

## Case report

Endometriosis-associated colorectal carcinosarcoma: A case report and review of the literature<sup>☆</sup>Ibrahim G. Tsolakian<sup>a</sup>, Aleia Crim<sup>b</sup>, Amy Lynn<sup>b</sup>, Dani Zoorob<sup>a</sup>, Peter Klein<sup>b</sup>, Adam Walter<sup>b,\*</sup><sup>a</sup> University of Toledo College of Medicine and Life Sciences – Department of ObGyn, United States<sup>b</sup> ProMedica Toledo Hospital, United States

Endometriosis is a common female disease characterized by endometrial glands and stroma outside of the uterus. It occurs in 10–15% of women of reproductive age. Endometriosis can occur in many organs, including the ovaries, fallopian tubes, vagina, and cervix. Extra-gonadal sites include the gastrointestinal tract, bladder, and even the skin. Intestinal involvement of endometriosis is most commonly found at the sigmoid colon and rectum. Malignant transformation of ovarian endometriosis is well documented, but extra-ovarian cancer associated with endometriosis is rare, with the first case being described in 1925 (Li et al., 2018). Some researchers suggest that endometriosis-associated malignancies arise from atypical endometriosis as an intermediate lesion between endometriosis and cancer. Moreover, several genetic alterations, like loss of heterozygosity (LOH), PTEN, ARID1A, and p53 mutations, have been found in both endometriosis and endometriosis-associated malignancies (Krawczyk et al., 2016). Mullerian Carcinosarcoma (MC), or malignant mixed Mullerian tumor (MMMT) is an uncommon tumor of the female genital tract (<5% of all gynecological malignancies). The tumor is composed of malignant mesenchymal and epithelial elements that exhibit sharp demarcation on histology. It has a worse prognosis compared to high-grade uterine endometrial carcinoma (Zhu et al., 2015). Although the uterus is the most common site of origin, MC may arise in extrauterine sites, with rare occurrences in extragenital sites. A more infrequent occurrence would be of carcinosarcoma associated with endometriosis.

In this article, we report a case of endometriosis-associated Mullerian carcinosarcoma arising from the colon of a patient who had previously had a total hysterectomy and bilateral salpingo-oophorectomy for benign indications. The patient provided written consent and permitted the release of information regarding her case.

## 1. Case presentation

## 1.1. Patient information

This is the case of a 69-year-old Caucasian female who presented to our institution in January 2020, reporting large bloody bowel movements concurrent with a 1-month history of constipation and mucus in stool. The patient had a colonoscopy four years prior to presentation, which demonstrated a benign polyp. The patient has a history of total abdominal hysterectomy bilateral salpingo-oophorectomy (TAH-BSO) in 1987 due to endometriosis. She did not receive hormone replacement therapy (HRT) after surgery. Additionally, her medical history is complicated by a spontaneous pulmonary embolism in 2019 treated with Apixaban.

## 1.2. Diagnostic assessment

CT scan of the abdomen on presentation (Fig. 1) (Supplementary figure 1) revealed a 4.7 cm × 3.8 cm × 3.4 cm mass in the distal sigmoid and proximal rectum, possibly neoplastic in nature, as well as multiple low-attenuation foci throughout the liver with the largest measuring 14 mm, likely metastases.

MRI of the pelvis was suggestive of a mid to high rectal tumor arising approximately 8–10 cm from the anorectal junction. The mass measured 4.1 cm in maximum dimension with definitive invasion beyond the right lateral bowel wall. T2 hyperintense loculation along the inferior right lateral margin was reported, likely representing a mucinous component. Invasion was noted along the cephalad aspect of the tumor through the peritoneal reflection.

Prominent lymph nodes were noted along the superior rectal vein with the most cephalad node measuring 0.6 × 0.8 cm. Morphologically abnormal and heterogeneous lymph nodes/deposits were reported

<sup>☆</sup> In this article, we report a case of endometriosis-associated Mullerian carcinosarcoma arising from the colon of a patient who had previously had a total hysterectomy and bilateral salpingo-oophorectomy for benign indications. This case reports presents the 5<sup>th</sup> documented case of endometriosis associated colorectal carcinosarcoma and provides updates regarding the latest treatments for this entity.

\* Corresponding author at: 5308 Harroun Rd., Suite 285, Sylvania, OH 43560, United States.

E-mail address: [Adam.WalterMD@promedica.org](mailto:Adam.WalterMD@promedica.org) (A. Walter).

throughout the mesorectal fat, with the largest measuring  $0.9 \times 0.8$  cm immediately adjacent to the tumor. The second-largest deposit was seen along the mesorectal fascia measuring  $0.9 \times 0.7$  cm with at least 6–7 additional suspicious deposits/nodes identified.

These findings were consistent with at least T4a, probably T4b mid to high 4 cm rectal tumor with probably early involvement of the right vaginal cuff.

Colonoscopy showed an infiltrative, partially obstructing mass in the rectum, which was nearly circumferential, 10 cm from the anal verge. The surface of the mass appeared normal.

The colon biopsy showed poorly differentiated carcinoma which was negative for cytokeratin 20 and CDX2 (excluding a colorectal primary) and positive for cytokeratin 7 and PAX8 supporting Müllerian origin. In addition, fine needle aspiration and core biopsy of the liver showed benign unremarkable hepatic parenchyma (Supplementary figure 3).

The patient underwent an exploratory laparotomy, resection of the pelvic and rectal mass, lower anterior resection, diverting loop ileostomy, appendectomy and liver biopsies.

The low anterior resection specimen demonstrated a 4.8 cm nodular mass protruding into the bowel lumen, thinning the colonic mucosa and with central erosion (Fig. 2) (Supplementary figure 2). The pale tan and pink mass was centered on the muscularis propria and infiltrated into the submucosa and perirectal soft tissue. Microscopically, the tumor demonstrated cribriform glands lined by highly atypical glandular cells and solid growth of epithelial cells with abundant eosinophilic cytoplasm accompanied by malignant spindled cells and highly pleomorphic cells forming a sarcomatous component. Residual endometriosis was found adjacent to the tumor within the muscularis propria as well as within a peritoneal biopsy. The findings were consistent with endometriosis-associated carcinosarcoma. No primary colonic tumor was identified. Metastatic tumor was found in five of thirty lymph nodes and five tumor deposits were noted. The core liver biopsy failed to show metastatic neoplasm. Immunohistochemical staining (IHC) showed that the tumor was weakly positive for Estrogen Receptor (ER): 20% and Progesterone Receptor (PR): 15%. In addition, somatic tumor sequencing analysis showed that the tumor was positive for ARID1A, PIK3CA and KRAS gene mutations.

The patient was discharged home with a plan for outpatient chemotherapy of 6 cycles of carboplatin/paclitaxel.

The patient was admitted two weeks postoperatively with generalized fatigue and abdominal pain. CT abdomen-pelvis showed marked progression in liver lesions and a small pelvic fluid collection. She underwent IR drainage of the fluid (negative cytology) and was discharged



**Fig. 2.** Cross Section Of the Tumor. The figure demonstrates a centrally cavitated tumor massively expanding into the muscularis propria (yellow diamond arrow) with invasion into the submucosa causing thinning of the colonic mucosa (yellow arrow). Tumor also infiltrates the perirectal soft tissue (yellow circular arrow). Normal colonic mucosa (white arrow), uninvolved muscularis propria (white diamond arrow) and uninvolved perirectal soft tissue (white circular arrow) are noted for comparison. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

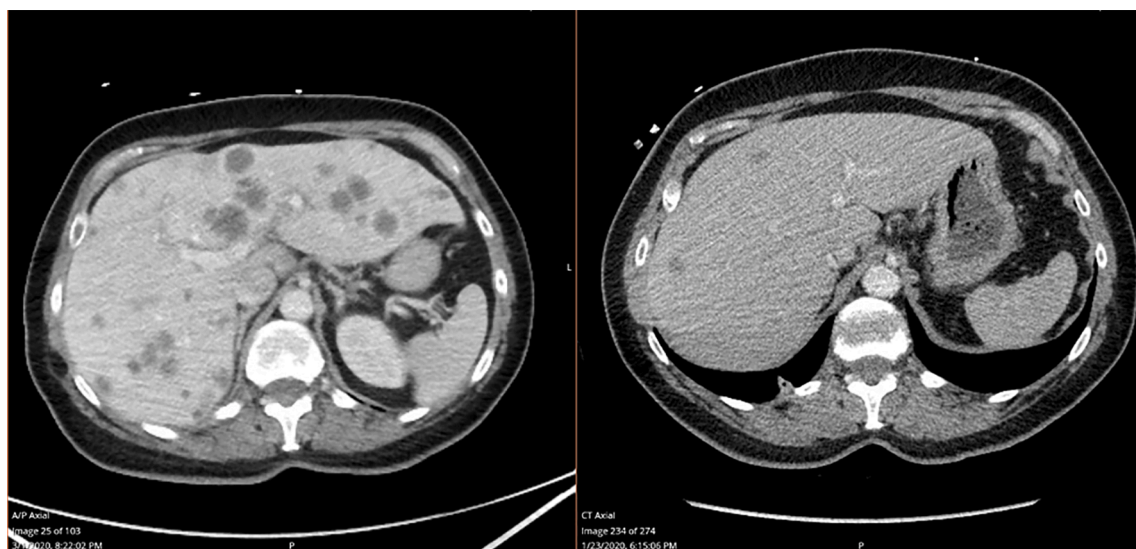
after stabilization. She also received her first dose of Carbo/Taxol during admission.

The patient was readmitted on March 2 with fever, chills, and during this admission, got a core biopsy and FNA of her liver lesions that were positive for adenocarcinoma, consistent with metastasis from the known carcinosarcoma (Fig. 1).

## 2. Discussion

The first case of endometriosis-associated intestinal tumor (EAIT) was reported by John Sampson in 1925. He proposed criteria for diagnosis that includes the presence of endometriosis in close proximity to the malignancy, the absence of a likely primary tumor, and histologic features supporting the origin from endometriosis.

It is uncommon to encounter endometriosis-associated intestinal tumors in postmenopausal women, mainly because of the inability to



**Fig. 1.** CT on 3/1/2020 compared to MRI done on 1/23/2020.

stimulate ectopic glandular tissue in the absence of estrogen. However, exposure to exogenous estrogen through HRT was the predisposing factor to EAIT as described by Agito et al. Although not on HRT, our patient did have a BMI of 27.7 - putting her in the overweight category. Larger adipose tissue storage has been shown to lead to increased conversion of androstenedione to estrone. This, in turn, can put obese patients with a history of endometriosis at a higher risk of developing EAIT compared to women who are at their ideal body weight (Agito et al., 2013). Even though estrogen might be a significant factor in the development of endometriosis associated tumors, it most probably is not the main factor in our case, where IHC studies have shown that the lesion was only weakly positive for ER and PR. In addition, multiple reports have discussed the presence of intrinsic genetic mutations that might be responsible of the progression from endometriosis to cancer. In 2016, Tse-Kiong Er and colleagues reported the presence of PIK3CA and ARID1A mutation in 60% and 50% of their studied samples, respectively, suggesting that mutations in these genes may promote malignant cell transformation (Er et al., 2016). The tumor in our case report was positive for both gene mutations, supporting the suggested idea of intrinsic genetic mutations in endometriosis associated tumors.

Although endometriosis-associated intestinal tumors are considered a rare entity, Mullerian carcinosarcoma-associated EAIT is even less common - with only 5 cases reported in the literature (including the case described in this review). The carcinoma component of Mullerian carcinosarcoma is most frequently endometrioid adenocarcinoma in nature, followed by clear cell carcinoma, and then squamous cell carcinoma. The sarcomatous component may include endometrial stromal sarcoma, leiomyosarcoma, undifferentiated sarcoma, rhabdomyosarcoma and chondrosarcoma.

Endometriosis-associated Mullerian carcinosarcoma has also been reported in the ovaries with a poor overall prognosis (Melilli et al., 2001). Patients with EAIT usually present with a pelvic mass, abdominal or pelvic pain/pressure, vaginal or rectal bleeding, and bowel obstruction. These symptoms, being similar to those of colorectal carcinoma, making it essential to promptly establish the correct diagnosis, as it affects treatment choice and survival rates (Table 1).

Being a rare entity, endometriosis-associated intestinal carcinosarcoma does not have an established treatment modality and is currently treated similar to uterine carcinosarcomas. Based on the current NCCN guidelines, carcinosarcomas are treated as high-grade carcinomas. Ifosfamide was historically considered the most active single agent for the treatment of such malignancies. Moreover, the combination of Ifosfamide with Paclitaxel has been shown to offer better overall survival and less toxicity than the previously used Cisplatin/Ifosfamide combination based on a phase III trial studying advanced carcinosarcoma. The former combination is still considered a Category 1 recommendation by the NCCN to treat the uterine carcinosarcoma. However, the toxicity of Ifosfamide has pushed researchers to identify alternatives (National Comprehensive Cancer Network, 2020).

A recent Phase III trial (GOG trial 0261, results presented at the 2019 ASCO annual meeting) compared Paclitaxel/Carboplatin to Paclitaxel/Ifosfamide. The study found that Paclitaxel/Carboplatin was not inferior to the regimen containing Ifosfamide. Additionally, Paclitaxel/Carboplatin was associated with prolonged progression-free survival in patients with recurrent carcinosarcoma of the uterus or the ovary (16 months vs. 12 months) (Powell et al.).

Due to the tumors' aggressive nature and the high likelihood of recurrence, clinical trials and molecular profiling may help determine subsequent therapy options.

### 3. Conclusion

In summary, endometriosis-associated tumors are rare entities that

**Table 1**  
Review of literature.

Reference	Age	History of hysterectomy	Tumor reaching the bowel mucosa
Weisz-Carrington et al. (1977) (No histologic evidence of endometriosis)	77	5 years prior to presentation due to endometrial adenocarcinoma	yes
Chumas et al. (1986)	67	2 years prior to presentation due to ovarian cystadenoma	Yes
Slavin et al. (2000)	50	2 year prior to presentation due to endometrial adenocarcinoma	Not reported
Agito et al. (2013)	85	40 years prior to presentation due to endometriosis	No

may present in postmenopausal women. It should be considered on the differential diagnosis of patients presenting with lower abdominal symptoms with a history of endometriosis or endometriosis-related complications.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2021.100696>.

### References

- Agito, M.D., Rehmus, E.H., Powell, A.T., 2013. Müllerian carcinosarcoma arising from intestinal endometriosis. *J. Clin. Oncol.* 31 (11), e175–e177.
- Chumas, J.C., Thanning, L., Mann, W.J., 1986. Malignant mixed mullerian tumor arising in extragenital endometriosis: report of a case and review of the literature. *Gynecol. Oncol.* 23 (2), 227–233.
- Er, T.K., Su, Y.F., Wu, C.C., Chen, C.C., Wang, J., Hsieh, T.H., Herreros-Villanueva, M., Chen, W.T., Chen, Y.T., Liu, T.C., Chen, H.S., 2016. Targeted next-generation sequencing for molecular diagnosis of endometriosis-associated ovarian cancer. *J. Mol. Med.* 94 (7), 835–847.
- Krawczyk, N., Banys-Paluchowski, M., Schmidt, D., Ulrich, U., Fehm, T., 2016. Endometriosis-associated malignancy. *Geburtshilfe Frauenheilkd.* 76 (2), 176.
- Li, N., Zhou, W., Zhao, L., Zhou, J., 2018. Endometriosis-associated recto-sigmoid cancer: a case report. *BMC Cancer* 18 (1), 1–6.
- Melilli, G.A., Nappi, L., Carriero, C., Lapresa, M., Loizzi, V., Caradonna, F., Quaranta, M., Putignano, G., 2001. Malignant mixed mullerian tumor of the ovary: report of four cases. *Eur. J. Gynaecol. Oncol.* 22 (1), 67–69.
- National Comprehensive Cancer Network, 2020. Uterine neoplasms (version 2.2020). Retrieved from [https://www.nccn.org/professionals/physician\\_gls/pdf/uterine.pdf](https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf).
- Powell, M.A., Filiaci, V.L., Hensley, M.L., Huang, H.Q., Moore, K.N., Tewari, K.S., Copeland, L.J., Secord, A.A., Mutch, D.G., Santin, A., Richards, W. A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naïve patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG Oncology trial.
- Slavin, R.E., Krum, R., Van Dinh, T., 2000. Endometriosis-associated intestinal tumors: a clinical and pathological study of 6 cases with a review of the literature. *Hum. Pathol.* 31 (4), 456–463.
- Weisz-Carrington, P., Bigelow, B., Schinella, R.A., 1977. Extragenital mixed heterologous tumor of Müllerian type arising in the cecal peritoneum: report of a case. *Dis. Colon Rectum* 20 (4), 329–333.
- Zhu, J., Wen, H., Bi, R., Wu, X., 2015. Clinicopathological characteristics, treatment and outcomes in uterine carcinosarcoma and grade 3 endometrial cancer patients: a comparative study. *J. Gynecologic Oncology* Dec 2;27(2).