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Primary colonic extrauterine endometrial stromal sarcoma: A case and review of the literature

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1. Background

Endometrial stromal sarcoma (ESS) is an uncommon uterine mesenchymal neoplasm, accounting for < 10% of uterine sarcomas and < 1% of all primary malignant tumors of the uterus. The 2014 WHO classification of tumors of the female reproductive organs subclassifies endometrial stromal tumors into 4 subtypes based on clinical and pathological features: benign endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS). ESN and LG-ESS are distinguished on the bases of myoinvasive growth pattern and lymphovascular invasion. ESN are well-circumscribed, which distinguishes them from LG-ESS. Tongue-like myoinvasion of at least 3 mm, in three separate areas, is the diagnostic criteria widely used to establish the diagnosis of LG-ESS. If vascular invasion is present, the diagnosis of LG-ESS is straightforward. The most common genetic alteration identified in ESN is t(7;17) (p15;g21), resulting in the fusion of the JAZFI-SUZ12 genes, which is also present in about 48% of LG-ESS (Conklin and Longacre, 2014).

The diagnosis of endometrial stromal tumors on hysterectomy specimen is not difficult, but requires extensive tissue sampling, immunohistochemical workup, or even molecular studies. However, a biopsy sample lacking endometrial glands may be interpreted as ESN or LG-ESS, as there are no histologic features or ancillary techniques that distinguish them.

Primary extrauterine endometrial stromal sarcomas can arise in the setting of endometriosis. While they are very rare, they have been reported in the ovary, bowel, abdomen, peritoneum, pelvis, and vagina. There are only a few reported cases of endometrial stromal sarcomas arising from the gastrointestinal tract, which are highlighted in Table 1. These tumors tend to be low-grade and indolent in nature, but since they often present at advanced stage, disease recurrence is common (Baiocchi et al., 1990; Yantiss et al., 2000; Bosincu et al., 2001; Mourra et al., 2001; Cho et al., 2002; Kovac et al., 2005; Chen et al., 2007;

Ayuso et al., 2013; Wang et al., 2015; Son et al., 2015). This paper will present a patient diagnosed with LG-ESS arising from endometriosis of the sigmoid colon and highlight how molecular technology can be used in the diagnosis of endometrial stromal sarcoma on a biopsy specimen.

2. Case study

The patient is a 37-year-old Caucasian female, G2P2-0-0-2, who presented with abdominal pain and bright red blood per rectum with no other symptoms or significant medical, surgical and gynecologic history. A colonoscopy showed a 4.0 × 2.6 cm mass in her sigmoid colon. As part of her evaluation, she had CT scan and MRI of the chest, abdomen, and pelvis. There were no abnormalities noted in the uterus and fallopian tubes. Both ovaries had simple cysts measuring up to 2.5 cm. An ill-defined lesion in the subcapsular region of the hepatic dome with possible extension through the diaphragm into the lung base was identified.

Based on the suspicion for colon carcinoma, a biopsy of the colonic mass was performed. Pathology showed endometrial stromal proliferation without endometrial glands, involving full thickness of the colonic mucosa (Fig. 1, image A-C). The differential diagnosis based on this biopsy included an under-sampled focus of endometriosis or LG-ESS. Due to inconclusive histologic results and imaging findings concerning for a neoplastic process, further workup was performed. A CT-guided biopsy of the liver lesion was attempted but was unsuccessful due to the location of the lesion. Endometrial biopsy showed proliferative endometrium with no evidence of a neoplasia. Given that up to 50% of LG-ESS show the characteristic t(7;17)(p15;g21) translocation, the laboratory performed the Archer® FusionPlex® Sarcoma panel on the biopsy specimen. This test identified the presence of JAZF1/SUZ12 fusion gene, which confirmed the diagnosis of LG-ESS.

The patient subsequently underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid colectomy with primary anastomosis, resection of right

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Table 1
Summary of all cases of ESS arising in the colon in the literature, clinical and pathological features.

	Author, Year	Age	History of Gyn Surgery/History of Endometriosis	Symptoms at Presentation	Involving Colon Site	Gross findings, colon	Presence of endometriosis	Dissemination	Surgical Management	Adjuvant Treatment	Follow up
1	Baiocchi 1990	38	TAH, BSO for endometriosis	Abdominal pain and pressure	Ascending and transverse colon, terminal ileum	A large multilocular mass involving the transverse, ascending colon, and the terminal ileum	Ovary and colon	Local (mesentery, pelvis, and falciform ligaments)	Partial ileal resection, resection of the transverse and ascending colon	Etoposide, bleomycin, and cisplatin × 3 cycles followed by progesterone agent	NED 16 months
2	Baiocchi 1990	50	TAH, RSO for endometriosis	Abdominal pain	Transverse colon, junction of the descending and sigmoid colon	A large grapelike tumor, with individual nodular areas 2 × 2.5 cm	Ovary	Omentum	LSO, radical omentectomy	Megace	NED
3	Yantiss 2000	63	None/No	Change in bowel habits	Rectum	2 cm polypoid mass	NA	NA	Partial colectomy	RT	Recurrent 3 years
4	Bosincu 2001	42	None/Yes	Fever and abdominal pain	Rectum	Large polypoid and ulcerated pelvic mass with transmural infiltration into the rectum	Adventitial rectal layer	Local (uterine serosa, parametria, peritoneal lymphatics)	TAH, BSO, omentectomy, colorectal resection	Adriamycin and cyclophosphomide × 4 cycles	NED 20 months
5	Mourra 2001	61	None/No	Epigastric pain	Rectosigmoid colon	A 2.7 cm polypoid mass with stenosis of the lumen involving all layers of the rectal wall	Posterior wall of right broad ligament	None	Resection of rectosigmoid Dilation & Curettage	None	NED 30 months
6	Cho 2002	48	TAH for uterine fibroids, and LSO for endometriosis	Tenesmus	Sigmoid colon	Multinodular masses of 1 to 3 cm involving the whole layer of the intestine and extending to the urinary bladder and ureter	Left ovary and sigmoid colon	Local (mesentery, bladder, ureter)	Resection of rectosigmoid and regional lymph node dissection	None	NED 4 months
7	Kovac 2005	46	TAH, RSO for uterine fibroids/Yes	Stenosing process	Rectosigmoid colon	6 cm mass	Rectosigmoid colon	Omentum and left ovary	Oophorectomy, omentectomy, and resection of colon	None	NED 11 months
8	Chen 2007	42	None/No	Rectal bleeding and tenesmus	Sigmoid colon	Multiple 1 to 3 cm nodular masses involving mucosa and pericolic fat	Sigmoid colon	Omentum and left adnexa	TAH, BSO, resection of rectosigmoid	None	NED 1 year
9	Ayuso 2013	80	TAH, BSO/Yes	Rectal bleeding and chronic rectal discharge	Sigmoid colon	5 cm mass involving mucosa, muscularis, and peritoneum	None	Pelvic side wall	Laparoscopic lower anterior colon resection	Megace	NED 4 years
10	Wang 2014	40	TAH for uterine fibroid and right ovarian cystectomy/No	Change in bowel habits and rectal bleeding	Rectum	Nodular masses 1 to 3 cm scattered in the intestinal walls and mesentery	Colon	Mesentery and extensive intra-abdominal metastases	Unresectable, palliative transverse colostomy to relive stenosis and intraoperative peritoneal chemotherapy	NA	DOD 18 months
11	Son 2015	52	None/No	Constipation and hematochezia	Sigmoid colon	Polypoid 3.8 × 2.5 transmural mass	None	Bilateral ovaries with endometrial stromal nodules	Laparoscopic low anterior resection, TLH, BSO	None	NED 4 months
12	Our case	37	None/No	Rectal bleeding	Sigmoid colon	6 cm multilobulated sigmoid mass	Right ovary and liver lesion	Peritoneum, omentum, diaphragm, vascular, and perineural invasion	TAH, BSO, rectosigmoid resection, omentectomy, resection of diaphragmatic mass, resection of liver lesion	Megace	POD at 3 months, switched to Letrozole, now NED 2 years

EESS, extrauterine endometroid stromal sarcoma; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; BSO, bilateral salpingo-oophorectomy; LSO, left salpingo-oophorectomy; RSO, right salpingo-oophorectomy; RT, radiotherapy; NED, no evidence of disease; DOD, death of disease; POD, progression of disease; NA, not available.
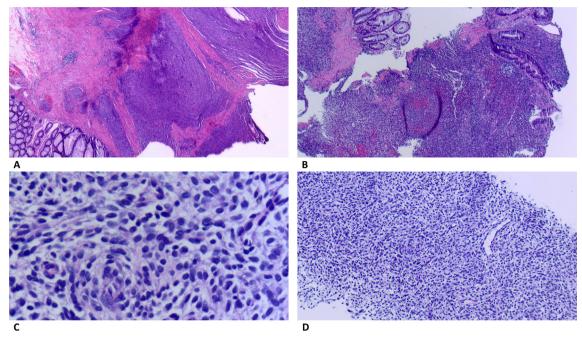
Fig. 1. (A) Low power view of the initial colon biopsy (H&E stain 100× magnification): proliferation of small blue cells in the colonic mucosa. (B) Repeat biopsy of the sigmoid mass (H&E stain, 200× magnification): proliferation of uniform small cells, that resemble stroma of proliferative phase endometrium. (C) Repeat biopsy of the sigmoid mass (H&E stain, 400× magnification): characteristic appearance of endometrial stromal tumors, small spindled to oval uniform tumor cells with somewhat whirling arrangement around spiral arterioles. (D) Colon resection specimen: sigmoid colon full thickness (H&E stain 100× magnification): involvement of the entire bowel wall by low grade endometrial stromal sarcoma.

diaphragmatic mass, segmental resection of the right lobe of the liver, and omentectomy. Intra-abdominal findings were more extensive than expected. The patient was found to have a 6 cm sigmoid colon mass, a 6 cm right diaphragm lesion, and multiple omental nodules. All gross disease was resected. Her postoperative course was unremarkable, and she was discharged home one week postoperatively.

Histologic examination of the specimens showed the characteristic features of LG-ESS, with extensive perineural and vascular invasion (Fig. 1, image D). The sigmoid colon lesion was 5.8 cm in its largest dimension, and there was transmural involvement by LG-ESS. Metastatic LG-ESS was evident in the omentum and diaphragm. Lymph nodes, uterus, and the adnexal structures were all negative. She had an endometriotic cyst in her ovary. The tumor was strongly positive for ER, PR, and CD 10.

Given her final diagnosis and that the tumor was strongly positive for estrogen and progesterone receptors, she was started on megestrol acetate as adjuvant therapy and counseled on continued surveillance for recurrence. The patient's disease progressed on Megace, with an increasing liver lesion noted on surveillance CT three months after surgery, and was switched to Letrozole, which she remains stable on with no evidence of disease on scans.

3. Discussion

LG-ESS arising from primary extrauterine sites is uncommon. There are 11 cases reported of LG-EESS arising in the colon and their findings are summarized in Table 1 (Baiocchi et al., 1990; Wang et al., 2015). Our patient's case is similar to the ones reported, with the exception that she presented with widespread metastatic disease at the time of diagnosis.

It is known that LG-ESS can occur in the setting of endometriosis. Our patient did not have a known clinical history of endometriosis, but it was histologically confirmed in the ovary. LG-ESS is rare but is the most common mesenchymal malignancy arising from endometriosis. Yantiss et al. (2000) reported the largest case series of primary malignancies arising from gastrointestinal endometriosis. They identified a

total of 14 cases, which included 8 cases of endometrioid adenocarcinomas, 4 cases of a Mullerian adenosarcoma, 1 case of a borderline endometrioid tumor, and 1 case of an LG-ESS arising in the colon, seen in Table 1.

The largest published series of LG-ESS cases is a report of 63 cases from MD Anderson Cancer Center by Massand et al. They report that LG-ESS is commonly associated with endometriosis, and that given its indolent nature, long-term follow up is recommended for late recurrences. Endometriosis was noted in 30 of the 63 cases, and close to 25% of cases had an initial pathologic diagnosis other than LG-ESS, including sex cord stromal tumor, gastrointestinal stromal tumor, and leiomyosarcoma. Only 50% of the tumors were initially diagnosed accurately. Of the 53 patients that were followed, 33 patients had recurrent disease, and 9 patients died from disease. There were no clinical or pathological characteristics predictive of poor outcome upon review of the patients who died (Masand et al., 1990).

The diagnosis of LG-ESS can be difficult with limited tissue sample for two reasons. First, the histologic features of malignancy in LG-ESS cannot be fully evaluated on a biopsy sample. Secondly, LG-ESS arising from extrauterine sites often mimics other more common primary mesenchymal tumors, which requires further studies. LG-ESS is diffusely and strongly positive for ER, PR, and CD 10 (Conklin and Longacre, 2014; Ladwig and Garg, 2016; Masand, 2018; McCluggage et al., 2001). A panel of immunohistochemical stains is recommended when differentiating stromal neoplasms from cellular leiomyomas or leiomyosarcoma (NCCN). Gastrointestinal stromal tumor (GIST) and ESS will stain for CD 10 and desmin, but h-caldesmon and SMMS-1 will be positive in GIST and negative in ESS (Masand, 2018). Gastrointestinal stromal tumor (GIST) and ESS have overlapping staining profile, as they both stain for CD10, desmin and smooth muscle actin (SMA), GIST is positive for c-kit (CD117) and DOG-1, while LG-ESS is negative.

It is imperative to correctly classify ESS based on the 2014 WHO Classification because of the implication this has for treatment options and prognosis. Endometrial stromal tumors are a genetically heterogenous group of tumors that harbor recurrent chromosomal translocations, producing specific gene arrangements. There are many gene

fusions reported for ESN and ESS including PHF1-JAZF1 t(6;7)(p21; p15), EPC1-PHF1 t(6;10;10)(p21;q22;p11.2) and JAZF1-SUZ12 t(7;17) (p15;q21). The JAZF1-SUZ12 translocation, discussed above, is the most common genetic abnormality occurring in 65% of ESNs and up to 48% of LG-ESSs (Conklin and Longacre, 2014). This translocation is specific for LG-ESS and is not present in other uterine mesenchymal neoplasms. Knowing this, we were able to identify the translocation diagnosing LG-ESS on our patient's limited tissue sample, and surgical treatment was planned.

Given the rarity of these tumors in extrauterine sites, evidence-based data is limited to help guide treatment decisions. Cytoreductive surgery is generally considered the treatment for ESS. ESS has a tendency to metastasize widely; despite this, most patients with ESS have prolonged disease-free intervals with late recurrences (Masand et al., 20130). The value of adjuvant therapy is controversial, with no prospective studies showing a survival advantage. LG-ESS tumors tend to be hormone receptor positive, and hormone therapy can be considered to lower the risk of recurrence. Per the NCCN guidelines for LG- ESS of the uterus, aromatase inhibitors are recommended and Megace is also an option (NCCN). Our patient was started on Megace because previous literature has shown success with this treatment in extrauterine cases (Baiocchi et al., 1990; Ayuso et al., 2013). When she progressed, she was switched to Letrozole with no evidence for now two years after surgery. This highlights the importance of this treatment, as no other extra uterine cases reported have used aromatase inhibitors. HG-ESS, which are negative for ER and PR, do not seem to respond to hormonal therapy and show poor clinical prognosis. Therefore, distinction of LG-ESS from HG-ESS is crucial (Ladwig and Garg, 2016; Oliva et al., 2002). Overall, lifelong surveillance is necessary, as prognostic predictors of ESS remain unclear and there is a risk of late recurrence. The NCCN guidelines recommend physical exam every three to four months for the two to three years and after that one to two times per year. As well a CT scan of the chest, abdomen and pelvis every three to six months for the first three years, then every six to 12 months for years four and five and once a year or every other year for years six through 10 and is to be determined by the individual physician based on tumor characteristics (NCCN).

Extrauterine LG-ESS poses a diagnostic challenge, as patients often present with non-specific or GI symptoms that can be misleading. Furthermore, imaging findings may suggest malignancy due to obstruction, mass effect, and adhesions. Tissue sample is often limited. The diagnosis of extrauterine LG-ESS should only be made when benign entities, like endometriosis, or when morphologic mimickers are excluded via ancillary studies. Molecular studies, if available, may be valuable in this setting, as they can easily be performed on limited tissue. Furthermore, the identification of specific translocations is not only helpful for confirming the diagnosis, but also for future targeted therapies.

4. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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