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Case series

Large bowel recurrence of endometrial adenocarcinoma years after treatment: A single-institution case series and review of the literature

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ABSTRACT

Endometrial cancer (EC) is the most common gynecologic cancer in the United States. A majority of new cases are diagnosed as low-grade International Federation of Gynecology and Obstetrics (FIGO) Stage I, with a recurrence risk cited as less than 9 % in the first 2–3 years post-treatment. In this case series, we present three unique cases of patients with FIGO 2009 Stage I EC who all went on to present with pelvic colonic recurrences years after their initial treatment, two of the patients outside of the 5-year standard surveillance period. These presentations are described in the context of the available literature on EC colonic recurrence.

A review of the literature suggests a previously cited association between endometriosis and unusual recurrence locations may not be as important of a risk factor as previously considered, as most of the cases in the series had no clinical or pathologic history of endometriosis. In addition, most of the included cases did not report a history of endometriosis and 60% of the cohort had received postoperative adjuvant radiation and still went on to experience locoregional recurrence. Further study on the associations between endometriosis, MMR status and EC recurrence, particularly for uncommon anatomic recurrence sites, are warranted to ensure appropriate and timely treatment.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic cancer in the United States. There are multiple histologic subtypes that fall under the designation of EC, with the endometroid type most common and with the best prognosis (Fader et al., 2016). A majority of new cases are diagnosed as low-grade International Federation of Gynecology and Obstetrics (FIGO) Stage I, with one recent population-cohort study citing an overall recurrence rate of 8.3 % with a median time to recurrence of 22.6 months (range 3.2–59.3) (Åkesson et al., 2023).

As the first couple of years post-treatment are the time at which patients are most likely to experience recurrence, National Comprehensive Cancer Center (NCCN) guidelines accordingly recommend more frequent visits for the first 2–3 years of survivors' 5-year surveillance period (NCCN, 2023). When EC does recur, high-grade histologic subtypes are more likely to recur locally in the vagina or pelvis, in the pelvic or *para*-aortic nodes, or, if distant, in the lungs (Kurra et al., 2013). Of those who recur, the most common sites are quoted at 42 % for vaginal cuff recurrence and 49 % for pelvic lymph nodes (Anstadt et al., 2012). Less common sites of recurrence include extra-abdominal nodes, the liver, musculoskeletal system, or the central nervous system (Kurra et al., 2013).

Here, we describe three unique cases of patients with FIGO 2009 Stage I endometrioid adenocarcinoma who all went on to present with colonic recurrences years after their initial treatment, two of the patients outside of the 5-year standard surveillance period. These presentations are described in the context of the available literature on EC colonic recurrence.

2. Informed consent statement

Written consent was obtained from the patients for the publication of this series. Review of these cases was approved by the medical center's Institutional Review Board (#24728).

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3. Case series

3.1. Case 1

Case 1 was diagnosed with grade 1 endometrioid EC at age 58 years old (2015). She had a past medical history significant for diabetes, hypertension, anxiety, symptomatic cholelithiasis and Class I obesity (body mass index 32 kg/m^2). She had no significant family history of cancer. She underwent a robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection (eight total nodes, four nodes bilaterally) in July 2015 at an outside hospital. Her tumor was a FIGO 2009 Stage IA mismatch repair (MMR) proficient, grade 1. Her surgical pathology report noted endometriosis on both ovaries, and a p53 signature in her left fallopian tube. Table 1 details pathologic characteristics of her case.

Eight years later (2023) she presented with painless rectal bleeding. Time of her last follow up was unknown. Computed-tomography scan of the abdomen and pelvis demonstrated a 7.7 cm necrotic pelvic mass in contact with the left anterior portion of the rectum and enlarged retroperitoneal nodes. Colonoscopic biopsies revealed ulcerated rectal mucosa and inflammation, with no malignant cells present. Biopsy of the retroperitoneal nodes revealed recurrent EC based on positive PAX8 and estrogen receptor (ER) immunohistochemistry (IHC) staining.

She was taken to the operating room for an exploratory laparotomy, pelvic mass resection, pelvic lymph node and peritoneal tumor debulking, gastrocolic omentectomy, low anterior resection, diverting transverse loop colostomy and a cholecystectomy. Residual tumor was noted on the diaphragm.

Surgical pathology returned with involvement in the resected colon and associated lymph nodes (15/28), posterior vagina, retroperitoneal nodes (2/5), omentum, and peritoneal implants. She was treated post-operatively with hormonal therapy (tamoxifen and megestrol acetate) with stable disease.

3.2. Case 2

Case 2 was diagnosed at age 46 years old with synchronous FIGO 1988 Stage IB EC and FIGO Stage IC3 endometroid ovarian cancer (2007). Her medical history is significant for a past history of tobacco use and several provoked venous thromboembolic events with an inferior vena cava filter in place. She denied any history of endometriosis. Her relevant family history is notable for a maternal aunt and grandmother with breast cancer.

She initially presented with large pelvic mass and a CA-125 of 350. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and *para*-aortic lymphadenectomy, and pelvic washings in March 2007. She received adjuvant chemotherapy for the ovarian cancer. Table 1 details the pathologic characteristics available from her case.

She remained in surveillance and without evidence of disease recurrence for 16 years, seen for annual visits. In 2023 she developed painless rectal bleeding and underwent a colonoscopy with biopsies demonstrating well-differentiated colonic adenocarcinoma; this report was later addended by the outside pathologist after additional staining "demonstrated an immunoprofile consistent with metastatic endometrioid carcinoma". This diagnosis was overread by institutional pathologists who agreed. Her tumor markers were normal. Pre-operative imaging demonstrated extension but no invasion toward the right pelvic sidewall, and no enlarged pelvic nodes. She underwent a robotic-assisted low anterior resection and diverting loop ileostomy, with surgical pathology returning EC involving the rectosigmoid colon and 0/17 lymph nodes. IHC staining was strongly positive for PAX8 and CK7, with negative CK20 staining. She underwent an ileostomy reversal in May 2023, with no residual or recurrent tumor on post-operative imaging.

3.3. Case 3

Case 3 was diagnosed at age 65 years old with FIGO 2009 Grade 2 Stage IB endometroid EC. Her medical history was otherwise significant for depression and a thyroid goiter. Her family history was notable for maternal colon cancer, paternal melanoma, and endometrial cancer in her sister.

She underwent a robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic

Table 1

	Genetic testing	Surgical staging[1]	FIGO 2009 Stage/ Grade at diagnosis	Initial surgical pathology	Adjuvant treatment	DFI	Location of recurrence	Endometriosis
Case 1	pMMR TMB: 6.2 NGS	Yes	IA/1	Endometrial invasion only No LVSI 0/8 involved lymph nodes Endometriosis P53 signature on left fallopian tube Pelvic washings with "rare mildly atypical cell groups, favor reactive mesothelial cells"	None	91 mo	Rectum Pelvic nodes Peritoneum	Yes, Pathology-proven
Case 2	dMMR[2] BRAF negative Negative hereditary testing[3]	Yes	IA/1	6/29 mm MMI No LVSI 0/5 involved lymph nodes Pelvic washings with "adenocarcinoma, well to moderately differentiated"	None[4]	179 mo	Rectosigmoid colon	No, per patient report
Case 3	dMMR[2] Negative hereditary testing[5]	Yes	IB/2	17/22 mm MMI Tumor size greatest dimension 3.5 cm No LVSI Endometrial polyp 0/13 involved lymph nodes	VCBT	19 mo	Sigmoid colon Pelvic nodes Vaginal cuff	Not discussed

Abbreviations: DFI = disease-free interval; dMMR = mismatch repair deficient; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; MMI = myometrial invasion; NGS = Next-generation sequencing; pMMR = mismatch repair proficient; TMB = tumor mutational burden; VCBT = vaginal cuff brachytherapy.

[1] Comprehensive surgical staging" taken to mean total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment, per NCCN guidelines (NCCN, 2023).

[2] This patient's mismatch repair testing was notable for loss of MLH1 and PMS2 expression. MLH1 methylation was detected on subsequent analysis.

[3] This patient underwent Myriad myRisk ® testing in 2021 that was negative for any germline pathogenic variants.

[4] This patient received systemic chemotherapy for her synchronous ovarian cancer, not endometrial cancer. Review of her notes from her gynecologic oncologist at that time notes no adjuvant therapy was indicated for the endometrial cancer.

[5] This patient underwent Ambry Genetics ® testing in 2018 that was negative for any germline pathogenic variants.

lymphadenectomy in November 2015. She subsequently completed adjuvant vaginal cuff brachytherapy the following year.

Two years later, she presented to the emergency room with severe abdominal pain and was diagnosed with perforated diverticulitis (2018); at this time, she was still undergoing surveillance. She continued to report pain and gastrointestinal symptoms after recovery, and imaging demonstrated concern for vaginal cuff and colon metastatic disease. She was referred for a colonoscopy, however due to a sigmoid stricture this procedure was aborted and her vaginal cuff mass was biopsied. While awaiting results of the cuff biopsy, given the history of complicated diverticulitis she went to the operating room with colorectal surgery and underwent a sigmoid colectomy with primary anastomosis and loop transverse colostomy, which was eventually reversed. Surgical pathology returned metastatic EC with 1/17 lymph nodes involved. She underwent 6 cycles of carboplatin and paclitaxel l with intensity-modulated radiation therapy to the pelvis. Post-treatment imaging demonstrated resolution of pelvic metastases. Two years later, she underwent additional imaging demonstrating a second cuff recurrence and underwent salvage interstitial brachytherapy, completed in February 2020. The cuff recurrence progressed and she was offered pelvic exenteration or pembrolizumab given her tumor was mismatch repair deficient (Table 1). She opted for pembrolizumab and was started on this in October 2020. She received 11 cycles of pembrolizumab through August 2021, at which point she transferred her care to a different institution to be closer to her daughter. At time of manuscript preparation, she has received 25 cycles of pembrolizumab. Her stable vaginal cuff mass is routinely monitored and has not progressed in several years.

4. Discussion

This case series reviews three unique cases of patients with EC who went on to have unusual colonic recurrences years post-treatment. The patient in Case 1 recurred approximately 7.5 years after her initial surgery, the patient in Case 2 recurred nearly 16 years after her initial operation, and the patient in Case 3 recurred over 2.5 years after completion of her adjuvant therapy. This recurrence pattern is unique given the location, low-risk of recurrence and Stage I status of all patients. Of note, FIGO 1988 staging was used at time of initial treatment in Case 2, so for the purposes of this discussion the patient was re-staged with FIGO 2009 staging, which would have made her Stage IA. None of the patients possessed a known germline genetic mutation, though the disease in Case 1 was MMR proficient and disease in Cases 2 and 3 were MMR deficient, both hypermethylated.

Given the rarity of this disease pattern, a review of the literature was performed. PubMed was queried with the search terms “endometrial cancer” AND “metastasis” OR “recurrence” AND “colon” or “bowel” for 19 results. The abstracts were reviewed and the relevant abstracts were pulled, with their references additionally reviewed. Studies were included if they detailed treatment and disease-free interval (DFI) (defined as the time from treatment to recurrence) data on a primary EC of any histologic sub-type that recurred at any later time point in the large bowel. Studies were also excluded if the endometrial cancer recurred in the small bowel or were non-English publications. A total of ten additional cases were identified from nine published studies (Table 2).

Of the cases identified in the literature (Table 2), a majority (7/10) presented with Stage I disease of the endometrioid histologic subtype (9/10). Only 3 of the patients referenced complete surgical staging, defined as mean total hysterectomy, bilateral salpingo-oophorectomy, and nodal assessment per NCCN guidelines, though all the patients underwent a hysterectomy as part of the treatment for their endometrial cancer (NCCN, 2023). The authors of this study surmise that given most of these case reports were published in gastroenterology literature, the significance of nodal status as part of comprehensive surgical staging may have been overlooked at time of publication. 60 % (6/10) of the cases received postoperative adjuvant radiation. The DFI ranged from 1 month to over 28 years (Table 2). In this small cohort, the median DFI was 72 months, and the average DFI was 87.3 months, or approximately 7 years. Six out of the ten patients recurred outside of the standard 5-year surveillance window.

In our review of literature, several authors of the included publications have suggested an association between rarer sites of EC recurrence and a history of endometriosis. While there are reports of primary EC arising from endometriosis implants, of the cases in this review that included these details (n = 5), none of these patients reported any clinical or pathologic history of endometriosis (Chen, 2002). The association, if any, of endometriosis remains unclear. Overall, the risk of malignant transformation for endometriosis implants is exceedingly

Table 2

Publication	FIGO Stage/Grade at Diagnosis	Histology	Treatment	Adjuvant therapy?	DFI	Location of recurrence	Hx of Endo?	Genetic susceptibility?
Bailey and Gilbert (2002)	Not included in publication	endometroid	Surgery[1]	RT[2]	5 yrs[3]	Rectal	Not stated	Not stated
Bailey and Gilbert (2002)	Not included in publication	endometrioid	Surgery[1]	RT[2]	7 yrs[3]	Rectal	Not stated	Not stated
Addison et al. (2012)	1B/3	Adeno-squamous	Surgery[1]	EBRT	10 yrs[3]	Appendix	Not stated	Not stated
Anstadt et al. (2012)	1B/2	Endometrioid	Surgery[1]	No	17 mo	Recto-sigmoid	No	Not stated
Wou et al. (2014)	1B/2	Endometrioid	Complete surgical staging[4]	No	7 yrs	Rectal	Not stated	Not stated
Chedid et al. (2015)	1B/Unknown	Endometrioid	Surgery[1]	No	>10 yrs[3]	Sigmoid	Not stated	Not stated
Franchello et al. (2015)	1B/”Low-grade”	Endometroid	Surgery[1]	VCBT	>28 yrs[3]	Rectal	No	MLH1 somatic mutation
Hubers and Soni (2017)	1B/1	Endometroid	Complete surgical staging	VCBT	3 yrs[3]	Sigmoid	No	Not stated
Jauregui et al. (2021)	3B/3	Endometroid	Complete surgical staging	No	1 mo	Sigmoid	No	Not stated
Koury et al. (2021)	1A/1	Endometroid	Surgery[1]	EBRT VCBT	15 mo	Sigmoid	No	Not stated

Abbreviations: DFI = disease-free interval; EBRT = external beam radiation therapy; Endo = endometriosis; FIGO = International Federation of Gynecology and Obstetrics; RT = radiation therapy; VCBT = vaginal cuff brachytherapy.

[1] Surgical management was simply denoted as hysterectomy and bilateral salpingo-oophorectomy with no mention of nodal status or evaluation

[2] Specific radiotherapy modality not stated in the publication

[3] Exact dates not provided in the publication

[4] ″Complete surgical staging” taken to mean total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment, per NCCN guidelines (NCCN, 2023).

low, cited at a frequency of less than 1 % (Chen, 2002). Given this real but minimal risk of malignant transformation, it would also be difficult to definitively prove recurrence versus new primary. While one patient in our series did have pathology-proven endometriosis, any association between endometriosis and large bowel recurrence remains to be determined.

There are several limitations to address in this case series and literature review. The small sample size of this case series obviously precludes any sort of robust analysis, which is not unexpected given the rarity of this presentation. Clinical and pathology information regarding the included cases, particularly Case 2, was incomplete. One question that arose during review of Case 2 was whether or not the recurrence was definitively endometrial, given her synchronous ovarian and endometrial primaries were both of endometroid histology. At time of her presentation with the synchronous primaries in 2007, her CA-125 was elevated to 350. The recurrence in 2023 was confined to the pelvis and was not associated with a CA-125 elevation; as such, it was determined to most likely be consistent with a recurrence of the endometrial cancer, especially since the patient did not receive any adjuvant radiation in 2007. The blocks and slides were not available for review given the length of time that had passed.

In the literature review, a majority of the studies (9/10) did not include any information regarding genetic molecular analysis. Universal testing for MMR proteins is now recommended per NCCN guidelines; however several of the studies were published prior to this becoming a widespread practice (NCCN, 2023). MMR deficiency is one of the genomic molecular subtypes that has been identified in recent studies to be clinically impactful particularly in regards to biomarker-directed adjuvant therapy (NCCN, 2023). A more thorough understanding of these patients' genomic profiles could help characterize their unique disease course. The authors acknowledge there may be previously published cases that have been missed in this review.

5. Conclusion

This limited case series reviews the course of three patients with Stage I endometrioid ECs who went on to present with colonic recurrence years after initial treatment. These cases are unique given their overall low likelihood to have recurred, the location of their recurrences, and the timeframe of recurrence. In the literature review undertaken to contextualize these cases, this series notes that most of the included cases did not report a history of endometriosis and 60 % of the cohort had received postoperative adjuvant radiation and still went on to experience locoregional recurrence. Further study on the associations between endometriosis, MMR status and EC recurrence, particularly for uncommon anatomic recurrence sites, and the utility of adjuvant therapy to mitigate the risk of recurrence are warranted to ensure appropriate, timely treatment at time the recurrence is diagnosed.

CRediT authorship contribution statement

Annalyn M. Welp: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Linda R. Duska:** Conceptualization, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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.

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