Non-synchronous bilateral metastatic ovarian cancer originating from small bowel adenocarcinoma with multidisciplinary treatment: A case report

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Abstract. Primary small bowel adenocarcinoma (SBA) is a rare gastrointestinal cancer with a low incidence of ovarian metastasis. Differential diagnosis of metastatic and primary ovarian cancer is often challenging. The present study reported the case of a 45-year-old woman with jejunal adenocarcinoma who presented with right ovarian, left ovarian, abdominopelvic implant and local recurrent bowel wall metastases successively after primary tumor resection. The ovarian masses of the patient originated from SBA, which was confirmed by immunohistochemical results. Following four comprehensive evaluations by an experienced multidisciplinary team (MDT) during the disease period, the patient underwent four operations, 28 cycles of chemotherapy, 24 cycles of targeted therapy and maintenance therapy for 8 months. As of February 2023, the patient has survived for 73 months and has a high quality of life. It is suggested that when a patient with SBA presents with an ovarian mass, the differential diagnosis between metastatic ovarian cancer and primary ovarian cancer mainly relies on immunohistochemistry. After a comprehensive evaluation by an experienced MDT, surgical resection is the primary treatment for advanced SBA, thus demonstrating some benefits for patients.

Introduction

Primary small bowel cancer refers to a gastrointestinal malignant tumor originating from the duodenum, jejunum, or ileum. The most common histological types of small bowel cancer are adenocarcinomas, neuroendocrine tumors, gastrointestinal stromal tumors and lymphomas (1). The clinical manifestations of small bowel adenocarcinoma (SBA) are atypical. Of patients with SBA, ~35-36.4% have distant metastases (2-4); among whom, ~1.6% develop ovarian metastases (5). Due to their similar clinical symptoms, the differential diagnosis between metastatic ovarian cancer and primary ovarian cancer primarily relies on histopathology and immunohistochemistry. Metastasectomy can prolong the median overall survival (OS) of patients with advanced SBA to 28.6 months (6). The present study reported the case of a 45-year-old woman with jejunal adenocarcinoma who developed tumor metastasis to the right and left ovaries as well as the abdominopelvic cavity successively after surgical resection of the primary site. As of February 2023, the patient has survived for 73 months and has a high quality of life. In this case, surgery after multidisciplinary team (MDT) evaluation in advanced SBA prolonged the patient's survival. Immunohistochemistry has also been reported as a method to identify primary ovarian cancers from secondary ovarian cancers. This case is presented following the CARE reporting checklist (available at https://www.care-statement.org/checklist).

Case report

In February 2017, a 45-year-old woman who presented with a change in bowel habits and abdominal pain was suspected of SBA and consequently underwent a small bowel tumorectomy (R0 resection) at Zhangzhou Hospital (Fujian, China). No history of familial syndromes such as familial adenomatous polyposis or Lynch syndrome and no medical-surgical history of interest were reported. The patient had no history of allergies and had never smoked or drank alcohol. The cancer was located intraoperatively at the upper end of the jejunum, ~80 cm from Treitz's ligament, with a size of ~4.0x5.0 cm. The postoperative pathology finding showed that the mass was a moderately to poorly differentiated SBA, which was of the ulcerated type and ~2.5x2.5x1.0 cm in size.

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The SBA mass invaded the adipose tissue of the serous layer of the small intestine and nerve fibers, but not the regional lymph nodes (0/13 next to the mass and 0/30 next to the intestine) or the upper or lower surgical margins. According to the AJCC 8th Edition (7), the tumor diagnosis was SBA (T4N0M0 stage IIB) and the patient was treated with four cycles of 5-fluorouracil hyperthermic intraperitoneal perfusion chemotherapy and eight cycles of SOX chemotherapy after surgery.

In February 2018, during a regular review at the Affiliated Hospital of Xiamen University (Fujian, China), the result of the positron emission tomography-computed tomography (PET-CT) examination suggested an irregular mixed image on the right side of the pelvic cavity, which was ~9.36x7.47 cm in size, partly hypermetabolic and poorly demarcated from the right appendage. A hypermetabolic small nodule was observed above the lesion, which was ~1.66x1.12 cm in size. The patient was then transferred to the Sino-German Gynecology Department of the Affiliated Hospital of Southwest Medical University (Luzhou, China) due to health insurance reimbursement policies. After the MDT evaluated the condition, the patient underwent a right adnexectomy and resection of small nodules of the jejunal serosa. The left ovary was explored intraoperatively and found to be clear of metastases. As the patient was not menopausal and requested to keep the left ovary, the left ovary was not removed. The specimens were fixed in 4% formaldehyde solution for 1 h at room temperature, and then subjected to gradient ethanol dehydration, paraffin embedding and sectioning (thickness, 3-5 μm) to make paraffin sections. After heating at 60˚C, paraffin sections were dewaxed with xylene and rehydrated in a descending alcohol series. Sections were successively stained with hematoxylin stain (cat. no. BA4021; Zhuhai Baso Biotechnology Co., Ltd.) for 5-10 min and eosin stain (cat. no. BA4022; Zhuhai Baso Biotechnology Co., Ltd.) for 3-5 min at room temperature. Finally, the sections were sealed with neutral gum resin. Immunohistochemistry was performed using the MaxVision two-step method. After sections underwent dewaxing, hydration and antigen retrieval, they were added with primary antibodies and incubated at 37˚C for 2 h. The primary antibodies used were mouse anti-human CK20 monoclonal antibody reagent (cat. no. MAB-0834; Fuzhou Maixin Biotech Co., Ltd.) and rabbit anti-human CDX2 monoclonal antibody reagent (cat. no. PA207; Suzhou Abcarta Medical Technology Co., Ltd.). They did not need to be diluted. Subsequently, sections were added with secondary antibodies and incubated at 37˚C for 30 min. The secondary antibody used was MaxVision™ HRP-polymer anti-mouse/rabbit IHC kit (cat. no. KIT-5020; Fuzhou Maixin Biotech Co., Ltd.), which had a peroxidase conjugate. It did not need to be diluted. Finally, the specimens were stained with MaxVision III UItra DAB (cat. no. KIT-0038; Fuzhou Maixin Biotech Co., Ltd.) at 25˚C for 3-5 min, re-stained with hematoxylin (cat. no. BA4021; Zhuhai Baso Biotechnology Co., Ltd.) at 37˚C for 3-5 min, dehydrated at 25˚C for 20 sec, clearing with xylene and sealed with neutral gum resin. Postoperative pathological findings (Fig. 1) showed that the jejunum nodule was granulation and scar tissue. The right ovarian adenocarcinoma was ~8.5x6.0x5 cm in size and the capsule was not involved. The most significant immunophenotypic results (Fig. 1) were CK20 (+) and CDX2 (+). Combined with histomorphological analyses, immunophenotyping and the history of the disease, the tumor was diagnosed as metastatic adenocarcinoma of the right ovary originating from SBA. Postoperative chemotherapy and targeted therapy were not administered.

In July 2018, during a regular review at the Affiliated Hospital of Xiamen University (Fujian, China), the result of ultrasonography showed a mixed echogenic mass (~5.3x3.9 cm in size) in the left adnexa uteri, while CDFI showed that it was visible on the Doppler blood velocity signal in the solid region. Therefore, the patient returned to the Sino-German Gynecology Department of the Affiliated Hospital of Southwest Medical University (Fujian, China). After evaluation of the condition by the MDT, the patient underwent a left adnexectomy and a total hysterectomy. The method used for histology was the same as aforementioned. The postoperative pathological findings (Fig. 2) showed that the left ovarian mass was an intestinal-type adenocarcinoma with necrosis, which was ~6.0x5.0x3.0 cm in size, without intravascular cancer embolus or neural invasion. No immunohistochemistry examination was performed due to the left and right metastatic ovarian adenocarcinomas sharing the same histomorphology. The tumor was diagnosed as metastatic adenocarcinoma of the left ovary originating from SBA. Postoperative chemotherapy and targeted therapy were not administered.

In June 2019, because of a change in bowel habits with stomach pains, the patient returned to the gastrointestinal surgery department of the Affiliated Hospital of Southwest Medical University (Fujian, China). PET-CT (Fig. 3) showed local bowel wall thickening of the upper rectum and sigmoid colon and splenic flexure of the colon with increased glucose metabolism (SUVmax: ~4.3), which suggested the possibility of tumor lesions. Following evaluation by the MDT, a left colectomy with partial ileectomy, large omentectomy, abdominal wall implant node resection, vaginal residue resection and bilateral bladder angle implant node resection (R0 resection) was performed (Fig. 4). The method used for histology and immunohistochemistry was the same as aforementioned. The primary antibodies used were mouse anti-human CK20 monoclonal antibody reagent (cat. no. MAB-0834; Fuzhou Maixin Biotech Co. Ltd.) and mouse anti-human villin monoclonal antibody reagent (cat. no. MAB-0540; Fuzhou Maixin Biotech Co., Ltd.). They did not need to be diluted. The postoperative pathological findings (Fig. 5) showed a low differentiated adenocarcinoma of the left colon, with a size of ~6.0x6.0x2 cm and of the terminal ileum, with a size of ~3.0x3.0x2.0 cm. The most significant immunophenotypic results (Fig. 5) were CK20 (+) and villin (+). Taken together, these findings suggested that the tumor was diagnosed as metastatic adenocarcinoma of the small intestine. The patient's samples were sent to the Guangzhou Clinical Laboratory Center for high-throughput sequencing of 21 colorectal tumor genes (Table I). Postoperatively, the patient was treated with five cycles of lobaplatin hyperthermic intraperitoneal perfusion chemotherapy, 12 cycles of cetuximab with mFOLFOX6, q14d and capecitabine 1,250 mg/m^2 d1-14 as maintenance therapy for 6 months. No recurrence or metastasis of SBA was found during regular follow-ups.

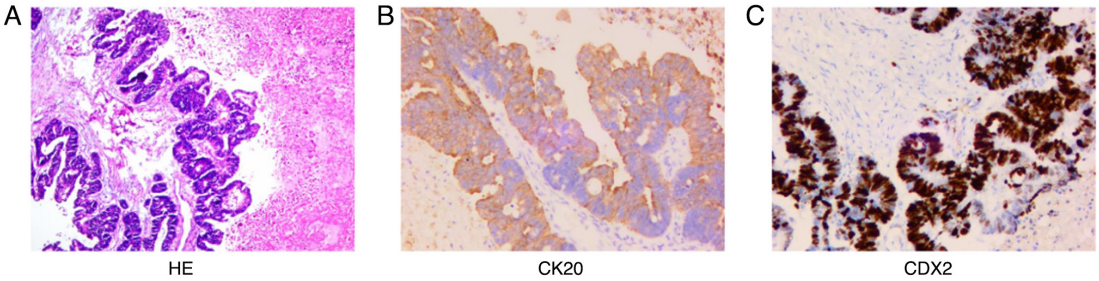

Figure 1. Histopathology and immunohistochemistry of the right ovarian mass. (A) Microscopically, hematoxylin and eosin-stained specimens revealed small bowel adenocarcinoma in the right ovary with extensive necrosis; magnification, x200. Immunohistochemical staining: positive for (B) CK20 and (C) CDX2, magnification, x200. MaxVision two-step method.

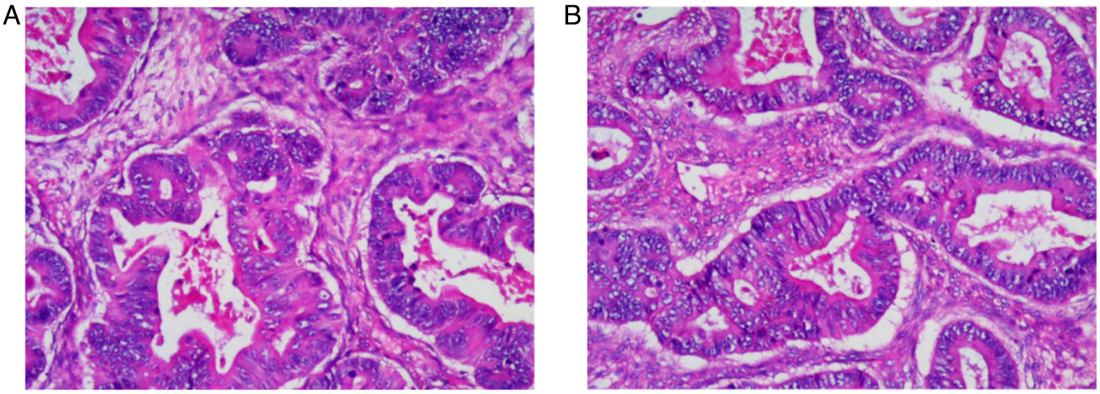

Figure 2. Histopathology of the left ovarian mass. Microscopically, hematoxylin-eosin-stained specimens revealed (A) an intestinal-type adenocarcinoma with necrosis in the left ovary and (B) histomorphology that resembles metastatic carcinoma of the left ovary; magnification, x200.

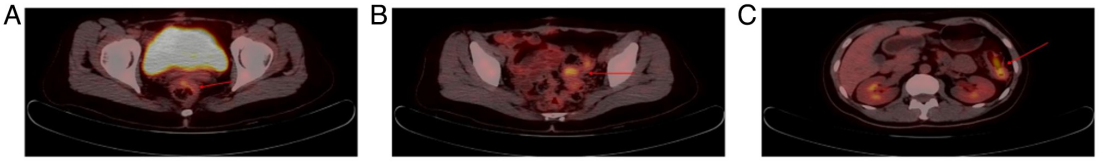

Figure 3. 18F-FDG positron emission computerized tomography. (A) Local bowel wall thickening of the upper rectum with increased glucose metabolism; (B) local bowel wall thickening of the sigmoid colon with increased glucose metabolism; and (C) local bowel wall thickening of the splenic flexure of the colon with increased glucose metabolism.

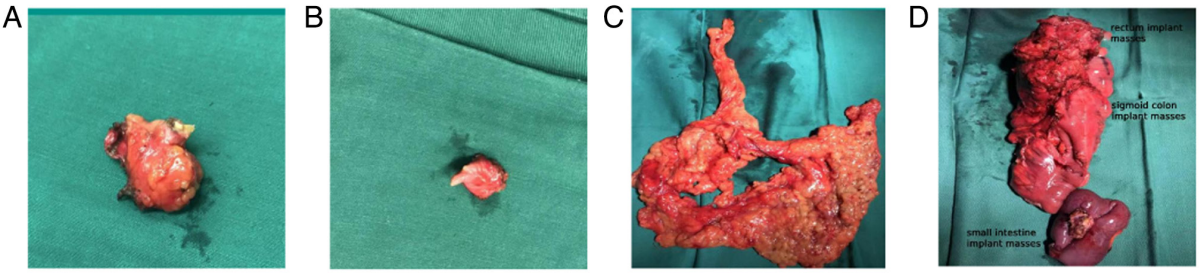

Figure 4. Resected metastatic lesions. (A) Resected left bladder mass; (B) resected right bladder mass; (C) resected large omental implant nodules; and (D) resected small intestine, rectum and sigmoid colon implant masses.

In January 2022, when the patient was reviewed at our hospital, PET-CT (Fig. 6) showed local bowel wall thickening, increased glucose metabolism on the right side of the presacral space and soft tissue nodules with slightly increased glucose metabolism on the left side of the aponeurosis area of the musculus obliquus externus abdominis; this suggested the possibility of tumor recurrence or metastasis (SUVmax: ~3.2). Following a comprehensive evaluation by the MDT, the lesion could not be precisely removed by surgery and therefore the patient was treated with eight cycles of bevacizumab plus

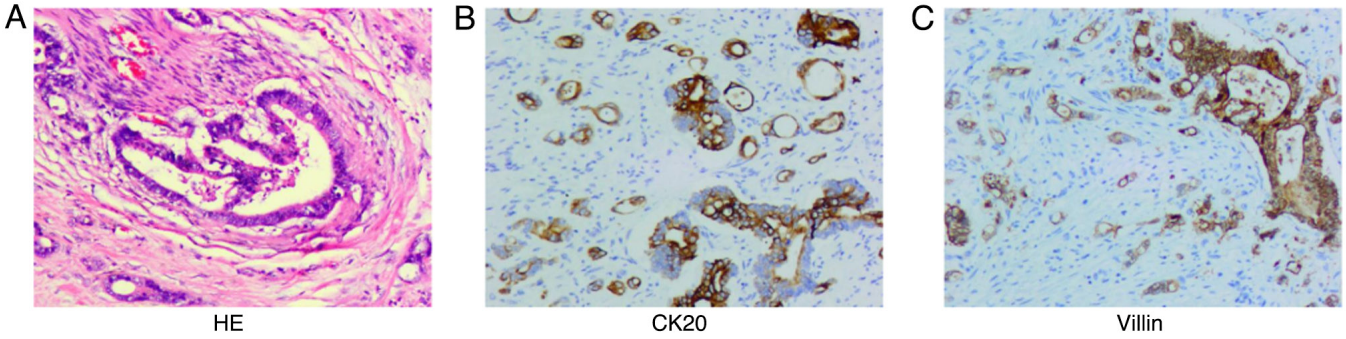

Figure 5. Histopathology and immunohistochemistry of resected metastatic lesions. (A) Microscopically, hematoxylin-eosin-stained specimens revealed a poorly differentiated adenocarcinoma found in the left colon and terminal ileum, magnification, 200x. Immunohistochemical staining: Positive for (B) CK20 and (C) villin; magnification, x200; MaxVision two-step method.

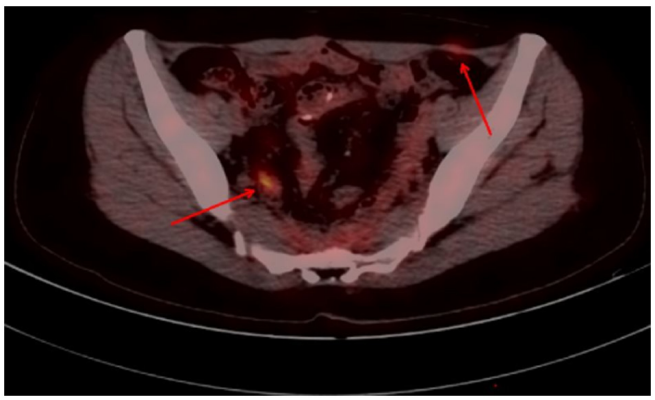

Figure 6. 18F-FDG positron emission computerized tomography. Local bowel wall thickening with increased glucose metabolism on the right side of the presacral space (red arrow on the left) and soft tissue nodules with slightly increased glucose metabolism on the left side of the aponeurosis area of the musculus obliquus externus abdominis (red arrow on the right).

mFOLFOX6, q14d. When the tumor was determined to show a partial response by PET-CT, the patient was given a regimen of bevacizumab 400 mg plus capecitabine 1.5 g q14d for four cycles of maintenance treatment (August 8, 2022). Then, the patient refused to continue medication maintenance. As of February 2023, the patient has survived for 73 months and has a high quality of life. The treatments were well tolerated by the patient. Serious or potential adverse reactions were not reported. Additionally, a timeline has been created to make it easier to follow the progress of the case (Fig. 7).

Discussion

SBA is a type of gastrointestinal cancer with a low incidence, accounting for only 3% of all gastrointestinal cancers (8), often occurring in the duodenum (52-57.9%), jejunum (15.6-29%), ileum (10-13%), or other locations in the small intestine (4-15.7%) (2-4). The onset of SBA is relatively insidious and some patients already have distant metastasis when diagnosed with SBA. Among them, ~1.6% of patients with SBA have ovarian metastasis, including left ovarian (16.7%), right ovarian (27.8%) and bilateral ovarian metastases (55.6%) (5). Therefore, the jejunal adenocarcinoma with ovarian metastasis reported here is rare.

The PubMed database was searched for literature on ovarian metastasis from small bowel cancer from January 1990 to September 2023, using the following search terms: (small bowel cancer) OR (small intestine cancer) OR (jejunum cancer) OR (duodenum cancer) OR (ileum cancer) AND (metastatic ovarian cancer). Only English-language literature were selected for documented case reports of ovarian metastases from SBA and there were 10 cases (Table II) (9-18). There are some differences between this case and cases in Table II. Of the 10 patients, 40% had bilateral ovarian metastases and 50% had right ovarian metastases. By contrast, the patient in this case developed right ovarian metastases, followed by left ovarian metastases. The patient has survived for 73 months after the primary cancer resection and 30 months without recurrence after the third metastasectomy. The patient's survival time is much longer than that of 10 patients in Table II. In the opinion of the authors, when the patient in this case presented with right ovarian, left ovarian and abdominopelvic implant successively, the three metastasectomies performed after MDT evaluations may have prolonged the survival time of the patient. There are also some similarities between this case and 10 cases in Table II. In this case, the patient also presented with SBA. The patient also developed ovarian metastases and underwent operations and adjuvant chemotherapy. Meanwhile, doctors used histopathology and immunohistochemistry to diagnose metastatic ovarian cancer.

The differential diagnosis of metastatic ovarian cancer and primary ovarian cancer is challenging. Imaging examinations such as ultrasound and PET-CT can only clarify the site of the lesion, but not the origin of the lesion. Histomorphologically, metastatic ovarian cancer may present with characteristic intraluminal necrotic debris (‘dirty necrosis’) (19); however, the use of immunohistochemistry is still needed to definitively diagnose cancer.

The immunophenotype and molecular mechanism of SBA are still unclear and the diagnosis and differential diagnosis of SBA primarily refer to the immunophenotype of colorectal neoplasms. Positive expression of CK20, CDX2 and SATB2 is found in colorectal metastatic ovarian cancer, all of which are considered sensitive markers for colorectal tumors. Primary ovarian cancer often shows the positive expression of CK7 and MUC2/5AC, while β-catenin, CA125 and CEA

Table I. High-throughput sequencing results of 21 colorectal tumor genes.

Type	Content			Result	Medication suggestions	Treatment
Genetic testing for targeted drugs	-	Genes	KRAS, NRAS, BRAF, PIK3CA, EGFR, PTEN, MET, HER2 and HRAS	No mutations	-	Recommended drugs: cetuximab, panitumumab or bevacizumab
Genetic testing for immunosuppressants	MSI testing	Microsatellite loci	BAT-25, BAT-26, D2S123, D5S346 and D17S250	MSS	Pembrolizumab and nivolumab with low sensitivity	
Genetic testing for chemotherapeutic drugs	Chemotherapeutic drugs	Platinum-based drugs	XPC, MTHFR, GSTP1 and XRCC1	-	Moderate risk of toxicity and poor efficacy	Optional drugs: fluorouracil, capecitabine or irinotecan
		Paclitaxel	ABCB1		High risk of toxicity	
		Etoposide	DYNC2H1		Good effective	
		Gemcitabine	NT5C2		Fast drug clearance	
		Capecitabine and flurouracil	DPYD, TYMS, UMPS and TP53		Low risk of toxicity and moderate efficacy	
		Cyclophosphamide	MTHFR, GSTP1 and SOD2		Low risk of toxicity and good efficacy	
		Methotrexate	MTHFR, ABCB1, SLCO1B1 and MTRR		High risk of toxicity	
		Irinotecan	UGT1A1, SEMA3C and C8orf34		Low risk of toxicity and moderate efficacy	
		Pemetrexed	MTHFR		Good effective	
		Anthracycline-based drugs	NQO1 and CBR3		High risk of toxicity	

MSI, microsatellite instability; MSS, microsatellite stability; XPC, xeroderma pigmentosum gene group C; MTHFR, 5,10-methylenetetrahydrofolate reductase; GSTP1, glutathione S-transferase pi-1; XRCC1, X-ray repair complementing defective repair in Chinese hamster cells 1; ABCB1, ATP-binding cassette, sub-family B (MDR/TAP), member 1; DYNC2H1, dynein cytoplasmic 2 heavy chain 1; NT5C2, 5'-nucleotidase, cytosolic II; DPYD, dihydropyrimidine dehydrogenase; TYMS, thymidylate synthetase; UMPS, uridine monophosphate synthetase; TP53, tumor protein p53; SOD2, superoxide dismutase 2; SLCO1B1, solute carrier organic anion transporter family, member 1B1; MTRR, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; UGT1A1, recombinant UDP glucuronosyltransferase 1 family, polypeptide A1; SEMA3C, semaphorin 3C; C8orf34, chromosome 8 open reading frame 34; NQO1, NAD(P)H quinone dehydrogenase 1; CBR3, carbonyl reductase 3.

Table II. Reported cases of ovarian metastasis from small bowel adenocarcinoma.

First author, year	Case no.	Age (years)	Primary tumor site	Side	Size (cm)	Pathology	Surgery	Adjuvant chemotherapy	Result	(Refs.)
Iijima *et al*, 2020	1	34	Jejunum	Both	3.3 (right) 1.3 (left)	Yes	ND	ND	Died 9.8 months after the initial diagnosis	(9)
Liu *et al*, 2018	1	53	Jejunum	Both	7 (right) 15 (left)	Yes	ATH + BSO + OMT + jejunectomy	ND	ND	(10)
Dunsmore and Lovell, 1998	1	12	Jejunum	Both	9x6.5x4 (right) 7x4x3.5 (left)	Yes	(1st) Jejunectomy (2nd) BSO	5-FU + leucovorin + α-interferon	Died 23 months after the initial diagnosis	(11)
Kilic and Abadi, 2000	1	53	Jejunum	Right	20x18x15	Yes	RSO + jejunectomy	No	Died 6 days after the surgery	(12)
Maekawa *et al*, 2010	1	50	Jejunum	Both	16x12x13 (right) 5x4x4 (left)	Yes	(1st) ATH + BSO + OMT + PLA (2nd) Jejunectomy	S-1	No recurrence for 24 months	(13)
Mitsushita *et al*, 2017	1	34	Jejunum	Right then Left	26x23x13 (right)	Yes	(1st) RSO (2nd) ATH + LSO + PAN + OMT + jejunectomy	Capecitabine + oxaliplatin + bevacizumab	Recurrence 26 months after the 2nd surgery	(14)
Tsuruchi *et al*, 1995	1	49	Jejunum	Right	25x18x12	Yes	ATH + BSO + OMT + PLA + PAN + jejunectomy	5-FU + cisplatin	No recurrence for 8 months	(15)
Iwata *et al*, 2020	1	59	Ileum	Right	8.5	Yes	ATH + BSO + OMT + ileectomy	Capecitabine + oxaliplatin	No recurrence for 24 months	(16)
Andresen *et al*, 2001	1	65	Ileum	Right	ND	Yes	Rightsided hemicolectomy + ileostomy	ND	Died 6 weeks after the surgery	(17)
Loke *et al*, 1997	1	44	Duodenojejunal flexure	Both	10.5 (right) 11 (left)	Yes	(1st) Small bowel resection (2nd) ATH + BSO + appendicectomy	ND	ND	(18)
Total	10	45.3[a]	Jejunum 7 Ileum 2 Duodenojejunal flexure 1	Both 5 Right 4 Right then Left 1	Maximum 1.3-26 diameter	10/10 (100%)	Surgery 9 ND 1	Performed 5 Not performed 1 ND 4		

[a]Mean age. 5-FU, 5-fluorouracil; ND, not documented; ATH, abdominal total hysterectomy; BSO, bilateral salpingo-oophorectomy; LSO, left salpingo-oophorectomy; RSO, right salpingo-oophorectomy; OMT, omentectomy; PLA, pelvic lymphadenectomy; PAN, para-aortic lymphadenectomy.

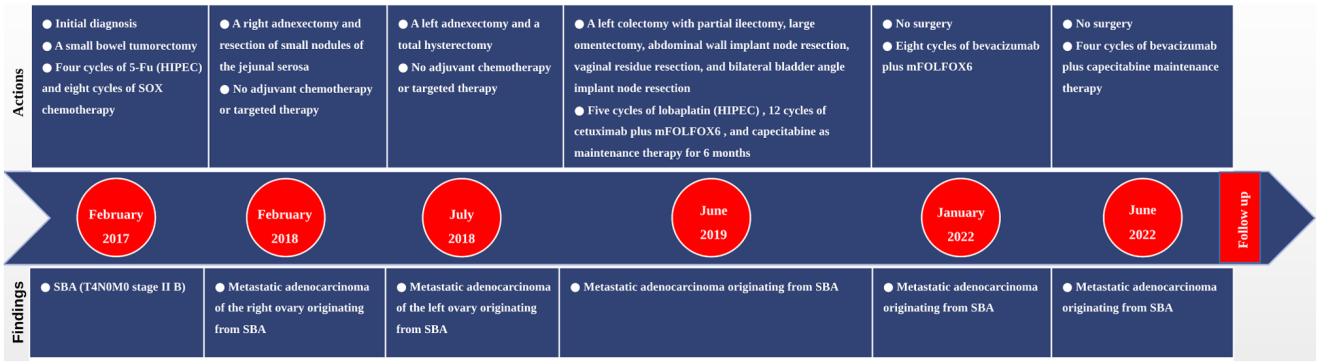

Figure 7. Timeline of the progress of the case. 5-FU, 5-fluorouracil; HIPEC, hyperthermic intraperitoneal peroperative chemotherapy; SBA, small bowel adenocarcinoma.

also have some significance in the differential diagnosis (9). In this case, when the patient developed non-synchronized bilateral ovarian metastasis, the MDT relied mainly on the histopathology and immunohistochemistry of the lesion to diagnose the disease.

Surgical resection is the primary treatment for SBA. Version 2.2022 of the NCCN guidelines for SBA (20) suggested that metastasectomy may be an option if the advanced tumor lesion is considered resectable following evaluation by an experienced MDT. Of patients with SBA, ~13% have synchronous peritoneal metastasis and a poor prognosis, with a median OS of 5.8 and 11 months for patients after primary cancer resection (21). Meanwhile, Rompteaux *et al* (6) reported a median OS of 28.6 months for patients with metastasectomy and a median recurrence-free survival (RFS) of 18.7 months. By contrast, the patient in the present study has survived for 73 months after the primary cancer resection, 61 months after the first metastasectomy, 45 months after developing abdominal implant metastases and 30 months without recurrence after the third metastasectomy. The survival time of the patient has far exceeded the median OS and RFS reported in the retrospective analysis above. This case demonstrates that appropriate surgery could prolong survival in patients with advanced SBA and that a comprehensive evaluation by the MDT is essential.

In conclusion, the jejunal adenocarcinoma with ovarian metastasis reported in the present report is rare. The differential diagnosis between metastatic ovarian cancer and primary ovarian cancer mainly relies on histopathology and immunohistochemistry. After a comprehensive evaluation by an experienced MDT, surgery can be of great benefit to terminal cancer patients with SBA. The present study also has some shortcomings. The MDT should consider the need for a hysterectomy plus bilateral adnexectomy when a patient presents with a metastatic lesion in the right ovary and chemotherapy and targeted therapy should be actively recommended after surgery. Moreover, the patient was treated with cetuximab after the resection of abdominopelvic implant metastases, which lacked a recommendation by SBA guidelines. Only a few cases of SBA have been reported in China and abroad; there is currently a lack of large prospective clinical trials and the efficacy of cetuximab is debatable.

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Availability of data and materials

The patient declined to allow the authors to upload the high-throughput sequencing data to a public database to protect privacy. The published article includes other data generated or analyzed during the study.

Authors' contributions

XH contributed substantially to data acquisition and analysis as well as writing the manuscript; YZ, AT, SD, JF and YJ contributed to the treatment of the diseases and the collection of case information; XX, DZ and LC contributed to the diagnosis of the diseases and the collection of case information; SC and XD contributed to data acquisition and analysis in addition to revising the study critically for important intellectual content; HY contributed substantially to the conception of the case study and agreed to be accountable for all of the aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; XH and HY confirmed the authenticity of all of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this manuscript and all of the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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