present a case of a 62-year-old patient diagnosed with a high-grade endometrial stromal sarcoma (HG-ESS) and a very rare *COL1A1-PDGFβ* fusion.

What is known and what is new?

- ESS are rare malignant mesenchymal tumors that represent less than 1% of uterine tumors with an incidence of 3 cases per million women. *COL1A1-PDGFβ* fusion is an extremely rare mutation in ESS tumors with only a handful of cases in the literature. *COL1A1-PDGFβ* fusion is suggestive of potential therapeutic benefit from imatinib administration.
- Despite its radicality, cytoreductive surgery is a valid option in cases where life quality has severely deteriorated, offering a few qualitative months of life.

What is the implication, and what should change now?

- Chemosensitivity and gene expression analyses should be considered for rare tumors since it may lead to personalized therapies with better survival rates.

Case presentation

We present a case of a 62-year-old postmenopausal patient initially diagnosed with HG-ESS 25 months ago as a random finding in a laparoscopic hysterectomy without bilateral salpingo-oophorectomy (BSO) due to an enlarged uterus (uterine size 5 cm × 5 cm and mass size 8 cm × 7 cm). After surgery, the patient underwent 6 cycles of taxol/gemcitabine. After treatment, her chest as well as upper and lower abdomen computerized tomography (CT) were free of disease. The same findings were also verified by a positron emission tomography (PET)-CT scan. After three months in the routine follow-up, a relapse in the vaginal vault and enlarged left iliac lymph nodes were detected. The patient accordingly received chemoradiation therapy with cisplatin (54 Gy in pelvis and 63 Gy in left iliac zone)

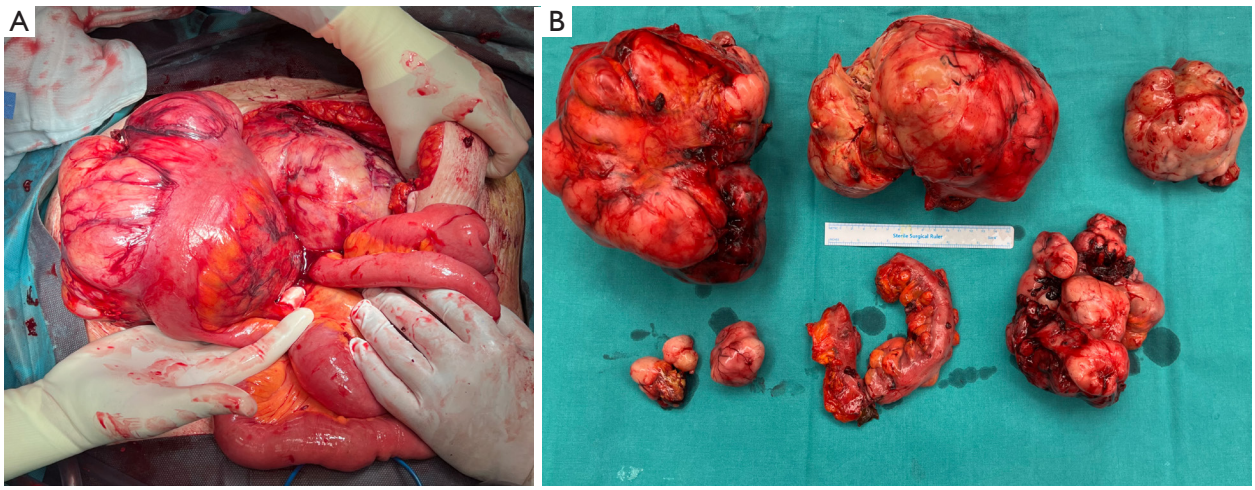

Figure 1 Intraoperative images of the laparotomic cytoreductive surgery. (A) Abdominal masses with small bowel, colon and mesenteric tissue involvement; (B) the excised abdominal masses.

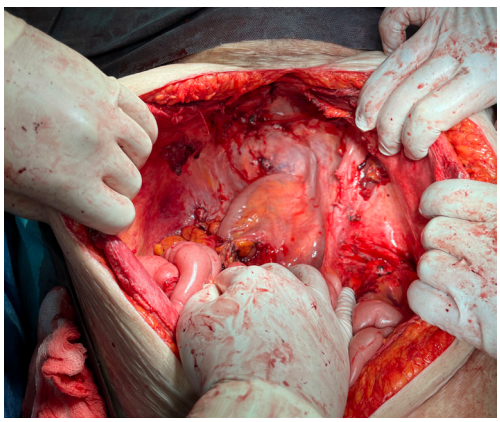

Figure 2 Complete and radical resection (R0) of the tumor in the pelvis with no visible residual disease.

and afterloading (14-Gy brachytherapy) weekly for two months. Her next follow-up showed a small regression of the pelvic tumor. Six months after the chemoradiation and 20 months from the initial surgery, the patient had multiple new abdominal globular lesions in the CT scan and received three cycles of epirubicin. The scan following the treatment revealed an exacerbation of the abdominal lesions. Hence, the patient received three cycles of trabectedin. Unfortunately, the patient did not respond to chemotherapy and the following scan showed a worsening of the abdominal lesions. At that point, the patient suffered from severe abdominal pain and her quality of life had severely deteriorated. The patient received a three-month course of dacarbazine and her next CT scan revealed a size increase of the abdominal masses. After careful consideration and extensive counseling with the patient, a cytoreduction laparotomic surgery was decided. *Figure 1A* illustrates the abdominal masses with small bowel, colon and mesenteric tissue involvement. *Figure 1B* illustrates the excised masses and *Figure 2* shows the complete resection (R0) of the tumor in the pelvis with no visible residual disease. Histological examination revealed tumor cells arranged in sheets and fascicles with oval to spindle shape and a variable amount of eosinophilic cytoplasm and vesicular nuclei. Few cells showed prominent nucleoli, moderate pleomorphism was seen and stroma was fibromyxoid. Mitotic activity increased with 12 mitoses per 10 high power field (HPF) (*Figure 3A*). Immunohistochemistry analysis was positive for CD10 and cyclin D1, mild positive for BCL6 and negative for estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), desmin, h-caldesmon, smooth muscle actin (SMA), C-Kit, programmed cell death ligand 1 (PD-L1) (antibody clone 28-8) and PD-L1 (antibody clone 22C3) (*Figure 3B-3F*). A tumor block and peripheral blood of the patient were sent for chemosensitivity and gene expression analysis (TherapySelect, Heidelberg, Germany) for the patient to receive a personalized therapy. The patient's chemosensitivity and gene expression analysis report showed a high tumor mutation burden (TMB-H) with 11 mutations/Mb and the detection of *COL1A1-PDGFβ* fusion. The tumor tissue was analyzed for fusion detection using semiconductor based next-generation

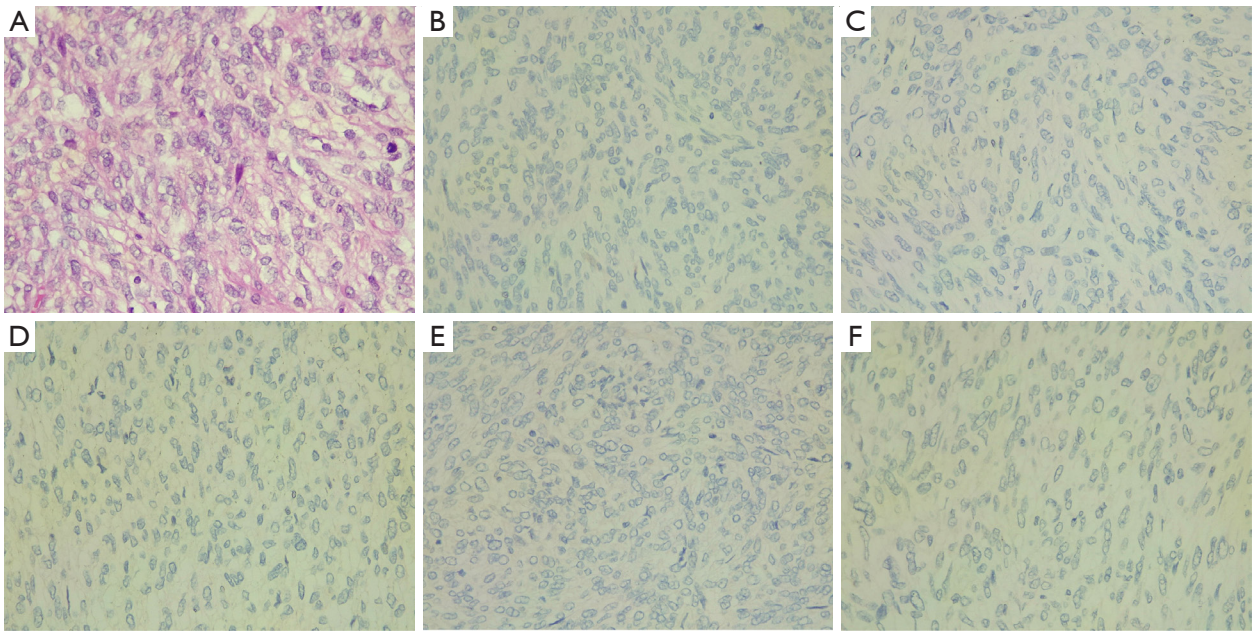

Figure 3 Histopathological and immunohistochemistry analysis of the excised tumor. (A) Light microscopic image of HE-stained section of FFPE block (40×). HE-stained sections from representative areas reveal tumor cells arranged in sheets and fascicles. Cells are oval- to spindle-shaped with variable amount of eosinophilic cytoplasm and vesicular nuclei. Few cells show prominent nucleoli. Moderate pleomorphism is seen. Mitotic activity is increased (10–15/10 HPF); (B) negative ER staining (100×); (C) negative PR staining (100×); (D) negative AR staining (100×); (E) negative PD-L1 (antibody clone 28-8) staining (100×); (F) negative PD-L1 (antibody clone 22C3) staining (100×). HE, hematoxylin & eosin; FFPE, formalin-fixed paraffin-embedded; HPF, high power field; ER, estrogen receptor; PR, progesterone receptor; AR, androgen receptor; PD-L1, programmed cell death ligand 1.

sequencing technology (NGS). High quality tumor tissue RNA extracted from the submitted specimen was subjected to target enrichment by multiplex polymerase chain reaction (PCR) amplification using a customized sarcoma fusion panel. Her postoperative care was unremarkable, and she was discharged in good condition. Despite the radicality of the surgery, the patient relapsed only three months after the surgery with multiple lesions in pelvis, liver and lungs.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

ESS are extremely rare malignant mesenchymal tumors that represent less than 1% of uterine tumors with an incidence of three cases per million women. In this case report, we present the management of a 62-year-old postmenopausal patient. The patient's diagnosis was based on a random finding after laparoscopic hysterectomy for a supposed benign etiology. Adjuvant chemotherapy was offered, and the patient relapsed in a very short period. After a few cycles of chemoradiation and chemotherapy with different drug specimens, a cytoreductive surgery was decided. The operation led to a complete resection of the tumors.

Following the operation, a chemosensitivity and gene expression analysis was performed. Interestingly, our patient's tumor had a *COL1A1-PDGFβ* fusion. Fusion of the collagen type I alpha 1 gene (*COL1A1*) at 17q22, with the platelet-derived growth factor beta gene (*PDGFβ*) at 22q13, forms the oncogenic chimeric fusion gene *COL1A1-PDGFβ*, and is a hallmark of dermatofibrosarcoma protuberans (DFSP) (15,16). It is an extremely rare mutation observed in ESS tumors with only a handful of cases in the literature. The first case with this mutation was published in 2019 (17). *COL1A1-PDGFβ* fusion is suggestive of potential therapeutic benefit

from imatinib with interval resolution of pulmonary nodules and significant decrease in peritoneal deposits (18). Apart from the *COL1A1-PDGFβ* fusion, our patient had a TMB-H assessment based on targeted genomic profiling of 511 genes. TMB, which is the total number of somatic coding mutations in a tumor, constitutes a promising predictive biomarker for immunotherapy response in cancer patients (19). Somatic mutations in tumor DNA can lead to mutation-derived neoantigens that are targeted by the immune system, especially after treatment with agents that activate T cells (20). Our patient's TMB was found at 11 mutations/Mb with a median TMB for ESS tumors to be reported at 1.7 mutations/Mb.

HG-ESS are rare and aggressive uterine malignancies that unlike their low-grade counterparts, HG-ESS lack the characteristic uniform oval or spindle-shaped neoplastic cells invading the myometrium. Instead, they are characterized by significant nuclear pleomorphism, high mitotic activity, and often tumor necrosis (21). These tumors often present with nonspecific symptoms, making early diagnosis challenging. Common symptoms include abnormal uterine bleeding, pelvic pain, and, in some cases, a palpable pelvic mass. Due to the aggressive nature of HGESS, patients may also experience symptoms related to metastatic spread, such as abdominal discomfort or bowel and bladder dysfunction. Diagnosis typically involves imaging studies, such as ultrasound and magnetic resonance imaging, to evaluate the extent of the tumor, followed by histopathological examination of biopsy samples. HG-ESS is characterized by high mitotic activity and cellular atypia, distinguishing it from LG-ESS. Immunohistochemical staining is often used to confirm the diagnosis, with markers such as CD10, cyclin D1, and BCOR aiding in differentiation.

Differential diagnosis includes other uterine malignancies such as leiomyosarcoma, USS, and LG-ESS. Accurate diagnosis is crucial, as the treatment approach varies significantly between these entities. Management of HG-ESS typically involves a combination of surgery, radiation, and chemotherapy. Total hysterectomy with BSO is the mainstay of surgical treatment, aiming to remove the primary tumor and any metastatic lesions (22). The role of lymphadenectomy remains controversial, as these tumors rarely metastasize to lymph nodes (21). Adjuvant therapy, including external beam radiation and systemic chemotherapy, may be recommended based on the stage and spread of the disease, but evidence is limited (22). Due to the high recurrence rate, regular follow-up with imaging and physical examinations is essential for early detection of recurrence. Novel therapies, such as targeted therapy and immunotherapy, are currently being explored to improve outcomes in this challenging malignancy. Despite aggressive treatment, the prognosis for HG-ESS remains poor, with 5-year survival rates ranging from 25–55% (22).

This case report presents a very rare case of a HG-ESS with *COL1A1-PDGFβ* fusion. This variant has strong therapeutic and prognostic significance and to our knowledge there are only a few cases in the literature where this fusion has been associated with a sarcoma. The fact that we conducted a thorough gene expression and fusion analysis utilizing semiconductor-based NGS technology is also a strength of this report. Case limitations include the absence of data regarding the initial operation and specimen. Furthermore, our sequenced data were analyzed using a customized pipeline which is limited to those variations and fusions included. This case highlights the importance of searching for mutations and fusions in rare tumors. Such findings can personalize the provided therapeutic approach and ultimately, increase the survival rates of patients. Future studies are required to identify the incidence of these mutations and further evaluate specific treatments to each mutation.

Conclusions

HG-ESS are rare tumors with intermediate prognosis. This case report presents a very rare *COL1A1-PDGFβ* fusion in a relapsed HG-ESS. There are very limited cases with this fusion in the literature and specific mutations are associated with different treatment options. Hence, this case highlights the importance of identifying them as early as possible and tailor the treatment options accordingly. Regarding surgical interventions, despite its radicality, cytoreductive surgery a valid option in cases where life quality has severely deteriorated, offering a few qualitative months of life to the patient.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-177/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-177/coif). D.B. is the General Director of the of the private Obstetrics, Gynecological and Surgical Clinic "Epicurus". The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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