CLINICAL VIGNETTE

A Rare Endometrial Stromal Sarcoma in the Absence of an Endometrial Primary

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A 37-year-old G0P0 and BRCA negative female presented with severe chronic pelvic pain. The pelvic pain worsened with her periods and during intercourse. She reported regular, intermittently heavy menses and was unable to get pregnant. She was referred to gynecology for further assessment. Pelvic ultrasound showed a bladder 1.2 cm cyst vs ureterocele and a 6.1 cm hypoechoic mass in the left adnexa. Follow up cystoscopy was unremarkable. CT of abdomen and pelvis revealed a uterine mass, most suggestive of a pedunculated fibroid. Subsequent pelvic MRI revealed a complex left ovarian mass along with increased signal intensity in the endometrium. The endometrial mass was thought to be endometrioma. However, MRI findings were suspicious with irregular signal in the endometrium with nodular enhancement, suggesting possible adenomyosis or fundal adenomyoma. Endometrial sampling revealed benign findings. Given the elusive diagnostic findings, she underwent laparoscopy, and exploratory laparotomy with sigmoid colectomy with side-to-side anastomosis, partial omentectomy and biopsy of the discovered peritoneal mass. Surgery was complicated by an anastomotic leak, requiring partial colectomy and creation of an end sigmoid colostomy. She was readmitted with sepsis and underwent CT-guided perisplenic abscess drainage. She had a prolonged recovery. Pathology revealed low grade endometrial stromal sarcoma (LG-ESS) arising in serosal endometriosis found in the peritoneum, omentum, and in the resected portion of the sigmoid colon. She underwent a repeat exploratory laparotomy, tumor debulking, lysis of adhesions, TAH, BSO, splenectomy, and reversal of colostomy, with creation of diverting loop ileostomy. The pathologic diagnosis was a rare endometrial stromal sarcoma arising from extrauterine and extraovarian sites, in the absence of a primary uterine lesion. Ovaries and the uterus were free of LG-ESS but uterus contained extensive endometriosis. The tumor characteristics were listed in Table 1.

Table 1: IMMUNOHISTOCHEMISTRY STAIN RESULTS

STAIN	*RESULTS*
Androgen receptor	Positive, nuclear
ER	Positive, nuclear
PR	Positive, nuclear
WT 1	Positive, nuclear
CD10	Focally positive, membranous
Caldesmon	Positive, membranous

The NGS panel revealed a low tumor mutational burden with 3.13 mutations/megabase. The tumor was microsatellite stable and was devoid of clinically significant mutations in AKT1, BRAF, NTRK. The PD-L1 Combined Positive score (CPS): <1.

A sarcoma targeted gene panel was performed by Mayo Clinic and identified *WWTR1-AFF2* rearrangement.

Given disseminated disease at presentation and the strongly positive estrogen and progesterone staining patterns, adjuvant aromatase inhibition therapy was started. At the time of preparation of this article, she remained in remission for more than 2 years with serial imaging monitoring.

Discussion

Malignant transformation endometriosis is uncommon, thought to occur in 0.7-1% of all cases.[1] Up to 37% of all cases of endometriosis may have involvement of an intestinal site, most notably the rectum and the sigmoid colon.[2] The most common malignancy arising from endometriosis is endometrial adenocarcinoma, and sarcomas are rare.[1,3] Kusaka M, et al reported one of the first cases of endometrial stromal sarcoma.[4] Endometrial stromal tumors are thought to represent 1% of all uterine neoplasms.[5] The 2014 World Health Organization (WHO) classification system recognizes[6] five categories of "endometrial stromal and related tumors".

- Endometrial stromal nodule (ESN)
- Low-grade endometrial stromal sarcoma (LG-ESS)
- High-grade endometrial stromal sarcoma (HG-ESS)
- Undifferentiated uterine sarcoma (UUS)
- Uterine tumor resembling ovarian sex cord tumor (UTROSCT)

The majority of LG-ESS are immunohistochemically positive for estrogen and progesterone receptors.[7] The most common translocations in LG-ESS involve the short arm of chromosome 7 and the long arm of chromosome 17 [t(7;17)]. This results in production of the JAZF1/JJAZ1 (or JAZF1/SUZ12) gene fusion protein. This fusion is characteristic of LG-ESS and present in up to 50% of the cases. Interestingly, this translocation has not been found in other uterine sarcomas or smooth-muscle neoplasms.[8,9] However, in our patient had a novel *WWTR1-AFF2* fusion. The clinical implications and the behavior of this translocation is poorly understood as there a paucity of data.[10]

An LG-ESS diagnosis in the absence of a primary uterine lesion is extremely rare. Only a few cases have been reported.[11,12] These cases had disease dissemination at diagnosis. The most common metastasis sites are the mesentery and omentum. Tumor dissemination does not necessarily imply a poor prognosis. Cytoreductive surgery seems to be the best therapy.[13] The merits of all adjuvant therapy remain controversial. Our patient was offered adjuvant endocrine therapy for her advanced stage LG-ESS. This follows the NCCN guidelines and currently available retrospective data.[14-17]

Conclusion

We report an unusual case of low grade endometrial stromal sarcoma (LG-ESS). Our patient is unusual for two reasons, 1) This LG-ESS appears to have risen from the extrauterine and extraovarian serosal endometriosis and 2) This LG-ESS was associated with novel *WWTR1-AFF2* fusion. The implications of the *WWTR1-AFF2* fusion are poorly understood. We hope future cases of LG-ESS with characterized *WWTR1-AFF2* fusion, could help delineate the pathogenesis, clinical behavior and therapy. Our patient is alive and remains in remission nearly 2 years after her diagnosis. She continues to be managed with adjuvant aromatase inhibitor therapy.[17]

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