Peer Review File

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Reviewer A

The occurrence of primary ovarian cancer originating from colorectal cancer is a significant phenomenon documented in the literature. It is essential for both colorectal surgeons and OB-GYN surgeons to be aware of this possibility.

1. However, this case involved a known colon cancer patient with poor adherence to the treatment, making it likely that the ovarian mass is a metastasis of the original neoplasia. Furthermore, ovarian metastasis from colon adenocarcinoma is not uncommon.

Reply: We would like to express our sincere gratitude to the reviewers for their insightful comments and suggestions.
First, we described and added the relevant background of OM-CRC in the introduction section based on the reviewers' suggestions.
Changes in the text:

81 Women with CRC face the risk of not only developing metastatic disease in the ovaries but
82 also the possibility of a primary ovarian cancer (9). Previous research has demonstrated a
83 correlation between CRC and the emergence of primary ovarian malignancies (10). The
84 occurrence of ovarian metastases from colorectal cancer (OM-CRC) has now been widely
85 reported, with a prevalence ranging from 2.1% to 13.6% in women following surgery for
86 colorectal cancer (11). ~~The incidence of ovarian metastasis from colorectal cancer (OM-CRC)~~
87 ~~is about 5–10%.~~ In addition, OM-CRC often occurs in perimenopausal women aged over 50
88 years, and has atypical manifestations, such as abdominal pain and distension, decreased body

2. Additionally, the general description of the disease timeline needs to be rewritten.

Reply: In addition, we modified the description of the disease timeline accordingly.
Changes in the text:

As the timeline shows (*Figure S1*), we followed the case for a total of 16 months. A 48-year-old woman underwent elective surgery for CRC (the pathological result of which is unknown) at a local hospital, underwent three rounds of Folfox chemotherapy after surgery. However, the patient's subsequent need to return to work in a timely manner led to her refusal of follow-up treatment. Fourteen months after surgery, the patient began to experience vaginal bleeding that lasted for 2 months. Subsequently, after the patient signed an informed consent form, it was discovered that the results of imaging and surgical exploration showed a large solid cystic mass in the patient's right ovary, and it was determined that there was a high probability of OM-CRC.~~a 48 year old woman was admitted to a local hospital for elective surgery for CRC (the pathological result of which is unknown). After the surgery, she re attended the hospital for chemotherapy, but refused follow up treatment after three rounds of chemotherapy with Folfox. Some 14 months later, the patient suffered from vaginal bleeding for 2 months. The patient signed an informed consent form.~~

3. It is also important to note that the IHC results are not defined in the figures of the manuscript.

Reply: Finally, we identified the figures of the immunohistochemical analysis results to be able to make readers clearly understand the results and contents of Figure 4.

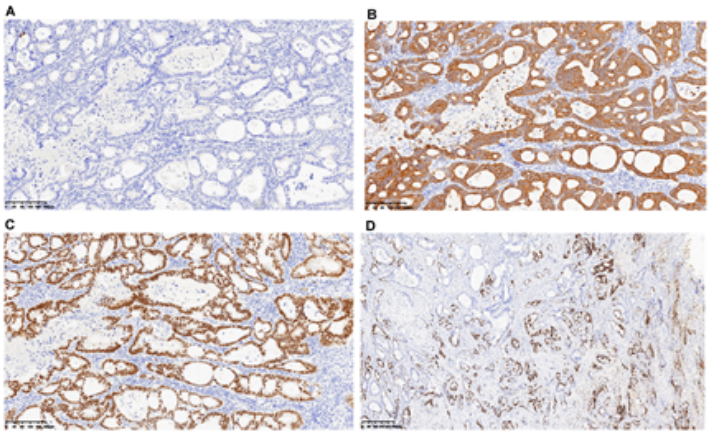


Figure 4 ~~The immunohistochemistry evaluation using Hematoxylin Eosin staining~~ Hematoxylin-eosin staining immunohistochemistry reveals extra-ovarian sources in patients. (A-D) Staining markers for $CK7^{-}$, $CK20^{+}$ (10X), $CDX2^{+}$ (10X), and $Ki\text{-}67^{+}$ (30%) (4X) of tissue samples are shown.

Reviewer B

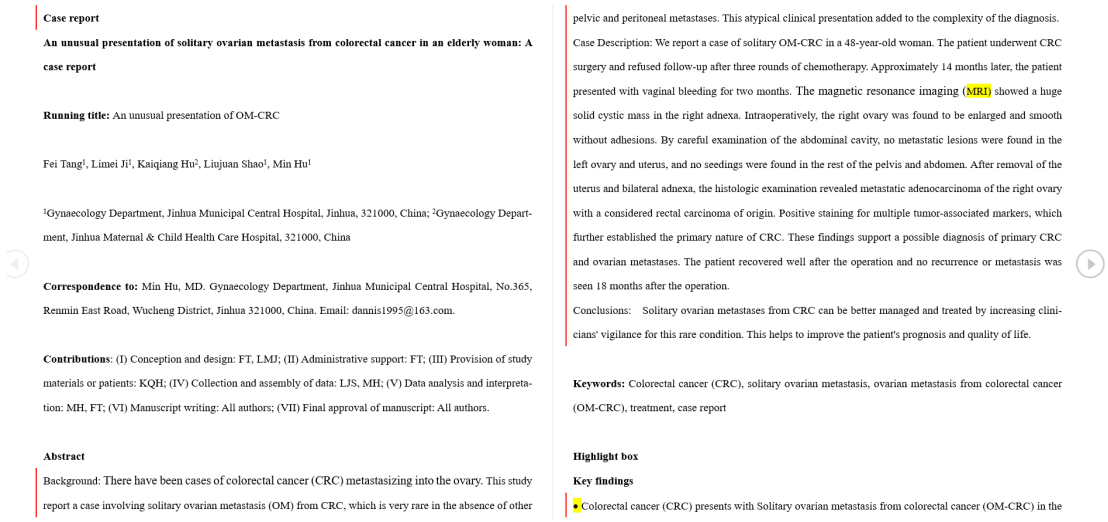
This is a case report of solitary ovarian metastasis from colorectal cancer.

1. I suggest the authors to explain the potential unique clinical contribution of this case in the background and explain why it deserved to be reported in the background of the abstract. In the case presentation of the abstract, please briefly report the short-term prognosis of elective surgery to treat of CRC and the efficacy and safety of its subsequent chemotherapy.

Please also report the follow up duration till this case report. The current conclusion in the abstract and main text is not informative and vague. The authors need to have detailed comments for the clinical implications, i.e., the early identification and effective treatment of solitary ovarian metastasis from colorectal cancer.

Reply: We sincerely thank the reviewer for their valuable feedback that we have used to improve the quality of our manuscript. First of all, we have rewritten all the contents of the abstract section of the manuscript in accordance with the reviewers' suggestions in order to make it more adequate and readable.

Changes in the text:



Case report

An unusual presentation of solitary ovarian metastasis from colorectal cancer in an elderly woman: A case report

Running title: An unusual presentation of OM-CRC

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Contributions: (I) Conception and design: FT, LMJ; (II) Administrative support: FT; (III) Provision of study materials or patients: KQH; (IV) Collection and assembly of data: LJS, MH; (V) Data analysis and interpretation: MH, FT; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Abstract

Background: There have been cases of colorectal cancer (CRC) metastasizing into the ovary. This study report a case involving solitary ovarian metastasis (OM) from CRC, which is very rare in the absence of other pelvic and peritoneal metastases. This atypical clinical presentation added to the complexity of the diagnosis.

Case Description: We report a case of solitary OM-CRC in a 48-year-old woman. The patient underwent CRC surgery and refused follow-up after three rounds of chemotherapy. Approximately 14 months later, the patient presented with vaginal bleeding for two months. The magnetic resonance imaging (MRI) showed a huge solid cystic mass in the right adnexa. Intraoperatively, the right ovary was found to be enlarged and smooth without adhesions. By careful examination of the abdominal cavity, no metastatic lesions were found in the left ovary and uterus, and no seedings were found in the rest of the pelvis and abdomen. After removal of the uterus and bilateral adnexa, the histologic examination revealed metastatic adenocarcinoma of the right ovary with a considered rectal carcinoma of origin. Positive staining for multiple tumor-associated markers, which further established the primary nature of CRC. These findings support a possible diagnosis of primary CRC and ovarian metastases. The patient recovered well after the operation and no recurrence or metastasis was seen 18 months after the operation.

Conclusions: Solitary ovarian metastases from CRC can be better managed and treated by increasing clinicians' vigilance for this rare condition. This helps to improve the patient's prognosis and quality of life.

Keywords: Colorectal cancer (CRC), solitary ovarian metastasis, ovarian metastasis from colorectal cancer (OM-CRC), treatment, case report

Highlight box

Key findings

• Colorectal cancer (CRC) presents with Solitary ovarian metastasis from colorectal cancer (OM-CRC) in the

2. Second, in the introduction, the authors need to analyze how the current case is unique, why it deserved to be reported, and what the unique clinical contribution of this case report is. Detailed comments on these information are needed.

Reply: Second, in the introductory section, we have also added a relevant description of the uniqueness of the current case and its significance for clinical care, based on your suggestions.

Changes in the text:

89 mass, and raised abdominal girth (12, 13). We report here a case of isolated ovarian metastasis
90 of CRC without other pelvic or peritoneal metastases. This is very rare in clinical practice,

91 and this solitary implies that the cancer has not yet spread widely. The importance of this
92 phenomenon lies in the need for colorectal surgeons and obstetricians and gynecologists to be
93 aware of this possibility for timely diagnosis and treatment. Therefore, early recognition and
94 aggressive surgical treatment may help to completely remove the tumor, which in turn
95 significantly improves the patient's prognosis and quality of life. ~~In view of these~~
96 ~~characteristics, OM-CRC has attracted significant attention from clinical practitioners. This~~
97 ~~article reports on a clinical case of a patient diagnosed with OM after surgery to treat CRC to~~
98 ~~extend understandings of OM-CRC at rare sites.~~

3. Third, in the case presentation, please describe the reasons for unwilling to receive chemotherapy and details of the chemotherapy. Please also report the short-term prognosis outcomes of surgical treatment and the adverse events and efficacy outcomes of chemotherapy. It is necessary to report the follow up duration till this submission.

Reply: Third, in the case presentation, we added relevant descriptions and explanations about the reasons or details of the patient's reluctance to undergo chemotherapy, the short-term prognostic results after surgical treatment, and the duration of follow-up before the report was submitted. Notably, we followed the case for a total of 16 months and observed the patient for 18 months after resection of the metastatic tumor.

Changes in the text:

"As the timeline shows (*Figure S1*), we followed the case for a total of 16 months. A 48-year-old woman underwent elective surgery for CRC (the pathological result of which is unknown) at a local hospital, underwent three rounds of Folfox chemotherapy after surgery. However, the patient's subsequent need to return to work in a timely manner led to her refusal of follow-up treatment. Fourteen months after surgery, the patient began to experience vaginal bleeding that lasted for 2 months. Subsequently, after the patient signed an informed consent form, it was discovered that the results of imaging and surgical exploration showed a large solid cystic mass in the patient's right ovary, and it was determined that there was a high probability of OM-CRC."

"Following surgery, the patient experienced a successful recovery, leading to the decision for adjuvant chemotherapy in a multidisciplinary consultation. Treatment consisted of 12 cycles of oxaliplatin, 5-Fluorouracil (5-FU), and folinic acid. To date, there have been no signs of relapse or metastasis 18 months post-operation."

4. Finally, please analyze why the patient has relative good prognosis. Please consider to cite several related papers: 1. Bodofsky S, Hong S, Botros GN, Sadimin E, Boland PM, Deek MP. Ovarian transposition and metachronous ovarian metastasis in a premenopausal colorectal carcinoma patient: a case report. J Gastrointest Oncol 2021;12(6):3141-3147. doi: 10.21037/jgo-21-558. 2. Lin L, Zeng X, Liang S, Wang Y, Dai X, Sun Y, Wu Z. Construction of a co-expression network and prediction of metastasis markers in colorectal cancer patients with liver metastasis. J Gastrointest Oncol 2022;13(5):2426-2438. doi: 10.21037/jgo-22-965. 3. Wang T, Tang L, Ouyang B, Chen X, Qi J. Clinical significance and changes to the immune microenvironment of colorectal cancer patients with liver metastasis. J Gastrointest Oncol 2023;14(1):206-212. doi: 10.21037/jgo-22-1169.

Reply: Finally, we carefully reviewed the three references provided by the reviewers and combined their main points with the discussion and introduction section in the manuscript, which in turn cited the above references. Once again, we appreciate your valuable input and will continue to work on refining our manuscripts to provide more comprehensive and in-depth insights.