

## Case Report

# Endometrial Metastasis from Primary Rectal Carcinoma: A Case Report and Literature Review

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## Abstract

Metastases to the uterine endometrium from an extra genital site are a rare event. As in primary endometrial carcinoma, abnormal uterine bleeding is the most common symptom of such metastases. The misdiagnosis of another original cancer as a primary endometrial carcinoma should be avoided. Here we report a case of endometrial metastasis from a primary rectal carcinoma. A 63-year-old Japanese woman was admitted to our hospital with postmenopausal abnormal uterine bleeding. Endometrial cytology revealed an adenocarcinoma. Endometrial sampling showed multiple fragments of proliferative endometrial tissue mixed with irregular glands lined by atypical cells with elongated, hyperchromatic nuclei and solid sheets of neoplastic cells. The neoplastic glands were positive for CDX2 and CK20 and negative for CK7. The tumor was histologically diagnosed as metastatic endometrial carcinoma originating in the rectum. The endometrial metastasis was treated solely by tumor removal. Although rare, extra genital sites should be considered as possible primary sites of metastatic endometrial carcinoma. In addition to the clinical history, a thorough histological examination including immunohistological staining is necessary to diagnose metastatic carcinoma.

**Keywords:** Endometrial carcinoma; Rectal carcinoma; Metastases; Abnormal uterine bleeding; Immunohistochemistry

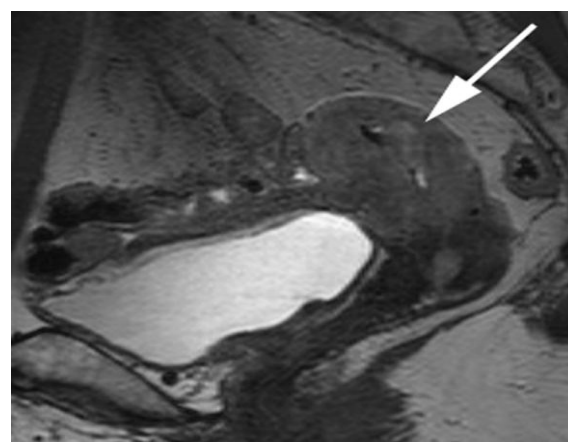
## Case Presentation

A 63-year-old postmenopausal Japanese woman (gravida1, para1) presented to our hospital with abnormal uterine bleeding, and an adenocarcinoma was detected by endometrial cytology. Five years previously she had undergone a laparoscopic low-anterior resection for primary rectal carcinoma (Stage IIIB, pT2N1M0). As adjuvant chemotherapy for the primary rectal carcinoma, she received seven cycles of combination chemotherapy with oral UFT\* (tegafur-uracil) (300 mg/m<sup>2</sup>/day) and leucovorin (UZEL) (75mg/body) for 4 wks, followed by 1 wk of rest. After this initial therapy, she had no symptomatic recurrence for over 42 mos. Four months prior to her admission to our hospital at a routine visit, a Computed Tomography (CT) scan, tumor marker analysis and colon fiberoscope confirmed that her response to the chemotherapy, according to the Response Evaluation Criteria in Solid Tumors (RECIST), was a complete response. She had a first-degree family history of pancreatic carcinoma. She had no complications or other notable history.

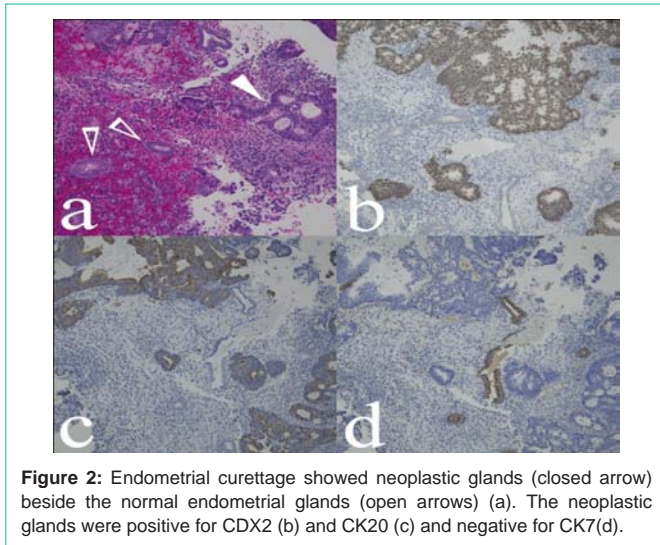
In a manual examination at her admission, a normoflexe uterus under a hen's egg size was palpated. A speculum examination showed a small amount of uterine bleeding and no remarkable findings regarding the uterine cervix. Trans vaginal ultrasonography showed endometrial hypertrophy, minimal free pelvic fluid, and no intra-pelvic mass. Magnetic resonance imaging (MRI) of the pelvis revealed a 40-mm mass lesion growing mainly from the posterior endometrium with expansive borders invading less than one-half of the myometrium; intact uterine serosa and a normal cervical canal and ovaries were observed (Figure 1). A CT scan revealed no enlarged lymph nodes or metastasis. The blood work revealed mildly elevated

CEA (7.3 ng/ml, normal range: ≤5 ng/ml). The levels of CA19-9 and CA 125 were normal. Endometrial sampling showed multiple fragments of proliferative endometrial tissue mixed with irregular glands lined by atypical cells with elongated, hyperchromatic nuclei and solid sheets of neoplastic cells (Figure 2a), which appeared similar to the resected specimen of the patient's primary rectal carcinoma. Immunohistochemically, the tumor cells were positive for CDX2 and CK20 (Figure 2b, d) and negative for CK7 (Figure 2c), ER, and PgR (data not shown). We diagnosed endometrial metastasis from the primary rectal carcinoma.

Because a whole body contrast enhance CT revealed the



**Figure 1:** Sagittal MRI (T2-weighted image) revealed a mass lesion with expansive borders infiltrating more than 50% of the posterior myometrium. Intact serosa was visible (white arrow).



**Figure 2:** Endometrial curettage showed neoplastic glands (closed arrow) beside the normal endometrial glands (open arrows) (a). The neoplastic glands were positive for CDX2 (b) and CK20 (c) and negative for CK7(d).

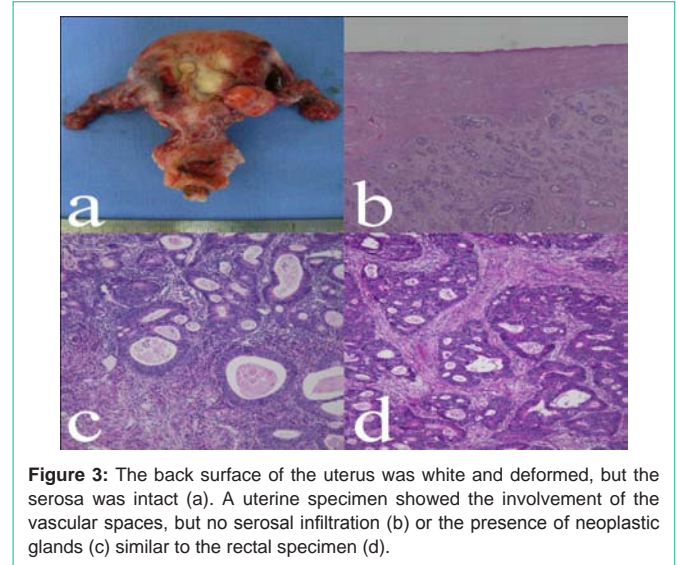
localization was solitary, we performed a total abdominal hysterectomy with a bilateral salpingo-oophorectomy. The operating time was 121 min and the blood loss was 120g. At the laparotomy, we noted minimal pelvic free fluid, a normal-size uterus with smooth serosa, and normal ovaries. Macroscopically, a 15-mm polypoid tumor had arisen from the posterior myometrium. The serosa overlying the posterior of the uterus was not infiltrated (Figure 3a). The peritoneal washing cytology was negative.

After the macroscopic examination, uterine sections were prepared for routine hematoxylin-eosin staining. The endometrial tumor showed irregular glands lined by atypical cells with elongated, hyperchromatic nuclei and a cribriform pattern, which infiltrated the myometrium but not the uterine serosa (Figure 3b). The tumor invaded vascular spaces. The tumor showed high columnar epithelium and moderate differentiation with histological features similar to those of the patient's rectal carcinoma (Figure 3c-d).

The histological examination of the tumor tissue established the diagnosis of metastatic carcinoma originating in the rectum. On postoperative day 10, the patient complained of bilateral ischial bone pain. Bone scintigraphy revealed bilateral ischial bone metastasis. She received second-line chemotherapy with seven cycles of FOLFOX4: oxaliplatin (85 mg/m<sup>2</sup> on day 1), leucovorin (400 mg/m<sup>2</sup> on day 1 and 200 mg/m<sup>2</sup> on day 2) and 5-fluorouracil (400 mg/m<sup>2</sup> as an intravenous [i. v.] bolus and 600 mg/m<sup>2</sup> as a 2-h continuous [i. v.] infusion on days 1 and 2) every 2 wks, and bevacizumab (5 mg/kg every 2 weeks starting on day 1). However, her condition did not respond to the FOLFOX4 treatment, and her ischial bone metastasis became worse during the second-line chemotherapy.

We switched her chemotherapy regimen to FOLFIRI: irinotecan (180 mg/m<sup>2</sup> on day 1), leucovorin (400 mg/m<sup>2</sup> on day 1) and 5-fluorouracil (400 mg/m<sup>2</sup> as an i.v. bolus and 1200 mg/m<sup>2</sup> as a 26-h continuous [i. v.] infusion on day 1) every 2 wks, and bevacizumab (5 mg/kg every 2 wks starting on day 1). Concurrently, she started palliative radiotherapy for the ischial bone metastasis, and the radiotherapy (39 Gy in 13 fractions) to the ischial bone relieved her pain.

Four months after the completion of the radiation radiotherapy,



**Figure 3:** The back surface of the uterus was white and deformed, but the serosa was intact (a). A uterine specimen showed the involvement of the vascular spaces, but no serosal infiltration (b) or the presence of neoplastic glands (c) similar to the rectal specimen (d).

the patient underwent a permanent colostomy for radiation-induced enterocolitis and a rectovaginal fistula. The FOLFIRI treatment resulted in a partial response according to the RECIST criteria. The patient is currently being treated with FOLFIRI and bevacizumab.

## Discussion

Metastasis of a colon adenocarcinoma (including rectal carcinoma) to the endometrium is generally considered an extremely rare event among cases in which a widely disseminated disease is not apparent. The extra genital carcinomas that can metastasize to the uterus include carcinomas of the lung, urinary bladder, kidney, and pancreas, as well as cutaneous melanoma, sarcoma and medullary thyroid carcinoma. Approximately 3% of all secondary carcinomas in the endometrium are of colonic origin [1]. The prognosis is unclear because of the rareness, but our patient had a poor prognosis because she had early postoperative recurrence and resistance to chemotherapy. Our patient had a metastasis of a colon adenocarcinoma to the endometrium hematogenously because of intact uterine serosa and vascular invasion. The primary symptom is abnormal uterine bleeding as well as a primary endometrial carcinoma, and she experienced abnormal uterine bleeding. Histologically, colon adenocarcinoma and endometrial adenocarcinoma share some morphological features, but morphological differences between the two neoplasms also exist. Low-grade endometrial carcinomas (so-called type I) are characterized by a mild nuclear grade and substantial monomorphism, whereas colonic adenocarcinomas show a higher nuclear grade and frequent mitotic figures. In our patient, we observed normal proliferative glands beside clearly neoplastic cells; no premalignant changes were present in the surrounding endometrium, and no squamous metaplasia was evident in the tumor.

High-grade endometrial carcinomas (so-called type II or non-endometrioid histologic type) are usually related to atrophic endometrium. They occasionally arise on a background of normal endometrium and are sometimes associated with intraepithelial carcinoma. For these reasons, immunohistochemistry is a valid diagnostic aid. Hernandez et al reported that the CK7-/CK20+ pattern for carcinoma cells in contrast to the CK7+/CK20- pattern

for residual endometrial epithelium strongly suggested a colonic origin of the adenocarcinoma [2]. This hypothesis was also confirmed by the nuclear positivity of carcinomatous cells for CDX2, in contrast to the nuclear negativity in residual endometrial cells [3].

In the present case, the endometrial tumor showed a higher nuclear grade, frequent mitotic figures, no premalignant changes in the surrounding endometrium, and no squamous metaplasia. We suspected a colonic origin of the adenocarcinoma, but we needed to conduct a differential diagnosis to be able to rule out the non-endometrioid histologic type. Immunohistochemistry showed the CK7-/CK20+/CDX2+ pattern in carcinoma cells in contrast to the CK7+/CK20-/CDX2- pattern in the residual endometrial epithelium. We diagnosed a colonic origin of the adenocarcinoma.

Zannoni *et al.* reported a colon adenocarcinoma metastasizing to the endometrium, presenting as abnormal uterine bleeding [4]. Unlike our patient's treatment, they used immunostaining for p53, CEA, CD34 and vimentin in addition to CK7, CK20, CDX2, ER and PgR. We did not use p53, CAE, CD34 or vimentin because the hematoxylin-eosin staining clearly showed the features of adenocarcinoma.

## Conclusion

We treated a patient with endometrial metastasis from a primary rectal carcinoma. Immunohistochemical staining provided important clues for determining the site of origin. Although metastatic endometrial carcinoma is rare, close attention should be paid to abnormal uterine bleeding, which may result from a secondary spread to the uterine endometrium from an extra genital primary carcinoma.

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