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Highly Invasive and Metastatic High-grade Endometrial Stromal Sarcoma With *BCOR* Gene Alterations: A Case Report

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Abstract. *Background: The coexistence of a uterine leiomyosarcoma and a high-grade endometrial stromal sarcoma (HGESS) is extremely rare, especially when one of the components causes metastasis. Case Report: A 46-year-old female with aggravated abdominal pain for more than 4 months was diagnosed with uterine malignant mesenchymal tumor composed of predominantly a leiomyosarcoma (99%) and a minor component of HGESS with BCL6 corepressor (BCOR) gene alterations (1%), with ovarian and pelvic metastases. Results: The volume of HGESS with BCOR gene alterations accounted for less than 1% of the tumor mass but caused ovarian and pelvic metastases. Conclusion: HGESS with BCOR gene alterations is extremely aggressive. We suggest that when both components of HGESS with BCOR gene alterations and uterine leiomyosarcoma are present in one patient, the HGESS with BCOR gene alterations needs to be highlighted in the pathological report, even if it accounts for less than 1% of the tumor volume.*

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Uterine leiomyosarcoma and endometrial stromal tumors are both mesenchymal tumors originating from the primitive paramedian duct. Uterine leiomyosarcoma accounts for 1% of uterine malignant tumors. In the current World Health Organization classification, endometrial stromal tumors are divided into four categories: Endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS), and undifferentiated uterine sarcoma (1). ESS accounts for 0.2% of malignant uterine tumors (2). Concerning chromosomal aberrations, little is known about benign and malignant endometrial stromal tumors. The analysis of array-comparative genomic hybridization has shown that ESN does not exhibit many copy number changes (CNCs). Frequent losses were observed from chromosomes 7p and 19, and gains on chromosomes 1q, 6p and 8q. LGESS was demonstrated to be an extremely heterogeneous group. Most cases revealed aberrations including losses from chromosomes 7 and 22, and gains on chromosome 1q or 11. Undifferentiated endometrial sarcoma presented a high number of chromosomal aberrations (3). Essentially, CNCs were found on every chromosome. The most frequent alterations comprised losses on chromosomes 1q, 2q (3/4, 75%) and 13, and gains on chromosomes 1q and 17p. Thus, the number of CNCs from ESN to LGESS and to undifferentiated endometrial sarcoma was shown to increase. Interestingly, chromosomal alterations differed significantly between ESN, LGESS and undifferentiated endometrial sarcoma cases, and therefore a linear tumor progression was suggested to be unlikely (4). Few therapeutic options are established for the treatment of patients with ESS. The effects of suberanilohydroxamic acid (SAHA) in combination with LY294002, an inhibitor of phosphatidylinositol-4,5-*bis*phosphate 3-kinase (PI3K), rapamycin inhibition of mammalian target of rapamycin (mTOR) pathway, and their

combination on cell growth and the PI3K pathway in two separate ESS cell lines, namely ESS-1 and MES-SA as well as a non-neoplastic cell line HESC, revealed that SAHA reduced growth of three cell lines by inhibiting AKT serine/threonine kinase 1 (protein kinase B; AKT) and mTOR/p70S6K cascade activation. SAHA in combination with LY294002 or rapamycin, or both, synergistically reduced phospho-p70S6K and phospho-4E-binding protein-1 levels. The combination of all three also resulted in a strong growth inhibition and slowest growth recovery among the combination treatments. Thus, SAHA in combination with inhibition of PI3K and mTOR pathway might represent an efficient therapeutic option for women suffering from ESS (5).

The coexistence of leiomyosarcoma and HGESS in a patient is extremely rare, especially when the HGESS is much smaller than the leiomyosarcoma, but the HGESS causes metastases. Here we present such a case in which the volume of HGESS with *BCOR* gene alterations accounted for less than 1% of the tumor mass but caused ovarian and pelvic metastases, which highlights the fact that HGESS with *BCOR* gene alterations is extremely aggressive.

Case Report

The clinical sample used in the present study was obtained from a patient at the Affiliated Hospital of Southwest Medical University (Luzhou, Sichuan, China). The present study was approved by the Medical Ethics Committee of the Institutional Review Board of the Affiliated Hospital of Southwest Medical University (No. KY2019254).

A 46-year-old female who had a history of abdominal pain for more than 4 months, with aggravated pain for half a month, presented at the hospital in December 2019. Examination on admission revealed a palpable mass of approximately 20 cm in diameter on palpation of the abdomen. The mass was hard, with poor movement, a poor boundary, and no tenderness. Total abdominal enhanced computed tomography showed multiple solid intrapelvic masses with accessory blood supply (Figure 1). A 17×13×19 cm solid mass was under the serous membrane of the anterior uterine wall. There was no polyp or mass in the uterine cavity. The thickness of the endometrium was approximately 0.1 cm. The left ovary was enlarged, sized approximately 6×5×3 cm. There was a solid mass of approximately 2.8×2.4×2.2 cm in the left pelvic cavity (Figure 1). The patient underwent resection of the uterus, bilateral ovaries, fallopian tubes, and pelvic metastases under general anesthesia.

The pathological sections were stained with hematoxylin and eosin and observed under a microscope. Most tumor cells were fusiform and fascicular with abundant eosinophilic cytoplasm, moderate to severe nuclear atypia, coarse chromatin, and prominent nucleoli. Hemorrhage and necrosis (indicative of coagulative necrosis), as well as multinucleated giant cells and vascular infiltration, were obvious. There were approximately 11 mitotic figures per 10 high-power fields. Most tumor cells were diffusely positive for α-smooth muscle actin vimentin, desmin and Wilms tumor-1 and partly positive for H-caldesmon, estrogen receptor and progesterone receptor. The Ki-67 proliferation index was approximately 10% (Figure 2). In summary, the diagnosis of leiomyosarcoma was supported by morphology and immunohistochemistry. This component accounted for more than 99% of the volume of the mass.

However, after adequate sampling of the endometrial lining, we found that endometrial glands were absent, as was the normal structure of the entire uterine lining. In some areas of the uterus, some of the normal endometrium had been replaced by round or oval cells. Compared to leiomyosarcoma cells, these other tumor cells were larger and more heteromorphic, hyperchromatic, and pleomorphic, similar to tumor giant cells, and they had higher mitotic activity (50 mitotic figures per 10 high-power fields). Tumor cell necrosis and vascular invasion were visible. These tumor cells were so few that their total volume was less than 1% of leiomyosarcoma.

Tumor cells in these areas had grown diffusely around the thin-walled vasculature. The sections were diffusely positive for CD10 and vimentin and partly positive for cyclin D1. The Ki-67 proliferation index was approximately 40%. α-Smooth muscle actin, H-caldesmon, desmin, Wilms tumor-1, estrogen receptor and progesterone receptor were not expressed (Figure 2). The morphology and immunohistochemical results tended to indicate highly malignant ESS. HGESS can demonstrate multiple distinct molecular characteristics (6), two of which are the most common: tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon (*YWHAE*)–family with sequence similarity 22A/B (*FAM22*) gene fusion (7), and BCL6 corepressor (*BCOR)* gene alteration (8). Therefore, alterations in the *YWHAE* and *BCOR gen*es were investigated by fluorescence *in situ* hybridization [Gene Special Probe (GSP) *YWHAE* and GSP *BCOR*; Guangzhou LBP Medicine Science and Technology Co., Ltd., PR China], which identified the presence of *BCOR* gene alterations but not *YWHAE* gene alterations (Figure 3). Few than 1% of the tumor cells were diagnosed as HGESS with *BCOR* gene alterations, a newly described subtype of HGESS (9). More interestingly, the metastases on the left ovary and pelvis showed the same histological morphology and immunophenotype as the HGESS.

Chemotherapy and follow-up. According to the National Comprehensive Cancer Network Guidelines Version 1.2022 (10), the patient was treated with combination chemotherapy with docetaxel and gemcitabine for three courses after surgery. In each course, 75 mg/m^2 docetaxel on the first day and 1,000 mg/m^2 gemcitabine on the first and eighth days were administered intravenously. The duration of each

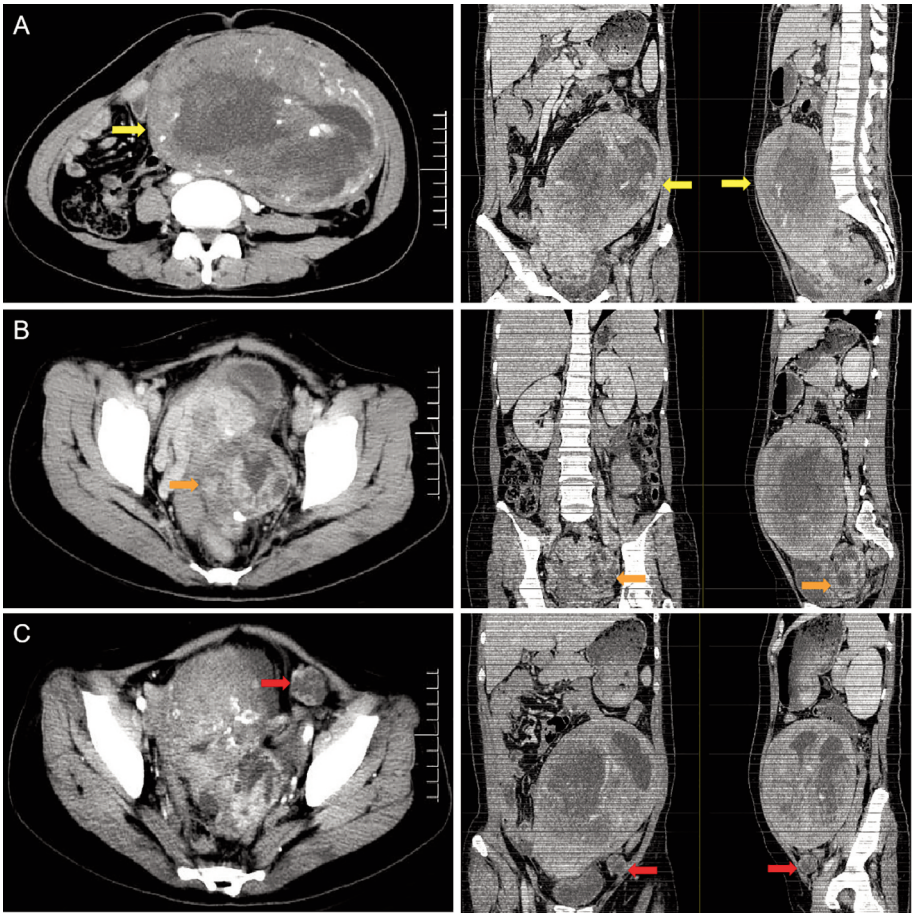

Figure 1. *Computed tomography (CT) findings in the axial (left) and coronal and sagittal planes (right). A: CT showed the solid mass in the enlarged uterus (yellow arrows). B: The enlarged cystic solid mass in the ovary was shown by CT (orange arrows). C: CT showing the mass in left pelvic cavity (red arrows).*

chemotherapy course was 21 days. No recurrence or metastasis was observed within 27 months after surgery.

Discussion

The presence of both leiomyosarcoma and ESS with ovarian and pelvic metastases in the same patient is extremely rare. Immunohistochemistry is a very useful adjunctive method to identify ESS and leiomyosarcoma, and also helped in the present case. As far as this case was concerned, although only one mass was visible, we were more inclined to assume there were two primary tumors. This decision was based on several reasons: Firstly, there were significant differences in the morphology and mitotic activity of the two kinds of tumor cells. Secondly, as the results of hematoxylin and eosin staining and immunohistochemistry proved, there was a clear dividing line between them. In addition, fluorescence *in situ* hybridization revealed that the genetic changes of the tumor components were different: *BCOR* gene alterations were only detected in the HGESS and neither *BCOR* gene alterations nor *YWHAE* gene alterations were detected in the leiomyosarcoma. Of course, ESS can be accompanied by smooth muscle differentiation.

Uterine tumors composed of a prominent component of smooth muscle and endometrial stroma have received little attention in the literature (11). It is accepted that such tumors should be diagnosed as *mixed endometrial stromal and smooth muscle tumor* if a minimum of 30% of the minor component is present in an otherwise typical stromal neoplasm or leiomyoma. In other words, mixed tumors are those in which each of the two components comprises at least 30% of the area of the whole tumor (9). Obviously, this case was not a mixed tumor. In addition, it was reported that mixed endometrial stromal and smooth muscle tumors are benign or low-grade (12), which is inconsistent in this case, because both kinds of tumor cells were malignant and poorly differentiated. Based on this knowledge, we considered that HGESS and leiomyosarcoma coexisted in this patient. The

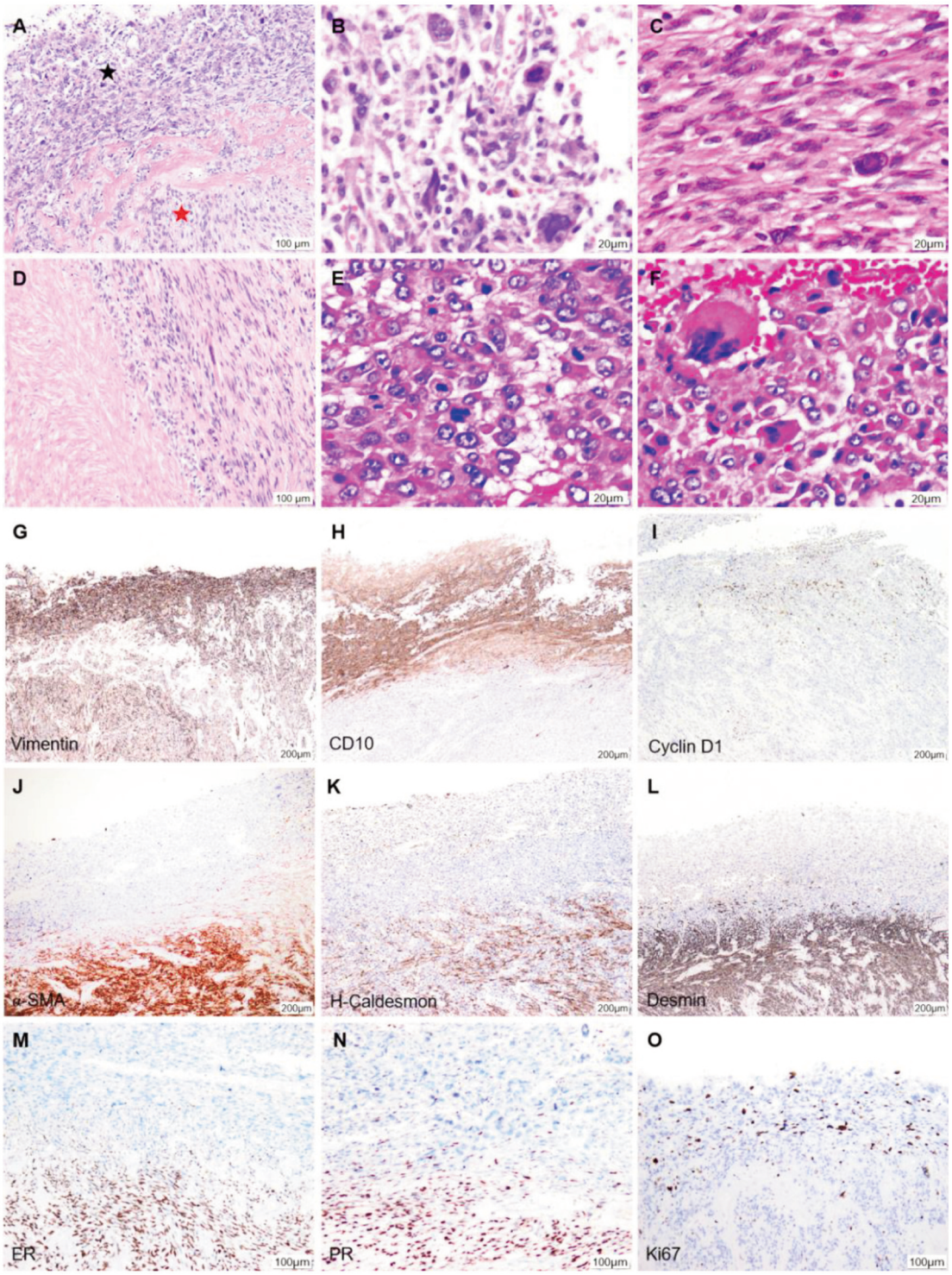

Figure 2. *Hematoxylin and eosin staining (A-F) and immunohistochemical analysis (G-O). A: The two types of cells can be seen to be separated by hyalinized collagen, with a clear dividing line: Endometrial stromal sarcoma with round-like tumor cells (black star) and leiomyosarcoma with spindled tumor cells (red star), ×40. B: Endometrial stromal sarcoma, ×400. C: Leiomyosarcoma, ×400. D: Coagulative necrosis in leiomyosarcoma, ×100. E: Ovarian metastasis, ×400. F: Pelvic metastasis, ×400. G: Vimentin was diffusely positive in both tumor cells, ×40. H-N: Partial immunophenotyping (CD10, cyclin D1, α-smooth muscle actin, H-caldesmon, desmin, estrogen receptor and progesterone receptor) of the two cell types showed almost opposite results. H-L: ×40, M-N: ×100. O: The Ki-67 proliferation index was about 10% for leiomyosarcoma and 40% for endometrial stromal sarcoma, ×100.*

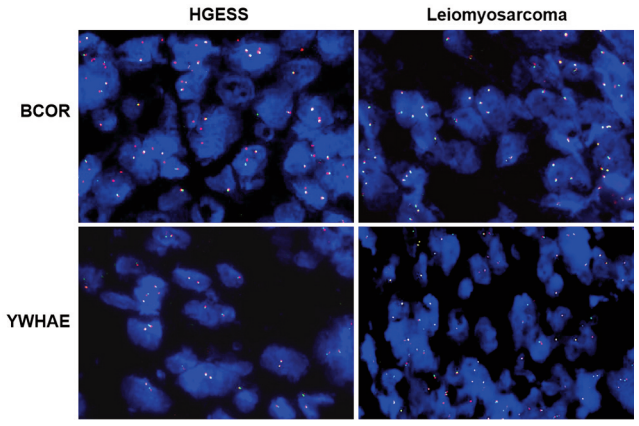

Figure 3. *Fluorescence in situ hybridization (red probe centromeric, green probe telomeric). High-grade endometrial stromal sarcoma (HGESS) cells were confirmed to have BCL6 corepressor (BCOR) rearrangements but not tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon (YWHAE) rearrangements. BCOR or YWHAE rearrangements were not detected in leiomyosarcoma cells.*

volume of the leiomyosarcoma was so large that the uterine structure was deformed, and the mass formed by the HGESS was compressed. As a result, only one mass was observed.

In the current classification of HGESS by the World Health Organization, the subtype of *YWHAE–FAM22* HGESS is described separately, but HGESS with *BCOR* alterations are only briefly mentioned. A recent study described a rare subtype of ESS with high-grade features and *BCOR* alterations, caused by either a gene fusion between *BCOR* and zinc finger CCCH-type containing 7B *(ZC3H7B),* or a mutually exclusive somatic internal tandem duplication of exon 15 of *BCOR* (13). Other types of morphologically HGESS lacking *YWHAE,* JAZF zinc finger 1 *(JAZF1),* PHD finger protein 1 (*PHF1*), and cyclin D1 (*CCND1*) rearrangements have also been described (9, 14). In the few cases reported in the literature to date, it has been proposed that HGESS with *BCOR* gene alterations is more aggressive than other types of HGESS (9). The present case has confirmed the existence of *BOCR* gene alterations in this tumor type.

Some questions about this case remain: According to the principle of superiority, HGESS with *BCOR* gene alterations which accounts for less than 1% of the volume of a tumor mass may easily be neglected in a pathological diagnosis. In our case, the HGESS with *BCOR* gene alterations metastasizing to the left ovary and pelvis would naturally seem to be the key factor determining the patient's clinical prognosis. Does this finding indicate that HGESS with *BCOR* gene alterations metastasizes earlier than leiomyosarcoma? Does the HGESS drive the disease prognosis when both tumors are coexistent? At present, limited case reports cannot answer these questions. More similar case reports are needed to enrich the existing sparse knowledge of these rare tumors.

Given the high aggressiveness of HGESS with *BCOR* gene alterations, we suggest that when both HGESS with *BCOR* gene alterations and other malignant tumors such as leiomyosarcoma coexist in a patient, the presence of the HGESS with *BCOR* gene alterations needs to be noted in the pathological report even if it accounts for less than 1% of the tumor mass.

Conflicts of Interest

None declared.

Authors' Contributions

Feng Ling and Si Bei Ruan performed immunohistochemical staining and molecular experiments. Huiling Chen was responsible for clinical data collection. Xiao Ming Xiong contributed to morphological observation. DongMei Zhao performed radiographic observation. Cui Wei Zhang and Johannes Haybaeck participated in and supervised the whole progression, wrote the article, and provided funding support. All Authors read and approved the final article.

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