Synchronous rectal and endometrial cancer: A case report and literature review

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Abstract. Rectal cancer (RC) and endometrial cancer (EC) are among the most prevalent malignancies globally. However, their synchronous occurrence is rare. The current report presents a case of synchronous RC and EC, accompanied by a literature review, to provide insight into the diagnosis and management of such cases. A 54-year-old postmenopausal woman presented with intermittent vaginal bleeding and tenesmus. Diagnostic evaluations revealed synchronous endometrial adenocarcinoma involving the cervix of the cervix and rectal adenocarcinoma. Following a multidisciplinary team (MDT) discussion, an open radical resection was performed. Postoperative pathological examination confirmed the diagnoses. The patient is currently undergoing adjuvant chemotherapy and radiotherapy. A total of five follow-up assessments have indicated that the patient's recovery is satisfactory. Synchronous carcinomas are uncommon, particularly those involving both the rectum and endometrium. The etiological factors include genetic mutations, obesity and hormonal influences. Early diagnosis is critical for treatment decision-making. Radical resection remains the cornerstone of treatment, although the prognosis of synchronous carcinomas is generally poorer than that of metachronous carcinomas. The present case highlights the importance of MDT collaboration in managing complex malignancies.

Introduction

Rectal cancer (RC) is among the most common malignancies in humans, ranking third in global incidence. In China, it is the second most prevalent cancer, with a standardized incidence rate of 30.32 cases per 100,000 individuals in 2022 (1). Endometrial cancer (EC), a leading malignancy of the female genital tract, ranks second among cancers of the reproductive system, with an incidence rate of 11.25 cases per 100,000 individuals (1). Multiple primary malignant tumors (MPMTs) are defined as the occurrence of two or more independent malignancies in the same individual; they are further categorized as synchronous cancers (SCs) when diagnosed within 6 months of each other or metachronous cancers (MCs) when diagnosed >6 months apart (2). While MPMTs frequently involve the head, neck and digestive system (3), SCs affecting both the digestive and genital systems are rare. The current report presents a case of synchronous RC and EC, aiming to enhance therapeutic strategies for similar presentations.

Case report

A 54-year-old postmenopausal woman was admitted to the Department of Obstetrics and Gynaecology at Chongqing University Central Hospital (Chonqing, China) on August 2024 with a history of intermittent vaginal bleeding for 1 year, followed by the development of tenesmus 6 months after bleeding onset. The patient had entered menopause 2 years earlier and was not using exogenous estrogen replacement therapy. A colposcopic biopsy (Supplementary Methods) confirmed a diagnosis of endometrioid carcinoma (Fig. 1), with immunohistochemistry (IHC) analysis (Table SI) showing positivity for cytokeratin (CK)7 (Fig. 2A), estrogen receptor (ER) (Fig. 1C) and progesterone receptor (PR) (Fig. 1D), as well as a Ki-67 proliferation index >80% (Fig. 2B). Concurrently, fibrocolonoscopic biopsy revealed rectal adenocarcinoma (Fig. 3A), with IHC analysis (Table SI) demonstrating negativity for both ER (Fig. 3B) and PR (Fig. 3C), and positivity for CK20 (Fig. 4A) and sequence-binding protein 2 (Fig. 4B), alongside a Ki-67 proliferation index >70% (Fig. 4C). Enhanced magnetic resonance imaging (MRI) identified distinct lesions in the cervix and rectosigmoid junction (Fig. 5), confirming the presence of synchronous tumors.

Routine preoperative blood tests revealed severe anemia (hemoglobin, 52 g/l; normal hemoglobin value without pregnancy, ≥110 g/l) and hypoalbuminemia (33.1 g/l; normal albumin range, 40-55 g/l), necessitating corrective

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interventions. Following a MDT discussion, which included the Departments of Pathology, Imaging, Oncology and Hematology, Obstetrics and Gynecology, General Surgery, Urology, Blood Transfusion, Anesthesiology and Nutrition, the diagnoses were established as endometrial adenocarcinoma involving the cervix, staged as IB3 according to the International Federation of Gynecology and Obstetrics (4), and rectal adenocarcinoma, staged as T3N1M0 IIIb according to the TNM staging criteria of the American Joint Committee on Cancer (5) and Union for International Cancer Control (6). The MDT recommended two potential courses of action: i) Initial pelvic external radiotherapy, concurrent chemotherapy and vaginal brachytherapy, with imaging evaluations every 2 to 3 months to monitor tumor regression, followed by radical surgery; or ii) simultaneous radical resection of both cancers. MRI showed that the uterine lesion was mainly located in the cervix (Fig. 5), making cervical cancer a possibility. According to previous studies and guidelines, the progression-free survival (PFS) and overall survival rates associated with minimally invasive radical hysterectomy for cervical cancer are lower than those for open radical hysterectomy (7,8). Meanwhile, the rectal tumor did not affect the decision. Consequently, the patient opted for open radical resection surgery and provided signed informed consent. The operation was performed as scheduled and was smoothly completed in 260 min.

The postoperative gross specimen (Fig. 6) included a 12-cm segment of resected rectum and sigmoid colon. An adenomatous tumor, ~2 cm in diameter, encircled the rectal lumen. The uterine cavity was 10 cm deep. A lesion was identified at the junction of the endometrium and cervical mucosa, extending toward the cervix without penetrating it. Portions of the endometrium were still smooth.

Postoperative pathological examination (Supplementary Methods) revealed endometrial adenocarcinoma involving the cervix (Fig. 7B). The preoperative (Fig. 7A) and postoperative pathological results (Fig. 7B) were the same. The cancerous tissue had invaded the entire uterine cavity and extended downward to the cervical wall. Evidence of cancer thrombus formation was visible within blood vessels and lymphatic ducts; however, no invasion of nerve tissue was detected. Metastasis was found in the left and right pelvic lymph nodes (5/14 and 2/13, respectively). The rectum contained a moderately differentiated adenocarcinoma that had infiltrated the entire thickness of the rectal wall and perienteric adipose tissue, accompanied by lymph node metastasis (3/12), and was staged as T4aN1M0. The IHC results (Table SI) for the endometrioid adenocarcinoma were consistent with the preoperative biopsy. IHC analysis of the RC showed elevated expression of Postmeiotic Segregation Increased 2 (PMS2), MutL Homolog 1 (MLH1), MutS Homolog (MSH)2 and MSH6 (Fig. 8). Gene expression analysis (Table SII) using quantitative (q)PCR combined with amplification refractory mutation system (ARMS) showed that programmed death-ligand 1 (PD-L1) was expressed in <1% of tumor cells (tumor proportion score <1) and <1% of immune cells (immune cell score <1). Additionally, joint detection of *KRAS NRAS*, *BRAF* and *PIK3CA* (KNBP) genes in the RC sample identified a G12V mutation in codon 12 of exon 2 of the *KRAS* gene. No mutations were detected in the *NRAS*, *BRAF* or *PIK3CA* genes.

After an MDT discussion, the patient was scheduled to receive paclitaxel (175 mg/m^2) + carboplatin (AUC=5) + capecitabine (1,250 mg/m^2) chemotherapy and pelvic external beam radiotherapy lasting for 3 weeks. Presently, the patient has completed five cycles of chemotherapy, each lasting 3 weeks. Paclitaxel caused hair loss but no cardiotoxicity. Peripheral neuritis, nausea and mild diarrhea also occurred. A subcutaneous injection of 150 mg of granulocyte colony-stimulating factor was administered after the white blood cell count dropped to 2.1x10^9/l (normal white blood cell count, 3.5-9.5x10^9/l). With the aforementioned symptomatic treatment, the symptoms were relieved, and the patient was able to continue chemotherapy. At 3-months post-surgery, imaging results indicated a favorable response to treatment (Fig. 9) and this patient received an imaging examination every 3 months for follow-up. The patient has a favorable prognosis.

Discussion

The present report describes the case of a postmenopausal woman diagnosed with synchronous EC (ER$^+$/PR$^+$) and RC (ER$^-$/PR$^-$), meeting the Warren and Gates criteria for MPMTs (2). First, distinct IHC profiles (ER/PR discordance) and the presence of separate lesions confirmed by imaging supported the diagnosis of two separate tumors rather than metastatic disease. Moreover, both malignancies were identified within a 6-month interval, aligning with the SC classification. The patient had no known risk factors such as smoking, alcohol use, chemical or radiation exposure (9,10), circadian rhythm disruption (11), or specific factors such as infection, endocrine factors (12-14) or Lynch syndrome (LS). LS is caused by germline mutations in mismatch repair (MMR) genes, including *MLH1*, *MSH2*, *MSH6* and *PMS2*, which manifest as a loss of protein expression on IHC analysis. Obesity may be a risk factor for both EC and RC (2). The present patient was overweight, with a body mass index of 27.5 kg/m^2 and an abdominal wall fat thickness of 8 cm, which may have contributed to carcinogenesis, as reported in previous studies linking obesity to elevated EC and RC risks (2,15). Notably, while intrauterine devices (IUDs) are associated with a reduced EC risk (16), this patient's longstanding IUD use did not prevent the malignancy, suggesting that the etiologies leading to EC and the simultaneous occurrence of EC and RC may be multifactorial.

While most MPMT reports describe dual primaries, cases involving three or more malignancies are exceedingly rare (17). The present report adds to the limited body of literature on synchronous EC and RC, particularly in patients who do not have LS or a history of environmental carcinogen exposure. Studies (18,19) have emphasized the role of genetic syndromes in the synchronous development of EC and RC; for instance, the EC risk in women with LS is as high as 40 to 60% (18). The present case demonstrates that mutations in the *KRAS* gene can be detected through combined KNBP gene testing. The present case also suggests that obesity may be a potential driver for MPMTs, offering a distinct perspective on their pathogenesis.

Unopposed estrogen exposure due to progesterone deficiency is a well-established risk factor for EC in postmenopausal women (20). However, emerging evidence suggests that estrogen may also influence RC progression. Mouse models

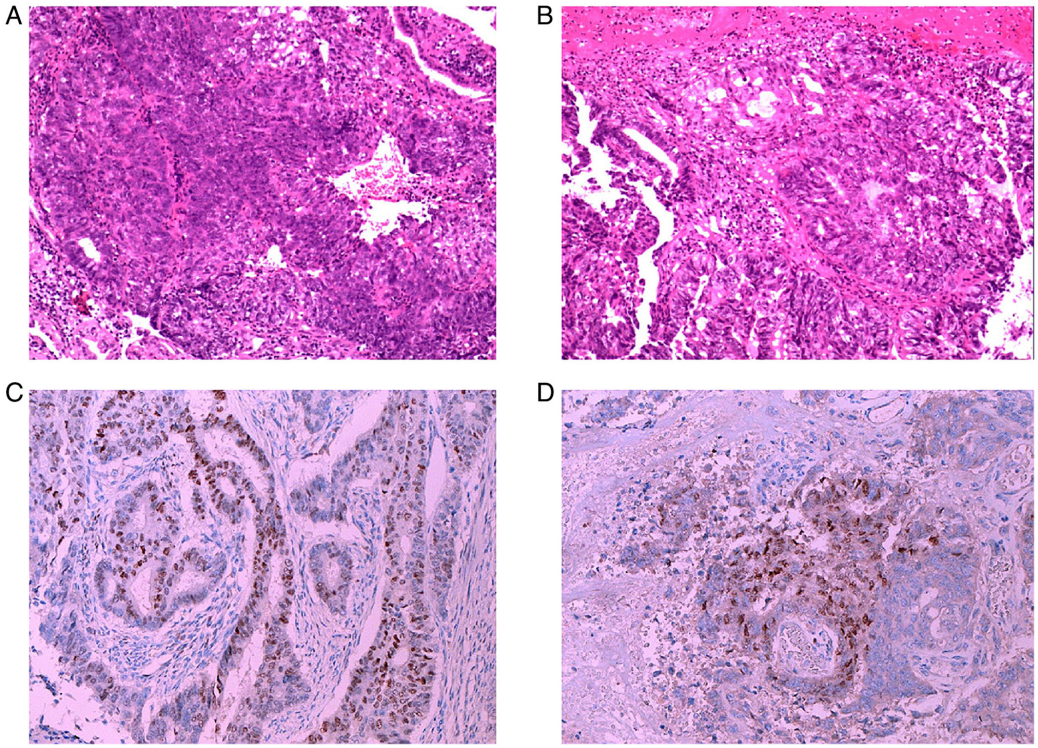

Figure 1. Pathological and immunohistochemical images of the patient's preoperative cervical biopsy. Hematoxylin and eosin staining of cervical tissue (A) core and (B) peripheral areas (x100 magnification). (C) Cervical immunohistochemistry results indicating estrogen receptor positivity (x100 magnification). (D) Cervical immunohistochemistry results indicating progesterone receptor positivity (x100 magnification).

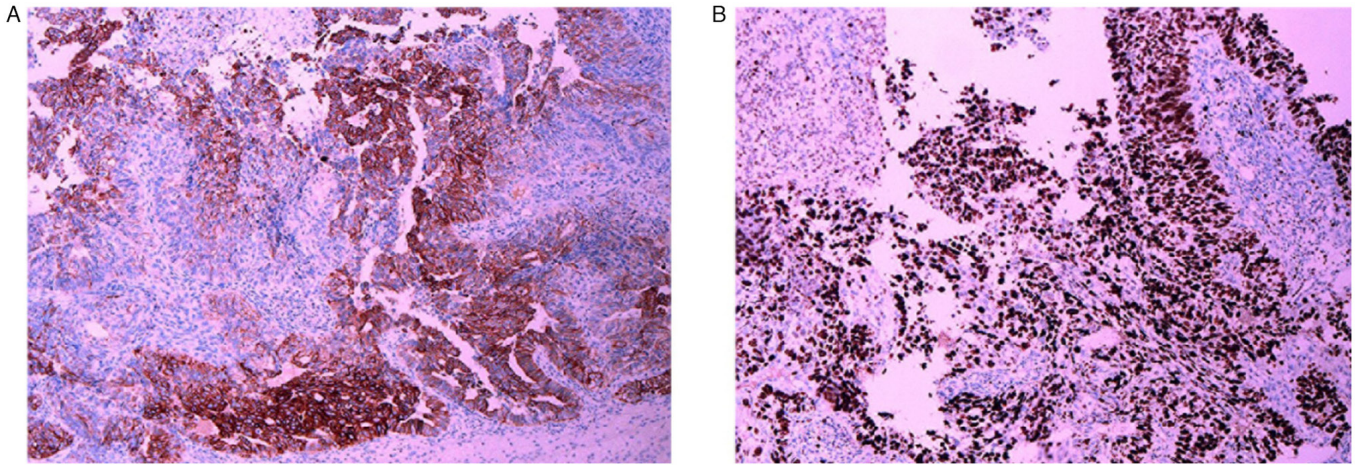

Figure 2. Pathological and immunohistochemical images of the patient's preoperative cervical biopsy. (A) Cervical immunohistochemistry results indicating cytokeratin 7 positivity (x100 magnification). (B) Cervical immunohistochemistry results indicating a Ki-67 proliferation index >80% (x200 magnification).

have demonstrated that estrogen deprivation accelerates RC growth by altering the tumor immune microenvironment (21). Although ERβ is expressed in rectal tissues and may exert a protective effect, its expression levels are low (22). However, hormone replacement therapy is not recommended for the sole purpose of preventing RC, as the literature demonstrated that there were no statistically significant associations between hormone replacement therapy use and overall RC risk (23). Furthermore, some RC cells synthesize estradiol via the G protein-coupled estrogen receptor (GPER) pathway, which may potentially induce endometrial hyperplasia (24). In the present patient, the EC was ER^+, while the RC was ER^-, suggesting that estrogen signaling is tissue-specific. Although EC proliferation was likely estrogen-driven, RC may have been influenced by paracrine or systemic estrogen derived from adipose tissue, given the patient's obese status. In other estrogen-independent pathways, human epidermal growth factor receptor 2 (HER2) status shows no significant association with the clinicopathological features of RC (25). However, the activation of HER2 signaling can lead to resistance to anti-epidermal growth factor receptor therapy in a subset of patients with RC and RAS wild-type tumors (25,26).

Adipose tissue serves as an extragonadal estrogen source through aromatase activity. Obesity increases EC risk [relative

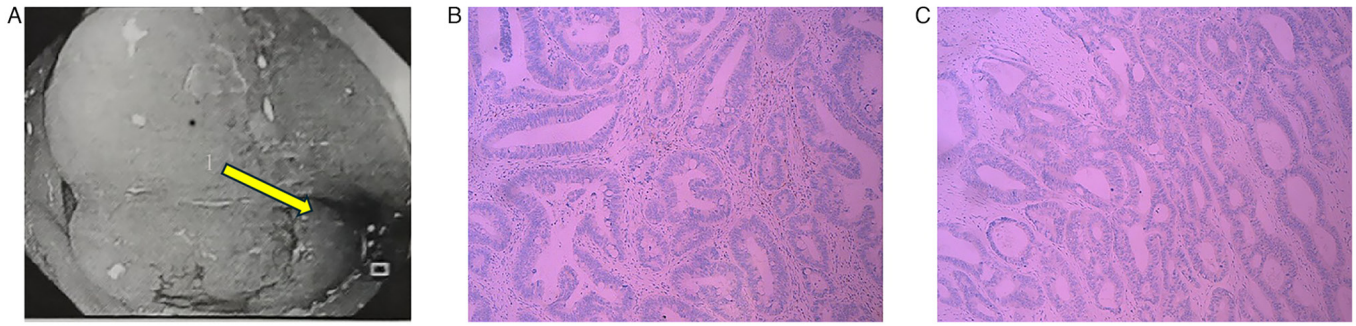

Figure 3. Fibrocolonoscopic biopsy images of the patient's preoperative rectal biopsy and preoperative rectal immunohistochemistry results. (A) Fibrocolonoscopic biopsy revealing the presence of rectal adenocarcinoma (indicated by arrow). Immunohistochemistry results indicating (B) an estrogen receptor-negative result (x100 magnification) and (C) a progesterone receptor-negative result for the rectal tumor (x100 magnification).

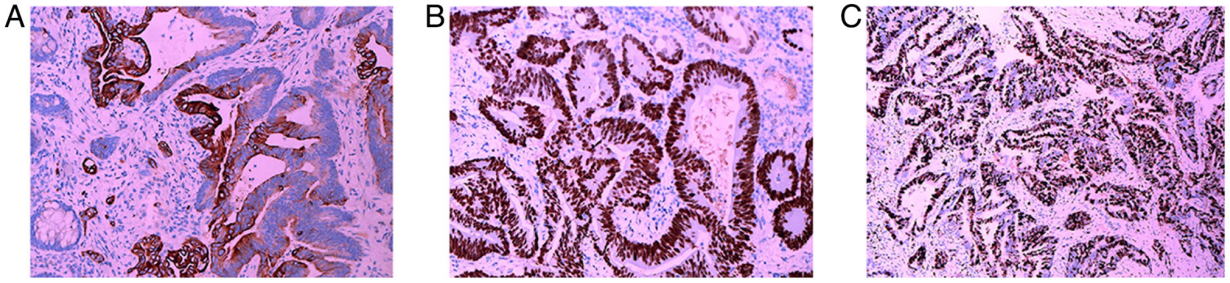

Figure 4. Preoperative rectal immunohistochemistry results. (A) Immunohistochemistry results indicating cytokeratin 20 positivity in the rectal tumor (x100 magnification). (B) Immunohistochemistry results indicating sequence-binding protein 2 positivity in the rectal tumor (x200 magnification). (C) Immunohistochemistry results indicating a Ki-67 proliferation index >70% in the rectal tumor (x100 magnification).

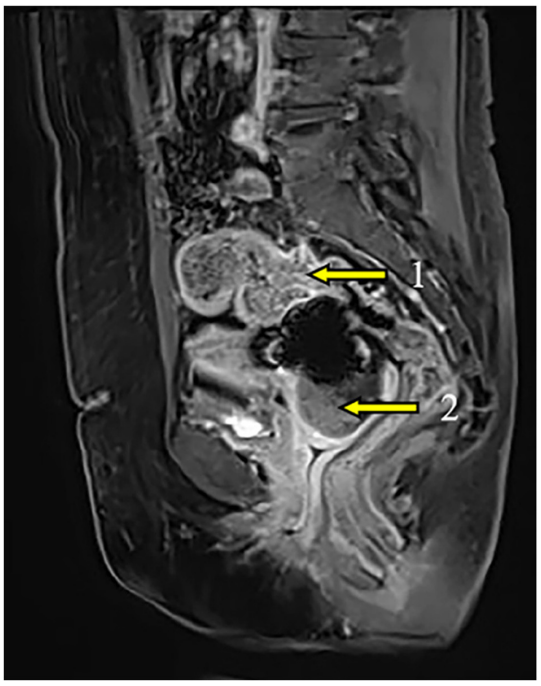

Figure 5. Enhanced pelvic magnetic resonance imaging scan. Arrow 1 and arrow 2 point to the rectal lesion and the uterine lesion, respectively.

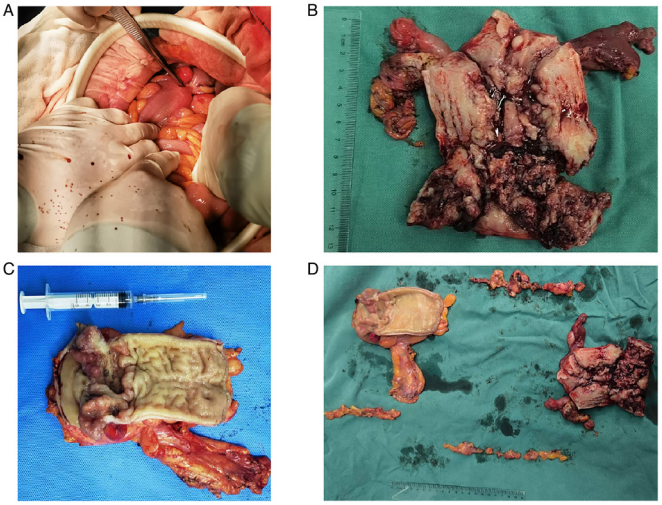

Figure 6. Postoperative gross specimen of the resected rectum and sigmoid colon, the resected uterus, uterine adnexa and lymph nodes. (A) The tumor was located at the junction of the rectum and sigmoid colon. There was no association with the uterine lesion. (B) Endometrial cancer specimen. (C) Rectal cancer specimen. (D) Rectum and uterus (split specimen: Uterine adnexa and lymph nodes).

risk (RR), 7.1] and RC risk (RR, 1.5-1.8) (15), likely via chronic inflammation, insulin resistance and adipokine dysregulation. In the present study, the patient's abdominal adiposity (8 cm fat thickness) may have created a pro-tumorigenic milieu that synergized with hormonal pathways, thereby promoting the development of synchronous malignancies.

Gene mutations can lead to the occurrence of MPMTs (27). Studies (28-30) have identified several genetic and epigenetic changes that affect synchronous RC and EC. For instance, elevated expression of the gene encoding

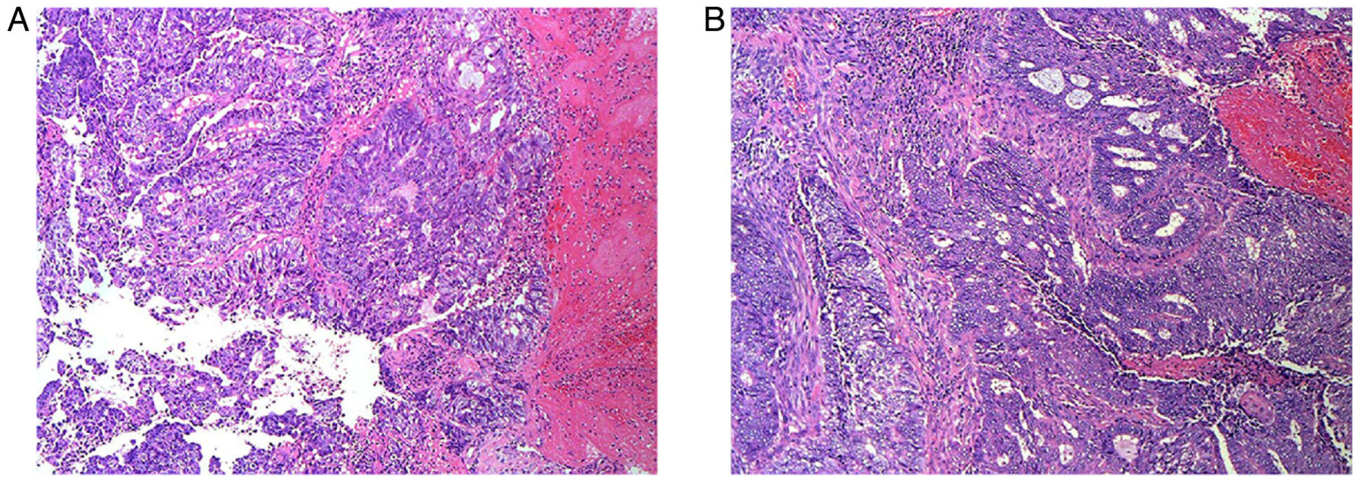

Figure 7. Preoperative and postoperative pathological examination revealing endometrioid adenocarcinoma of the cervix. (A) Hematoxylin and eosin staining of the patient's preoperative cervical biopsy (x100 magnification). (B) Hematoxylin and eosin staining of the patient's postoperative cervical biopsy (x100 magnification). The cancerous tissue invaded the entire uterine cavity and extended downward to the cervical wall.

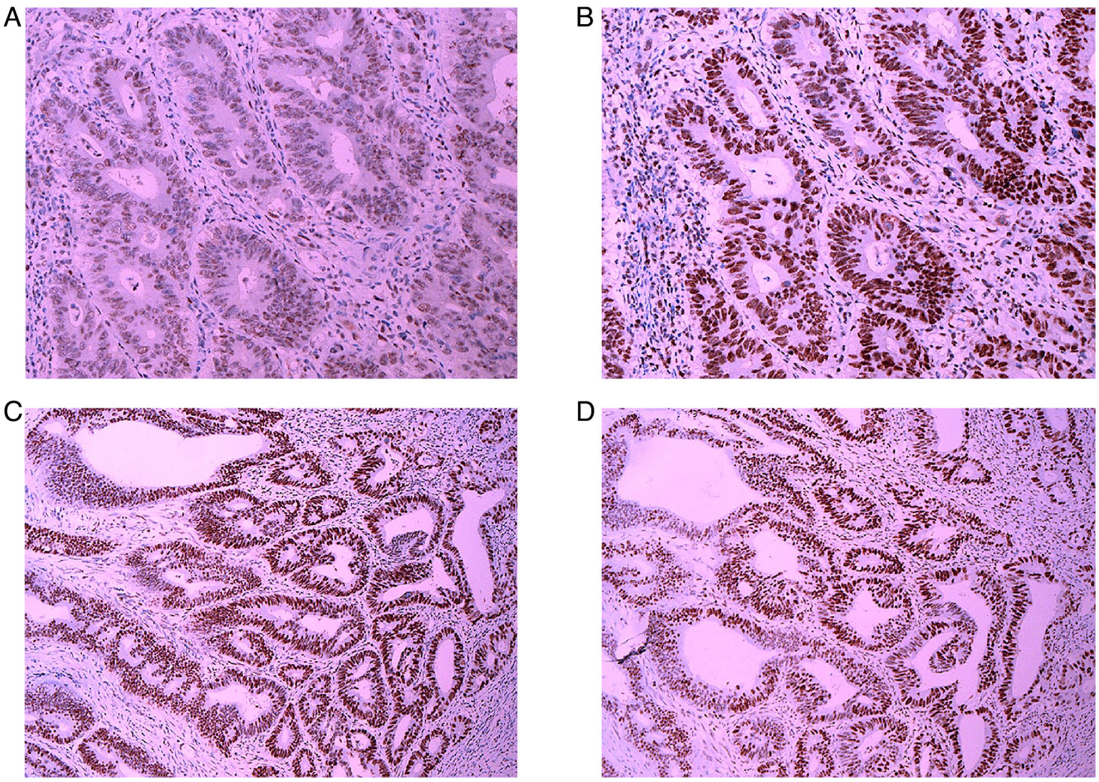

Figure 8. Postoperative immunohistochemistry. (A) Rectal postmeiotic segregation increased 2 positivity (x100 magnification). (B) Rectal MutL Homolog 1 positivity (x100 magnification). (C) Rectal MSH2 positivity (x100 magnification). (D) Rectal MSH6 positivity (x100 magnification). MSH, MutS Homolog.

tetratricopeptide repeat protein 9A in RC correlates with a poor prognosis, whereas its hypermethylation in EC predicts worse outcomes (28). Additionally, the presence of elevated *Tac2-N* transcript levels in RC and promoter hypermethylation in both RC and EC point to epigenetic dysregulation as an underlying cause of synchronous RC and EC; however, the prognostic relevance of these alterations remains unclear (29). Meanwhile, rare germline variations in the dicer 1 ribonuclease III-encoding gene may be linked to both EC and RC (30). More cases are needed to support the aforementioned genetic and epigenetic findings, and to increase the understanding of the mechanisms involved in synchronous RC and EC occurrence. In this context, expanded genetic testing, including the use of next-generation sequencing (NGS), qPCR, microsatellite instability detection, circulating tumor cell (CTC) and circulating tumor DNA (ctDNA) detection, and microarray comparative genomic hybridization, could uncover novel variants, thereby providing more accurate diagnostic tools and more precise, individualized treatment schemes for SCs.

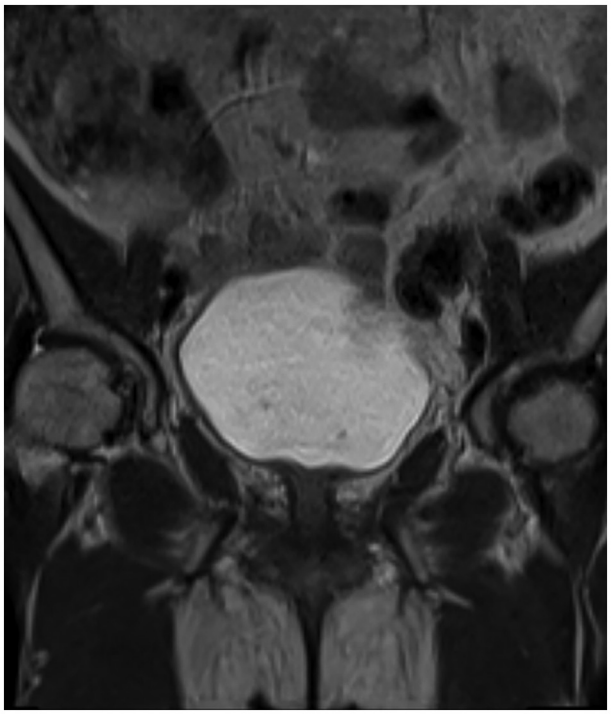

Figure 9. Magnetic resonance image captured 3 months after chemotherapy. No evidence of suspected regions of cancer was found after treatment.

The incidence of MPMTs ranges from 2.4 to 8.0% globally, with dual primaries predominating (17). In China, the incidence of MPMTs was reported to range from 0.52 to 3.66% in 2017 (31). Sex-specific patterns are notable, with prostate, colorectal and bladder cancer predominating in males, and breast cancer, colorectal cancer and EC being most common in females (32). The present case aligns with the female-predominant co-occurrence of EC/RC but is atypical given the absence of breast cancer, a frequent component of female MPMTs. This observation highlights the anatomical and hormonal heterogeneity underlying such occurrences.

SCs are under-reported relative to MCs (33), partly due to overlapping symptoms such as vaginal bleeding and tenesmus. The present patient's delayed tenesmus diagnosis stresses the need for holistic symptom assessment. Although positron emission tomography-computed tomography (PET-CT) is not routinely performed for RC, it has previously proven valuable in distinguishing synchronous lesions (34), a finding consistent with recent literature advocating the use of advanced imaging for the diagnosis of MPMTs (35). The present patient had no clinical manifestations of distant metastasis, and no distant metastasis was found on CT or MRI; therefore, the added diagnostic value of PET-CT was considered low. Furthermore, PET-CT was not used in this case due to the higher costs compared with other imaging modalities.

Although the therapeutic options for MPMTs are usually limited, radical resection remains the cornerstone of SC management (3,36). Laparoscopy combined with resection has been used for synchronous EC and rectal adenocarcinoma in women with obesity (37). Patients recover better after minimally invasive laparoscopic surgery, which is associated with less trauma. The enhanced recovery after surgery (ERAS) program can be implemented to shorten hospital stay and costs, reduce postoperative complications and improve health-related quality of life (38,39). However, the technical requirements for laparoscopy are typically high. If MPMTs cannot be radically cured by surgery alone, neoadjuvant (40) and conversion therapies can be used to reduce the tumor stage, thus providing an opportunity for radical surgery. According to European Society for Medical Oncology guidelines for RC and EC, adjuvant chemotherapy is required after RC surgery (41), whereas concurrent chemotherapy is required after EC surgery (42).

Patients with SCs generally have a worse prognosis compared with patients with MCs. The median PFS time for patients with synchronous RC and EC without defective MMR expression is 27 months, while the median PFS time of SCs linked with LS is 30 months. Thus, functional MMR proteins may confer a survival advantage. However, the prognosis of LS-associated SCs does not significantly differ from that of sporadic cases (43).

The early detection and diagnosis of MPMTs in clinical practice are of great importance for guiding treatment and predicting the prognosis of patients. The present case reinforces the necessity of thorough symptom evaluation. Secondary symptoms, such as tenesmus, must not be overlooked, particularly in high-risk groups such as postmenopausal women with obesity, as in the present case. Treatment planning was optimized through MDT discussions, emphasizing the need for institutional MDT protocols in MPMT management. Precision medicine and genetic testing may improve diagnosis and help monitor treatment responses and recurrence. While routine MMR testing excludes LS, broader panels, such as NGS and ctDNA detection, can identify targetable mutations such as those in *PI3K* and *KRAS* (44). Liquid biopsies (CTC/ctDNA) can also be used to monitor treatment responses and recurrence, although their utility in MPMTs requires validation (45). While open surgery ensured a complete resection in this case, minimally invasive surgery with ERAS should be considered in future cases to reduce morbidity (38). Although the patient's adjuvant regimen (paclitaxel/carboplatin/capecitabine + radiotherapy) adhered to guidelines, there is an evident need for studies comparing its efficacy in SCs vs. single malignancies.

Following a series of diagnostic procedures, MDT discussions and treatments, the patient in the present study experienced a smooth recovery. The patient was discharged after surgery and received regular follow-up examinations to monitor SC recurrence. Despite this positive outcome, this report has some limitations. As a single-case report, it inherently lacks generalizability due to a lack of statistical power. The absence of genetic/epigenetic profiling also limited mechanistic insights. Conclusions regarding long-term survival or recurrence are precluded by the short-term nature of the recovery data. Furthermore, the patient's incomplete genetic workup limited the understanding of the underlying mechanisms. For instance, while programmed cell death protein 1/PD-L1 negativity excludes the patient as a candidate for immunotherapy, it does not explain how the tumor evades the immune system.

Future research should prioritize four interconnected domains to advance SC management. First, large-scale genomic initiatives, building on The Cancer Genome Atlas, should employ multi-omics approaches to identify conserved

mutations and carcinogenic pathways underlying synchronous tumorigenesis. Second, the clinical validation of integrated PET-CT and liquid biopsy protocols requires the standardization of biomarker thresholds for the screening of multiple primary tumors. Third, for therapeutic optimization, comparative studies are needed to evaluate surgical outcomes (open vs. minimally invasive), along with targeted immunotherapy trials focusing on tumor microenvironment heterogeneity in PD-L1-positive subgroups. Finally, preventive strategies require mechanistic studies on adipokine-driven carcinogenesis, coupled with trials evaluating structured weight-loss interventions and GPER antagonists in genetically predisposed obese populations. This integrated approach, employing molecular profiling, diagnostic refinement, therapeutic personalization and precision prevention, could lead to the establishment of a translational framework that addresses the complexity of SCs through combined genomic, clinical and metabolic stratification, ultimately enabling tailored management for high-risk cohorts.

In conclusion, the present case of synchronous EC and RC illustrates the complex interplay among hormonal, metabolic and potential genetic factors in MPMT pathogenesis. The report also underscores the necessity for comprehensive diagnostic approaches, MDT collaboration and patient-tailored therapies. Despite existing limitations, the present findings contribute to the evolving field of precision oncology, prompting further research into SC-specific mechanisms and management frameworks for SCs.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

ZL and BZ made substantial contributions to conception and design. LP and QS acquired the data and performed its analysis and interpretation. ZL and BZ were involved in drafting the manuscript and revising it critically for important intellectual content. BZ gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final manuscript. ZL, LP, QS and BZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The patient provided written informed consent to participate. The requirement for ethical approval for this case report was exempted by Chongqing University Central Hospital (Chonqing, China).

Patient consent for publication

Written informed consent was provided by the patient for publication of the present study and the accompanying images.

Competing interests

The authors declare that they do not have any competing interests.

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