Clinicopathological features of endometriosis-associated adenocarcinoma of the rectum: A report of two cases

KE ZHAO[1], MIN HU[2], XIAOWEN LI[2], RUNFENG YANG[1] and YI HUANG[1]

[1]Department of Gynecologic Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430079, P.R. China; [2]Department of Pathology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430079, P.R. China

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Abstract. Endometriosis-associated adenocarcinoma of the rectum is rare and is usually misdiagnosed as colorectal carcinoma or other gynecological tumors. In the current report, the clinicopathological features of endometriosis-associated adenocarcinoma of the rectum in 2 patients were retrospectively analyzed and a literature review regarding this rare malignancy is presented. Case 1, a 49-year-old postmenopausal female patient, was admitted to Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) due to a pelvic mass. Pelvic MRI revealed a 4.5x3.7-cm mass in the rectal wall, which severely adhered to the uterine wall. Microscopically, moderately differentiated glandular adenocarcinoma diffusely extended throughout all intestinal wall layers. Adenomyosis was found in the uterine body adherent to the rectum. Case 2, a 38-year-old reproductive female patient, presented with hematochezia. Histopathology of the resected tumor demonstrated benign endometriosis foci and atypical hyperplasia glands contiguous with endometrioid carcinoma invading the intestinal wall, and no other primary tumor sites were found, which satisfied the criteria for the diagnosis of malignant transformation of endometriosis of the rectum. Immunohistochemical (IHC) staining of both tumors revealed a Müllerian origin but not an intestinal origin. Furthermore, next-generation sequencing detected mutations of the *BRCA1* (c.329dup), *KRAS* (c.35G>T), *PIK3CA* (c.3140A>G) and *PTEN* (c.750_751del) genes, and that microsatellite instability was high in case 1. In conclusion, endometriosis-associated adenocarcinoma of the rectum is a rare malignant tumor that should be distinguished from colorectal carcinoma for optimal treatment. Surgery and pathologic examination with IHC staining, even with molecular analysis, are essential for the final diagnosis. Primary cytoreductive surgery with resection of all macroscopic detectable lesions should be performed whenever possible. More prospective, multicenter, large-scale trials are required to examine the regimens and therapeutic value of adjuvant chemotherapy or radiology.

Correspondence to: Professor Yi Huang, Department of Gynecologic Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, 116 Zhuodaoquan South Road, Hongshan, Wuhan, Hubei 430079, P.R. China
E-mail: huangyt32@hotmail.com

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Introduction

Endometriosis is a common gynecological proliferative disease that occurs in 5-15% of reproductive women globally (1). It refers to abnormal growth of endometrial tissues (glands and stroma) outside the uterus, mainly in the ovaries and extra-ovarian sites, including the sigmoid colon, rectum, bladder and abdominal wall, which causes a series of clinical symptoms, including pelvic pain, dysmenorrhoea, non-menstrual pelvic pain and infertility (2).

Although endometriosis is not a premalignant disease, it may have malignant potential and become a malignancy (3). The incidence of malignant transformation of endometriosis ranges between 0.7 and 1%, with ~75% of cases involving the ovary and the remaining 25% developing from extra-ovarian endometriosis (4,5). The pathological criteria for the diagnosis of malignant transformation of endometriosis include benign endometrial tissues coexisting in the tumor, the demonstration of the neoplasm arising from endometriosis and not elsewhere, as well as the demonstration of the histological transition between benign and malignant endometriosis (6,7). However, with the overgrowth of cancer in some cases, the benign endometriotic foci are obliterated by malignant components (8). Thus, it is challenging to diagnose endometriosis-associated cancers due to a lack of histological evidence of endometriosis and malignant transformation. A pooled analysis of case-control studies has demonstrated that endometrioid carcinoma and clear cell carcinoma are the most common pathological types of endometriosis-related malignant tumors, which mostly develop from ovarian endometriosis (4). The mechanism of endometriosis-associated cancers is unclear, and studies of the molecular mechanism have confirmed these are related to mutations in the *CTNNB1*, *PIK3CA*, *ERBB2*, *KRAS*, *ARID1A* and *PTEN* genes, and microsatellite instability (9,10).

Extra-ovarian endometriosis-associated cancer involving the rectum is rare, making the diagnosis of the disease challenging. The present report describes 2 female patients with rectal lesions that were initially diagnosed as high-grade intraepithelial neoplasia of the rectum by endoscopic biopsy. Radical resection of the lesions with pathology and further mutation analysis in case 1 confirmed the diagnosis of endometrioid carcinoma of the rectum associated with endometriosis.

Case report

Case presentation. Case 1, a 49-year-old postmenopausal female patient, was admitted to Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) in September 2021 due to a pelvic mass on examination. Laboratory examination showed that the serum cancer antigen 125 level was elevated (247.300 U/ml; normal, 0-35 U/ml), while CA19-9 (0.64 U/ml; normal, <30 U/ml), CEA (1.895 ng/ml; normal, <5 ng/ml) and AFP (3.99 ng/ml; normal, <7 ng/ml) levels were within the normal range. A colonoscopy revealed an ulcerated fleshy neoplasm 12 cm from the anal margin, and it was possible to pass the endoscope beyond the lesion. The surface of the lesion was irregular and the surrounding mucosa was slightly rough. Pelvic MRI revealed a 4.5x3.7-cm mass in the anterior rectal wall, which severely adhered to the uterine wall (Fig. 1A). Since the endoscopic biopsy specimens indicated high-grade intraepithelial neoplasia (highly suspected adenocarcinoma), and the lesion was in the rectum and adhered to the uterine wall, partial rectal resection with total hysterectomy and bilateral salpingo-oophorectomy was performed. There was no evidence of macroscopic tumor present after the surgery.

Case 2, a 38-year-old reproductive female patient admitted to Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) in November 2023, presented with hematochezia during the past 2 weeks. The laboratory examination showed that the serum CA19-9 level was elevated (49.33 U/ml; normal, <30 U/ml), while the CEA (1.520 ng/ml; normal, <5 ng/ml) level was within the normal range. Pelvic MRI revealed eccentric rectal wall thickening with a rough serosa (Fig. 2A). The uterus and uterine endometrium were normal, and no abnormal signals were found in the pelvic wall. The endoscopic biopsy specimens at Hubei Provincial Hospital of Integrated Chinese and Western Medicine (Wuhan, China) indicated high-grade intraepithelial neoplasia, and a partial resection of the rectum was performed.

Pathology and mutation analysis. In case 1, a 4.5x3.7-cm hard mass involving the rectum and adherent to the posterior myometrium of the uterus was found. No other primary tumors were found in the endometrium, cervix or bilateral adnexa. Examination of the histopathological staining with hematoxylin and eosin according to a standard protocol indicated that moderately differentiated glandular adenocarcinoma diffusely extended throughout all layers of the intestinal wall (Fig. 1B). Intraluminal necrosis and segmental destruction of glands were not observed. The tumor cells were columnar with pseudostratified nuclei (Fig. 1C). Adenomyosis was found in the uterine body adherent to the rectum. A total of 26 regional lymph nodes (LNs) were assessed and showed reactive hyperplasia. Immunohistochemical (IHC) staining was performed as described in our previous study (11). The results showed that the tumor cells were positive for paired box gene 8 (PAX8; Fig. 1D), estrogen receptor (ER; Fig. 1E) and progesterone receptor (PR; Fig. 1F), and negative for caudal type homeobox 2 (CDX2; Fig. 1G), special AT-rich sequence-binding protein 2 (SATB2; Fig. 1H) and cytokeratin 20 (Fig. 1I). The mismatch repair proteins were detected by IHC staining, and mutL homolog 1 (Fig. 1J) and PMS2 (Fig. 1K) were lost. Next-generation sequencing (NGS) was then performed as described previously (12) using the formalin-fixed (4% neutral formaldehyde solution; room temperature; 12-24 h) and paraffin-embedded tumor tissue to elucidate mutation profiles for 41 genes in a panel that was designed to detect colorectal cancer-associated genes, including *BRCA1*, *BRCA2*, *ERBB2*, *BRAF*, *KRAS*, *NRAS*, *POLE*, *TP53*, *PIK3CA*, *PTEN*, *MSH2*, *MSH6*, *MLH1* and *PMS2*. The key mutations in the gene panel are listed in Table SI. Mutations of the *BRCA1* (c.329dup), *KRAS* (c.35G>T), *PIK3CA* (c.3140A>G) and *PTEN* (c.750_751del) genes were identified, and microsatellite instability (MSI)-NGS was detected to be high. The final diagnosis of rectal endometriosis-associated endometroid carcinoma was made. The patient received adjuvant chemotherapy with paclitaxel (175 mg/m^2) followed by AUC5 carboplatin on day 1 intravenously, every 21 days for 6 consecutive courses. The patient underwent tumor biomarker detection nearly every 3 months (Table SII), and the tumor biomarkers were within the normal range. The patient also received MRI or CT scans nearly every year, and there was no apparent recurrence or metastasis in December 2022 (Fig. S1), December 2023 (Fig. S2) and March 2024 (Fig. S3).

In case 2, a segment of the large bowel measuring 15 cm in length was examined, and a 1.7x1.5-cm ulcerated fleshy mass with greyish, solid and friable cut surface could be seen. Microscopically, well-differentiated endometrioid carcinoma was seen scatteredly infiltrating all layers of the intestinal wall (Fig. 2B), and benign endometriosis foci contiguous with endometroid adenocarcinoma, and atypical hyperplasia between the benign and malignant endometrial tissues could be observed (Fig. 2C). The tumor cells exhibited villo-glandular or confluent glandular architectures with focal squamous differentiation in the mucosa (Fig. 2D) and cribriform patterns in the muscularis propria to subserosa. Dusty blue secretion was observed in some benign endometrial glands. Tumor metastasis was observed in 5 of the 22 local regional LNs. No other primary tumor sites were found. IHC staining was performed in the same manner as IHC staining for case 1, and the details for the antibodies are listed in Table SIII. The results showed that the tumor cells were positive for PAX8 (Fig. 2E), ER (Fig. 2F), and variably positive for PR (Fig. 2G), whereas CDX2 (Fig. 2H) and SATB2 (Fig. 2I) were focally positive. The Ki67 index was 70% (Fig. 2J). The final diagnosis was endometrioid carcinoma derived from rectal endometriosis (5,6). The patient did not receive adjuvant chemotherapy, and was followed-up by detecting tumor biomarkers nearly every 3 months (Table SIV), and the tumor biomarkers were within the normal range. The patient also underwent CT examinations every half a year after resection, and there was no apparent recurrence or metastasis in July 2024 (Fig. S4).

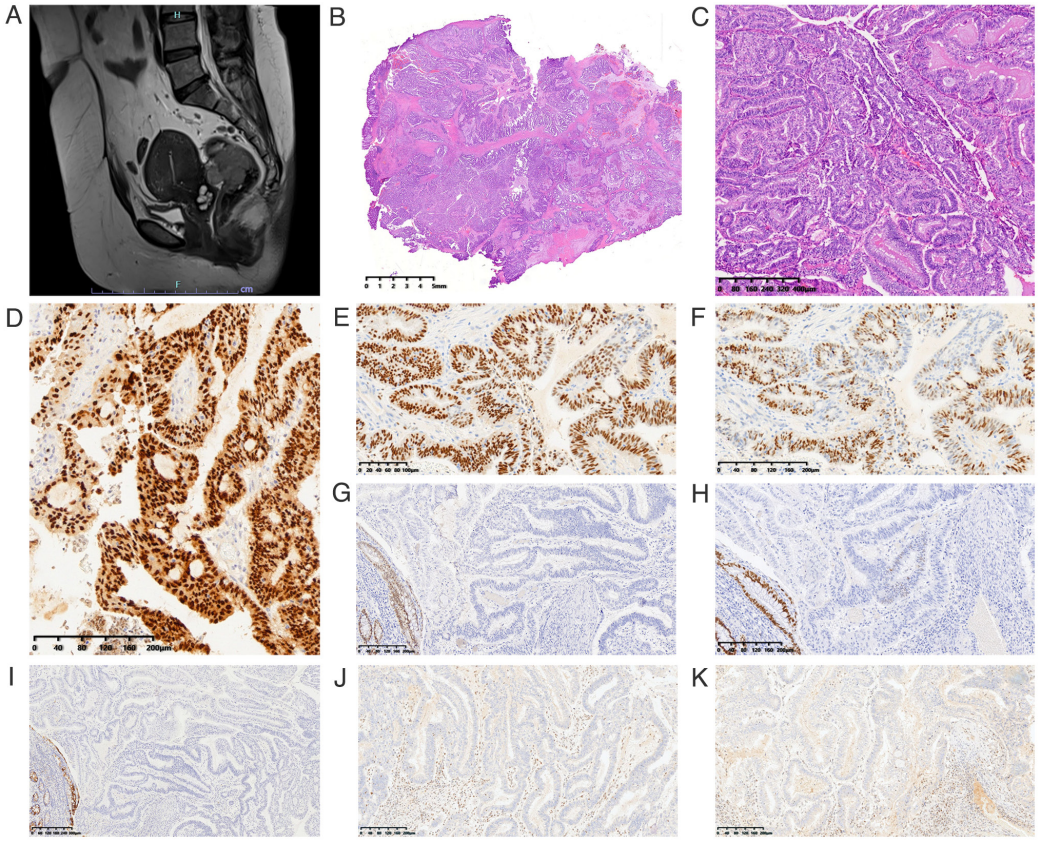

Figure 1. MRI and pathological features of case 1. (A) Pelvic MRI revealed a mass in the rectum that severely adhered to the uterine wall. Histopathologic features of the adenocarcinoma infiltrating the rectum: (B) Moderately differentiated glandular adenocarcinoma diffusely extending throughout all layers of the intestinal wall (scale bar, 5 mm). (C) Tumor cells were columnar with pseudostratified nuclei (scale bar, 400 μm). Immunohistochemical staining of the tumor revealed that (D) paired box gene 8 staining was positive (scale bar, 200 μm), (E) estrogen receptor staining was positive (scale bar, 100 μm), (F) progesterone receptor staining was positive (scale bar, 200 μm), (G) caudal type homeobox 2 staining was negative (scale bar, 200 μm), (H) special AT-rich sequence-binding protein 2 staining was negative (scale bar, 200 μm), (I) cytokeratin 20 was negative (scale bar, 300 μm), and (J) mutL homolog 1 (scale bar, 200 μm) and (K) PMS2 were lost (scale bar, 200 μm).

Discussion

Endometriosis is a common gynecological disease with malignant potential and local aggressive biology (3). In 1925, Sampson (6) first reported the malignant transformation of endometriosis. Subsequently, Scott (7) summarized and proposed four essential criteria for the diagnosis of malignant transformation of endometriosis: i) Both malignant and benign endometrial tissues coexisted in the tumor; ii) histology of the neoplasm consistent with an endometrial origin; iii) no other primary tumor sites can be found; and iv) demonstration of the histological transition between benign and malignant endometriosis. In the present case 2, benign endometriosis foci contiguous with endometroid adenocarcinoma invading the intestinal wall, and atypical hyperplasia between the benign and malignant endometrial tissues could be observed, and no other primary tumor sites were found, which satisfied the criteria (7) for the diagnosis of malignant transformation of the rectal endometriosis.

However, not all cases meet the aforementioned four criteria. In the present case 1, moderately differentiated glandular adenocarcinoma diffusely extended throughout all layers of the intestinal wall, while no evidence of endometriosis was detected microscopically. We hypothesized that with the overgrowth of cancer, the benign endometriotic foci are obliterated by malignant components. Therefore, it is challenging to diagnose endometriosis-associated cancers due to a lack of histological evidence of endometriosis and malignant transformation (8).

Since the biological behavior, therapeutic management and prognosis of endometriosis-associated rectal adenocarcinoma are different from those of colorectal adenocarcinoma (13,14), it is important to distinguish the two. Colorectal adenocarcinoma usually originates from the mucosal epithelium and gradually extends through the intestinal wall with the growth of the tumor. Endometriosis-associated adenocarcinomas invade the bowel wall from the outside, involving the serosa and subserosa, and occasionally the muscular propria and mucosa (13,14). Furthermore, cases of endometriosis-associated adenocarcinomas involve the mucosa, mimicking the intraepithelial neoplasia of the colorectal carcinoma, as shown in the endoscopic biopsy specimens of the present 2 patients. Therefore, it cannot be judged entirely from the growth pattern whether or not it is a primary tumor when the tumor extends through all layers of the intestinal wall. Secondly, the histological features of the tumors are helpful for differential diagnosis. Although both well-differentiated colorectal adenocarcinoma and well-differentiated endometrioid carcinoma could display glandular or cribriform growth patterns, marked cytologic atypia and a high mitotic index are

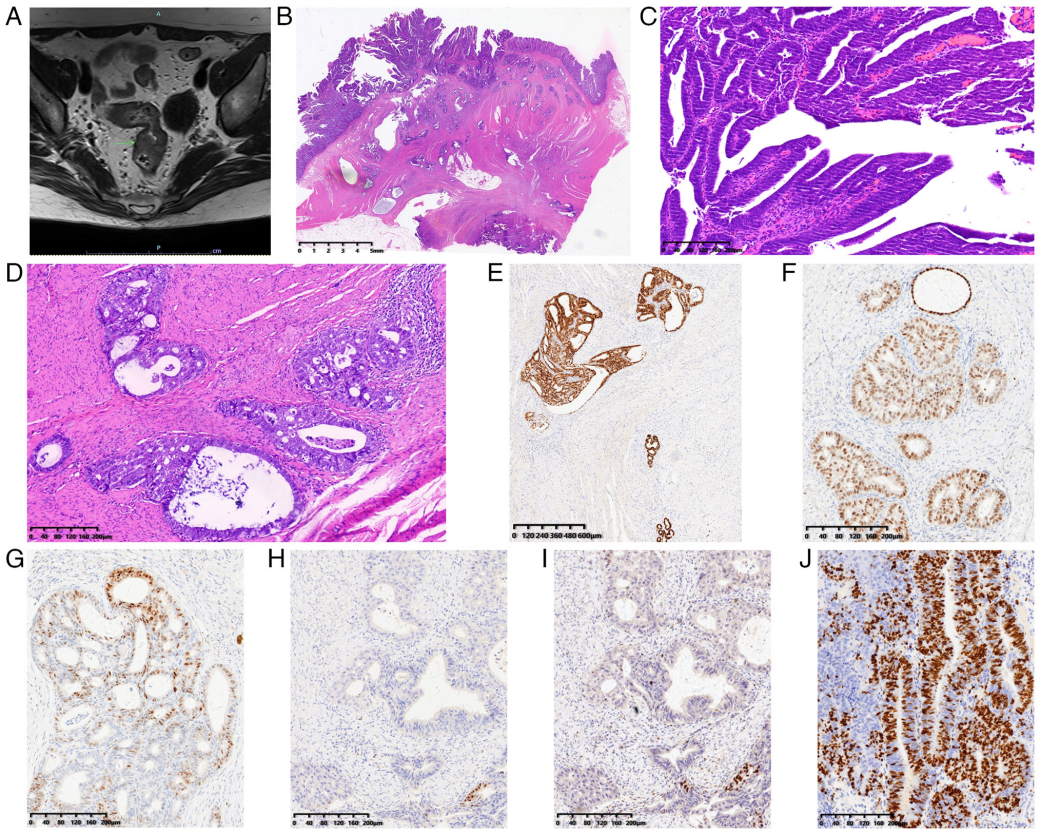

Figure 2. MRI and pathological features of case 2. (A) Pelvic MRI revealed eccentric rectal wall thickening with a rough serosa (green arrow, thickening rectal wall). (B) Well-differentiated endometrioid carcinoma scatteredly infiltrated all layers of the intestinal wall (scale bar, 5 mm). (C) Tumor cells displayed villo-glandular architectures in the mucosa (scale bar, 200 μm). (D) Tumor cells displayed cribriform patterns in the muscularis propria to subserosa, and endometriosis foci as well as atypical glands were seen adjacent to the neoplastic cells (scale bar, 200 μm). Immunohistochemical staining showed that the tumor cells were positive for (E) paired box gene 8 (scale bar, 600 μm) and (F) estrogen receptor (scale bar, 200 μm), (G) variably positive for progesterone receptor (scale bar, 200 μm), and focally positive for (H) caudal type homeobox 2 (scale bar, 200 μm) and (I) special AT-rich sequence-binding protein 2 (scale bar, 200 μm). (J) The Ki67 index was 70% (scale bar, 200 μm).

more often observed in colorectal adenocarcinoma (13,14). Abundant intraluminal 'dirty' necrosis and segmental destruction of glands are characteristics of colorectal carcinoma, while squamous differentiation is a characteristic feature of endometrioid carcinoma (14). IHC staining may be essential to confirm the diagnosis of colorectal endometrioid carcinoma. PAX8 is a highly sensitive and specific marker of Müllerian epithelial tumors, and a highly sensitive epithelial marker for extragenital endometriosis (15). Furthermore, ER and PR are expressed in most uterine endometrial carcinomas (16). CDX2 and SATB2 are sensitive and specific markers of colorectal carcinoma (17,18). Therefore, PAX8, ER, PR, CDX2 and SATB2 may be useful in distinguishing colorectal adenocarcinoma from endometrioid carcinoma. In the present report, both patients exhibited positive IHC staining for PAX8, ER and PR, and negative or focal staining for CDX2 and SATB2, compatible with a diagnosis of endometroid carcinoma.

Studies have demonstrated that gene mutations, such as *CTNNB1*, *PIK3CA*, *ERBB2*, *KRAS*, *ARID1A* and *PTEN* mutations, contribute to the malignant transformation of endometriosis (7,8). In case 1, diffuse endometrioid-like adenocarcinoma was observed throughout the intestinal wall. Since no other primary tumors were found in the endometrium, cervix or bilateral adnexa, and adenomyosis was found in the uterine body adherent to the rectum, we hypothesized that this case was caused by endometriosis of the rectum. Further NGS analysis detected *BRCA1*, *KRAS*, *PIK3CA* and *PTEN* gene mutations, and MSI-high in the formalin-fixed paraffin-embedded tumor tissue, which further confirmed the diagnosis of rectal endometriosis-associated endometroid carcinoma.

Since rectal endometriosis-associated carcinoma is rare, the clinicopathological features and treatments remain to be elucidated. A total of 10 full-text articles published in English in PubMed (https://pubmed.ncbi.nlm.nih.gov/) between 1978 and 2022 that described 11 patients with endometriosis-associated rectal malignancies were identified (19-28), and the characteristics of the 11 patients reported in the literature as well as the 2 patients in the present report are listed in Table I. The median age of the patients age was 52 years (range, 38-75 years), and the main symptoms were abdominal pain and rectal or vaginal bleeding. To the best of our knowledge, the etiology of endometriosis-associated rectal malignancies remains uncertain. Among the 13 cases, 8 (61.5%) patients had undergone previous pelvic surgery, including a hysterectomy for endometriosis (19,20,22,23,25-27), myomatosis (23) or myomectomy (26,28) years ago. Therefore, pelvic surgery could increase the risk of dissemination of endometriotic

Table I. Characteristics of patients with endometriosis-associated recto-sigmoid adenocarcinoma.

First author/s, year	Age, years	Signs/symptoms	Medical history	Histology	Treatment	LN metastasis	Follow-up	(Refs.)
Present case 1	49	Pelvic mass on examination	None	Endometrioid carcinoma	TH + BSO + RR + CT	None	NR after 27 months	-
Present case 2	38	Hematochezia	None	Endometrioid carcinoma	RR	Metastasis of 5 out of 22 LNs	NR after 3 months	-
Lott *et al*, 1978	53	Rectal bleeding	TH + BSO for PE 15 years ago	Endometrioid carcinoma	RRS	None	NR after 48 months	(19)
Jones *et al*, 2002	52	Rectal bleeding	TH + BSO for rectovaginal DIE 12 years ago	Endometrioid carcinoma	RRS	None	NR after 9 months	(20)
Takeuchi *et al*, 2004	67	Backache and abdominal pain	None	Endometrioid carcinoma	RH + pelvic and para-aortic LND + RRS + CT	Para-aortic LN metastasis	ND	(21)
Kobayashi *et al*, 2010	45	Hematochezia with abdominal pain	Estrogen therapy + RO 17 years ago	Endometrioid carcinoma	Resection of bilateral ovarian tumors + RRS + appendix + CT	Metastasis of 6 out of 8 LNs	ND	(22)
García-Marín *et al*, 2015	57	Rectorrhagia	TH + BSO for PE and myomatosis 15 years ago	Poorly differentiated adenocarcinoma	Neoadjuvant CT/RT + RR+ CT	ND	NR after 84 months	(23)
Palla *et al*, 2017	75	Abdominal pain and enterorrhagia	None	Endometrioid carcinoma	RS	ND	NR after 6 months	(24)
Li *et al*, 2018	55	Rectorrhagia and abdominal pain	Excision of bilateral ovarian chocolate cysts 25 years ago	High-grade serous carcinoma	TH + BSO + RR + CT	Metastasis of 8 out of 30 LNs	RE 22 months later	(25)
Yang *et al*, 2019	57	Vaginal bleeding and abdominal pain	Caesarean section and myomectomy >20 years ago	Endometrioid carcinoma	RH + BSO + pelvic LND + RR + pelvic peritonectomy + omentectomy + appendectomy + CT	None	NR after 12 months	(26)
Li *et al*, 2022	49	Hypogastralgia and diarrhea	RSO + myomectomy for right ovarian endometriosis cyst and uterine fibroid	Endometrioid carcinoma	RH + LSO + pelvic and para-aortic LND + RR + omentectomy + appendectomy + CT	None	NR after 10 months	(27)

Table I. Continued.

First author/s, year	Age, years	Signs/symptoms	Medical history	Histology	Treatment	LN metastasis	Follow-up	(Refs.)
Ulrich *et al*, 2005 (case 1)	41	Abdominal discomfort	None	Endometrioid carcinoma	RH + BSO + pelvic LND + RR + RT	None	NR after 24 months	(28)
Ulrich *et al*, 2005 (case 2)	51	Vaginal bleeding	TH for myomas 6 years	Endometrioid carcinoma	Resection of proximal vagina + RR + BSO + pelvic LND + RT	None	RE 24 months later	(28)

BSO, bilateral salpingo-oophorectomy; CT, chemotherapy; DIE, deeply infiltrating endometriosis; LN, lymph node; LND, lymph node dissection; LSO, left salpingo-oophorectomy; ND, not described; NR, no recurrence; PE, pelvic endometriosis; RE, recurrence; RH, radical hysterectomy; RO, right oophorectomy; RR, rectal resection; RRS, resection of the recto-sigmoid colon; RS, resection of the sigmoid colon; RSO, right salpingo-oophorectomy; RT, radiotherapy; TH, total hysterectomy.

tissues and malignant transformation of endometriosis in the rectum. The other 5 patients had no medical history, including 1 patient (28) with endometriosis foci deposited in the rectovaginal septum and 1 patient (case 1) with adenomyosis in the surgical specimen. We hypothesized that the possible mechanism is the deposition and growth of endometrial tissues in the peritoneal cavity via retrograde menstruation.

There is no consensus on the therapeutic approach for endometriosis-associated colorectal malignancies, since most of the literature reported are case reports (19-28), and the main treatment is radical resection and primary cytoreductive surgery of all macroscopic detectable lesions, with adjuvant chemotherapy and radiotherapy. However, the chemotherapeutic regimens have been individualized, and the overall effectiveness of chemotherapy or radiotherapy is unknown. Among the 13 cases, all patients underwent rectal or rectosigmoid colon resection, 8 underwent total hysterectomy and salpingo-oophorectomy (19,20,22,23,25-28), and 5 underwent para-aortic and pelvic LN dissections. A total of 4 patients exhibited LN metastasis, including 1 patient with para-aortic LN metastasis and 3 patients with local LN metastasis. Furthermore, 1 patient was offered neoadjuvant chemotherapy and radiotherapy before surgery. A total of 7 patients received chemotherapy as adjuvant therapy, and 2 patients received radiotherapy as adjuvant therapy. Therefore, chemotherapy may be the first-line adjuvant treatment and, similar to treatments for endometrial cancer, the chemotherapeutic regimens typically consist of platinum and taxane (29). Furthermore, 1 of the 2 patients who received adjuvant radiotherapy (28) suffered local pelvic recurrence 24 months later, and the patient could only receive chemotherapy for recurrence. Thus, radiation therapy may be performed after surgery or for treatment of local recurrence after the primary surgery and chemotherapy. Among 9 patients reported in the literature and the 2 patients in the present report, the median follow-up duration of rectal endometriosis-associated carcinoma was 22 months (range, 3-84 months), and 2 patients exhibited recurrence after 22 and 24 months, respectively.

In conclusion, endometriosis-associated carcinoma of the rectum is a rare malignant tumor that should be distinguished from colorectal cancer so that the optimal treatment is implemented. For patients who have previously received surgery for endometriosis who present with abdominal pain and rectal bleeding, the clinical suspicion of endometriosis-associated cancer of the rectum is suggested. Surgery and pathologic examination with IHC staining, even with molecular analysis, are essential for the final diagnosis. Since there is currently no consensus on the standard therapeutic approach for rectal endometriosis-associated malignancies, primary cytoreductive surgery with resection of all macroscopic detectable lesions should be performed whenever possible. Although surgery combined with chemotherapy was performed in most patients reported in the literature, the chemotherapeutic regimens were individualized, and the exact therapeutic value of chemotherapy is unclear. Therefore, more prospective, multicenter, large-scale trials are required for the treatment of rectal endometriosis-associated cancer.

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Availability of data and materials

The data generated in the present study are not publicly available due to protection of patient privacy but may be requested from the corresponding author.

Authors' contributions

KZ and YH were involved in the conception and design of the study. MH acquired and analyzed the data. XL and RY performed the research and assessed the results. KZ drafted the manuscript and MH revised the manuscript. KZ and YH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Hubei Cancer Hospital, Tongji Medical College of Huazhong University of Science and Technology (approval no. LLHBCH2024YN-016; Wuhan, China), and written informed consent to participate in the study was obtained from each patient.

Patient consent for publication

Written informed consent was obtained from each patient to publish their details and images.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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