Synchronous ovarian metastasis from colorectal cancer: A report of two cases

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Abstract. Ovarian metastasis of colorectal cancer is relatively rare. The present study reports two cases of synchronous ovarian metastasis from colorectal cancer, which were managed by cytoreductive surgery. In case one, a 60-year-old female patient presented with a multilocular pelvic tumor and ascites. Virtual colonoscopy revealed a mass in the sigmoid colon; however, no tumor cells were identified on histological examination. Ovarian metastasis from sigmoid colon cancer was suspected and adnexectomy was subsequently performed. Histological examination of the excised tumor revealed adenocarcinoma. Immunohistochemical analysis of the resected tumor revealed positive staining for cytokeratin (CK)20 and caudal-type homeobox 2 (CDX2), and negative staining for CK7, estrogen receptor, progesterone receptor and inhibin. The immunohistological results supported the diagnosis of ovarian metastasis from sigmoid colon cancer. In case two, a 56-year-old female patient presented with a multilocular pelvic tumor and ascites. Colonoscopy identified a rectal tumor, and histological examination revealed moderately-differentiated adenocarcinoma, which was confirmed by cytological analysis of ascites. Subsequently, ovarian metastasis from rectal cancer with peritoneal dissemination was diagnosed, and left ovariectomy and transverse colostomy were performed. Histological examination of the excised tumor revealed moderately-differentiated adenocarcinoma, and immunohistochemical investigation revealed positive staining for CK20 and CDX2, but negative staining for CK7. These immunohistological results indicated ovarian metastasis from rectal cancer. Both patients recovered well and are currently undergoing regular follow-up examinations. The observations from the two cases indicate that ovarian metastases of primary colorectal cancer may present as pelvic tumors and, thus, preoperative examination of the gastrointestinal tract is required. Furthermore, even in cases of widespread colorectal cancer metastases, excision of the ovarian tumor is required to establish a histological diagnosis for the selection of appropriate treatments.

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Introduction

Common sites for synchronous metastases from colorectal cancer include the liver, lung, peritoneum, bone and brain (1). The frequency of ovarian metastasis from colorectal cancer is 1.6-6.4%, however, this type of metastasis is difficult to distinguish from primary ovarian neoplasms (2-5). Furthermore, synchronous ovarian metastasis from colorectal cancer is generally poor, and the optimal first-line treatment strategy is debatable (6,7). The present study reports two cases of synchronous ovarian metastasis from colorectal cancer that were managed by cytoreductive surgery.

Case report

Case one. A 60-year-old female patient presented to Katsuta Hospital (Katsuta, Japan) in June 2014 with progressive abdominal distension and lower abdominal pain. The following day the patient was referred to Ibaraki Medical Center, Tokyo Medical University (Ami, Japan) with a suspected diagnosis of pelvic tumor. The patient's medical history was otherwise unremarkable. Physical examination revealed lower abdominal tenderness with a palpable mass. Laboratory data revealed slight hypoalbuminemia (albumin, 3.5 g/dl; normal range, >4.0 g/dl), and carcinoembryonic antigen (CEA; 11.1 ng/ml; normal range, <5.0 ng/ml) and carbohydrate antigen (CA) 125 (743.7 U/ml; normal range, <37.0 U/ml) levels were increased. Abdominal computed tomography (CT; Somatom Sensation Cardiac; Siemens, AG, Munich, Germany) revealed a multilocular cystic pelvic mass with a solid component measuring 17 cm in diameter and an irregular mass located in the sigmoid colon (Fig. 1). Extensive ascites were also present. Virtual colonoscopy (Synapse VINCENT; Fujifilm Corporatio, Tokyo, Japan) revealed stenosis with a mass in the sigmoid colon (Fig. 2), which was confirmed by traditional colonoscopy. However, no tumor cells were identified in the biopsy specimen

(which was obtained during colonoscopy) on hematoxylin and eosin histological examination. Ovarian metastasis from sigmoid colon cancer was suspected, therefore, adnexectomy was performed in July 2014. Intraoperatively, a disseminated tumor in the pelvic cavity was identified and cytology of the ascites using Papanicolaou staining revealed clusters of atypical cells exhibiting anisokaryosis, hyperchromasia and enlarged nuclei, yielding a diagnosis of adenocarcinoma. The resected tumor measured 17x14x8 cm, and macroscopic examination revealed multicystic walls and septa composed of solid and necrotic components (Fig. 3A). Hematoxylin and eosin histological examination of the formalin-fixed and paraffin-embedded excised tumor revealed moderately-differentiated adenocarcinoma forming in the septa with infiltration of the cystic wall (Fig. 3B). Immunohistochemical analysis of the tumor revealed positive staining for cytokeratin (CK)20 (mouse monoclonal; dilution 1:50; M7019; Dako, Glostrup Denmark) and caudal-type homeobox 2 (CDX2; rabbit monoclonal; dilution 1:1; 418011; Nichirei Biosciences, Inc., Tokyo, Japan), and negative staining for CK7 (mouse monoclonal; dilution 1:100; M7018; Dako), estrogen receptor (rabbit monoclonal; dilution 1:1; 107925; Roche Diagnostics, Basel, Switzerland), progesterone receptor (rabbit monoclonal; dilution 1:1; 109431; Roche Diagnostics) and inhibin (mouse monoclonal; dilution 1:50; M3609; Dako) (Fig. 4). These immunohistological results supported the diagnosis of ovarian metastasis originating from colon cancer of the sigmoid. Recovery was uneventful and the patient was discharged 12 days after surgery. From October 2014, the patient was administered modified FOLFOX6 [oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2) and fluorouracil (5-FU; 400 mg/m^2) intravenous infusion on day 1, followed by 2,400 mg/m^2 intravenous infusion of 5-FU over 46 h every 2 weeks] plus anti-vascular endothelial growth factor monoclonal antibody (bevacizumab; 5 mg/kg every 2 weeks) for primary sigmoid colon cancer with peritoneal dissemination. At present, the patient is regularly followed up every 2 weeks at the outpatient clinic of Ibaraki Medical Center, Tokyo Medical University, and her condition remains stable at the time of writing the present manuscript, in April 2016.

Case two. A 56-year-old female patient presented to Ryugasaki Saiseikai Hospital (Ryugasaki, Japan) in September 2014 with progressive abdominal distension. The following day the patient was referred to Ibaraki Medical Center, Tokyo Medical University, with a suspected ovarian tumor. The patient's medical history was otherwise unremarkable. Physical examination revealed abdominal distention with fluctuation, indicating abundant ascites. Laboratory data revealed increased lactate dehydrogenase (2,473 IU/l, normal range, 120-240 IU/l), CEA (93.9 ng/ml) and CA 125 (274.4 U/ml) levels. Abdominal CT (Somatom Sensation Cardiac) revealed a multilocular cystic pelvic mass with a solid component, measuring 12 cm in diameter, and ascites (Fig. 5). Cytology of abdominocentesis fluid using Papanicolau staining revealed clusters of atypical cells exhibiting anisokaryosis, hyperchromasia and enlarged nuclei, thus confirming adenocarcinoma, while colonoscopy revealed an elevated tumor with a central depression in the rectum, which did not involve the tumor. Biopsy of the tumor specimen

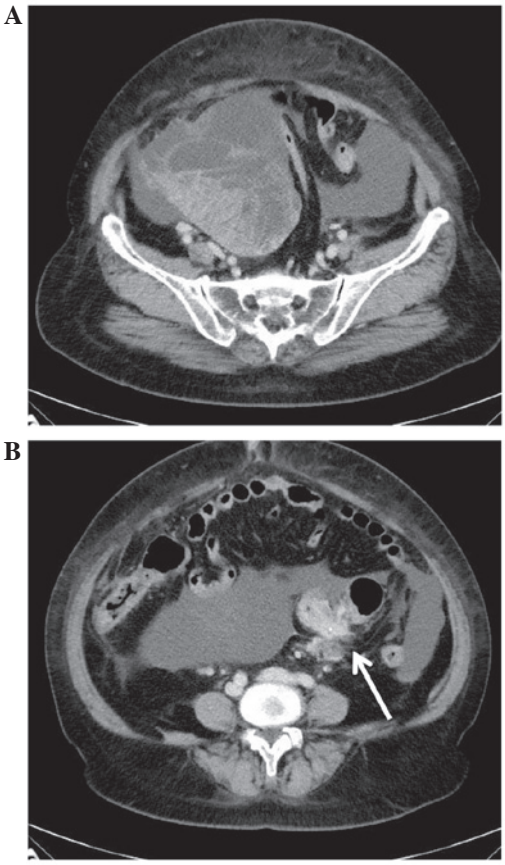

Figure 1. Case one. Abdominal enhanced computed tomography demonstrating (A) a multilocular cystic mass in the pelvic space and (B) an irregular mass located in the sigmoid colon (arrow).

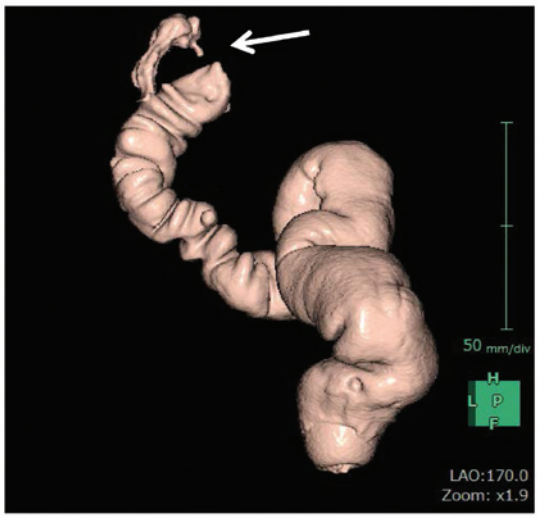

Figure 2. Case one. Virtual colonoscopy revealing stenosis with a mass in the sigmoid colon (arrow).

indicated moderately-differentiated adenocarcinoma. A diagnosis of ovarian metastasis from rectal carcinoma with peritoneal dissemination was established; therefore, left ovariectomy and transverse colostomy were performed in November 2014. The resected tumor measured 12x11x8 cm, and macroscopic examination revealed multicystic walls and septa composed of a solid component with hemorrhage

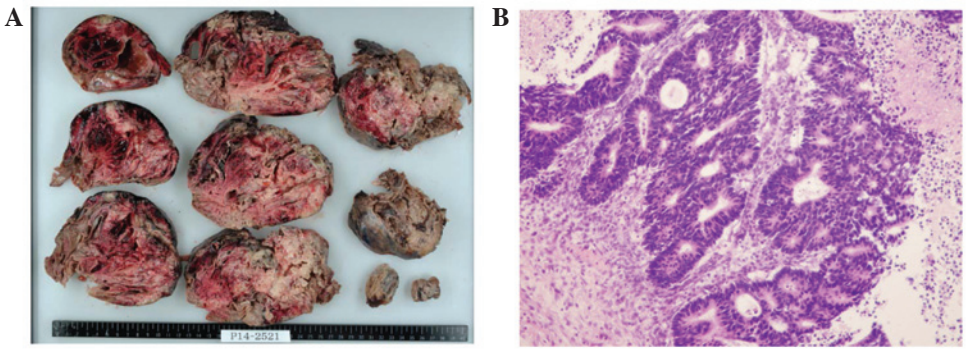

Figure 3. Case one. Macroscopic examination and histological analysis of the excised tumor specimen. (A) A multilocular cystic tumor, measuring 17x14x8 cm with multicystic walls and septa, containing solid and necrotic components was identified. (B) Histological staining revealing moderately-differentiated adenocarcinoma forming in the septa with infiltration of the cystic wall (stain, hematoxylin and eosin; magnification, x100).

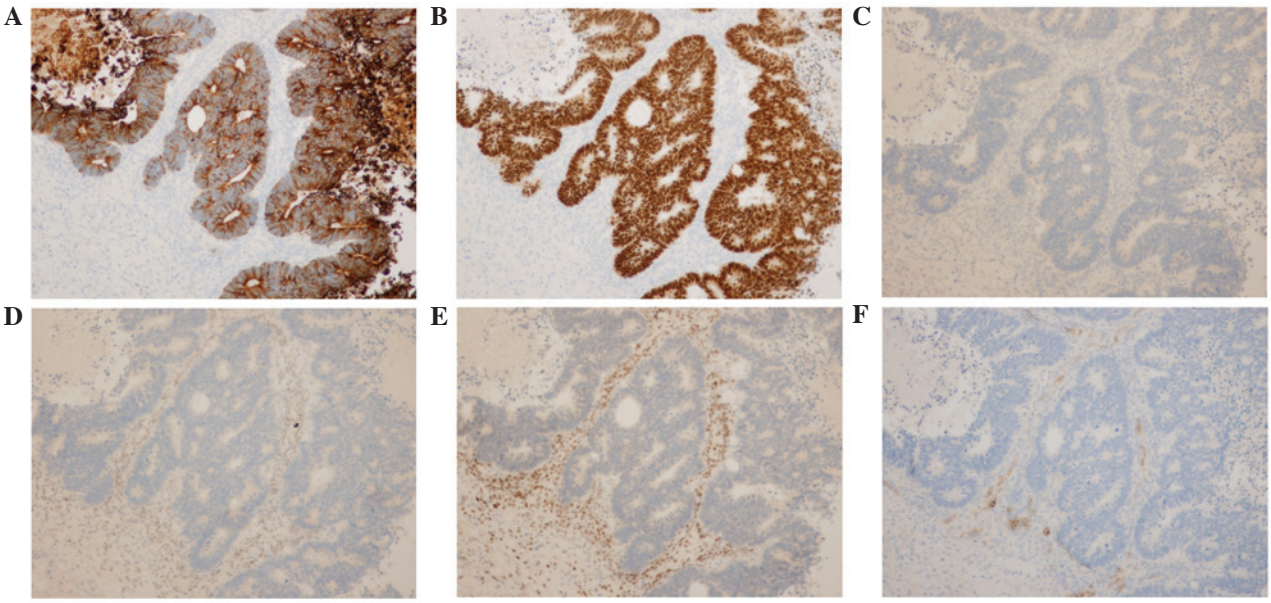

Figure 4. Case one. Immunohistochemical staining of the excised tumor revealed positive staining for (A) cytokeratin (CK)20 and (B) caudal-type homeobox 2, and negative staining for (C) CK7, (D) estrogen receptor, (E) progesterone receptor and (F) inhibin (magnification, x100).

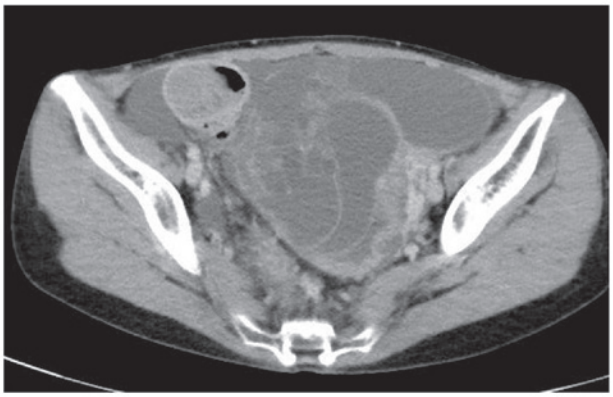

Figure 5. Case two. Abdominal enhanced computed tomography demonstrating a multilocular cystic mass and ascites in the pelvic space.

Figure 6. Case two. Macroscopic examination of the excised specimen revealing a multilocular cystic tumor measuring 12x11x8 cm, with multicystic walls and septa, composed of solid and necrotic components.

(Fig. 6). Hematoxylin and eosin histological examination of the formalin-fixed and paraffin-embedded excised tumor revealed moderately-differentiated adenocarcinoma (Fig. 7A), and immunohistochemical analysis identified positive staining for CK20 and CDX2, and negative staining for CK7 (Fig. 7B-D). These immunohistological results confirmed the diagnosis

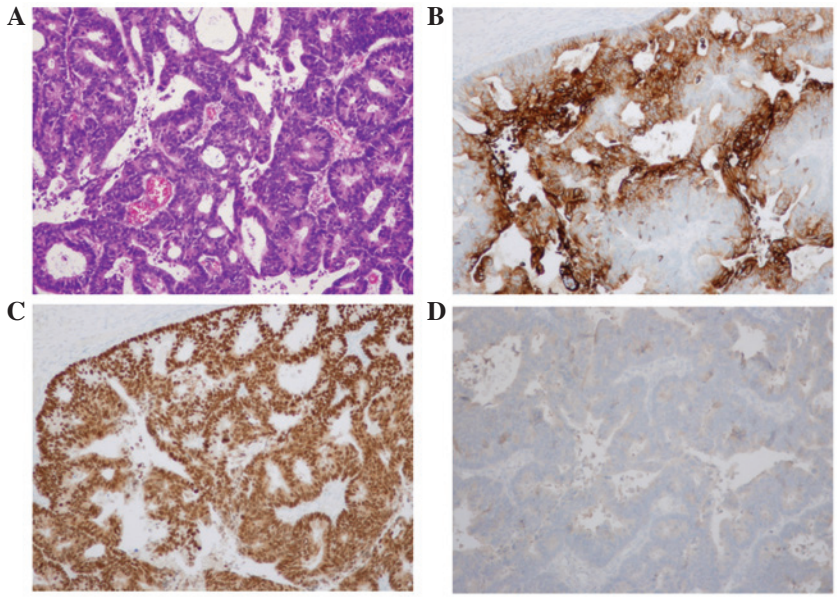

Figure 7. Case two. (A) Histological analysis of the excised tumor revealing moderately-differentiated adenocarcinoma forming in the cystic walls and septa (stain, hematoxylin and eosin; magnification, x100). Immunohistochemical staining of the excised tumor revealing positive staining for (B) cytokeratin 20 and (C) caudal-type homeobox 2 and (D) negative staining for CK7.

of ovarian metastasis from rectal cancer. Recovery was uneventful and the patient was discharged 13 days postoperatively. From December 2014, the patient was administered modified FOLFOX plus bevacizumab for primary rectal cancer with peritoneal dissemination. At present, the patient is undergoing regular follow-up examinations every 2 weeks at the outpatient clinic of Ibaraki Medical Center, Tokyo Medical University, and her condition was stable at the time of writing.

Discussion

Metastatic ovarian tumors account for ~21.5% of all malignant ovarian tumors and 3.7-7.4% of the cases metastasize from colorectal cancer (8-10). However, the process by which colorectal cancer metastasizes to the ovary remains unclear. Graffner *et al* (9) and Birnkrant *et al* (11) have postulated that, as there is no lymph flow between the colon and the ovaries, both hematogenous and disseminated peritoneal metastasis present possible metastatic pathways. In the two present cases, peritoneal dissemination was confirmed intraoperatively. Clinically, it is difficult to distinguish between primary and metastatic cancer of the ovary, which results in diagnostic problems for clinicians, radiologists and pathologists. Regarding radiological examination, Cho and Gold (12) reported that a mixed cystic and solid ovarian mass observed by CT scan must be regarded as a metastatic tumor in patients with a history of colonic or gastric carcinoma. In the present cases, the ovarian tumor presented as a multilocular cystic pelvic mass with a solid component. In addition, the patient in case two was preoperatively diagnosed with advanced rectal carcinoma with peritoneal dissemination. Regarding histological examination, Lee and Young (2) reported that bilaterality, microscopic surface involvement of epithelial cells and an infiltrative pattern of stromal invasion were strong indicators of metastatic ovarian carcinoma. In case one, histological examination of the sigmoid colon tumor did not reveal carcinoma cells, although virtual colonoscopy identified stenosis with a mass. However, resection of the ovarian tumor revealed moderately-differentiated adenocarcinoma, and immunohistochemical analysis of the tumor cells revealed positive staining for CK20 and CDX2, and negative staining for CK7, estrogen receptor, progesterone receptor and inhibin. In the majority of cases, primary ovarian neoplasms exhibit positive staining for CK7 and negative staining for CK20. By contrast, colorectal carcinomas most frequently exhibit negative staining for CK7 and positive staining for CK20 (13,14). *CDX2* is a homeobox gene encoding the CDX2 protein, which serves as a transcription factor that is expressed in the nuclei of intestinal epithelial cells (15). CDX2 is a useful marker for adenocarcinoma of the gastrointestinal tract, and for distinguishing between primary and metastatic carcinomas of the ovary (16-18). According to immunohistological examination, the results of case one support the diagnosis of metastatic ovarian carcinoma from sigmoid colon carcinoma.

The optimal first-line treatment strategy for synchronous ovarian metastasis from colorectal cancer remains controversial. The Japanese guidelines for colorectal cancer treatment recommend surgery for metastatic lesions if the primary colorectal and metastatic lesions are completely resectable, and if the patient is able to tolerate resection of the metastatic lesions (1). In the present two cases, tumor dissemination was intraoperatively detected in the pelvic cavity, however, complete resection was not possible for all lesions. Only excision of ovarian metastases was performed for the following reasons: i) Patients presented with progressive abdominal distension and excision of ovarian metastasis may have alleviated the symptoms (19); ii) it is difficult to distinguish between primary and metastatic cancer of the ovary by diagnostic imaging alone, thus, a definitive histological diagnosis was required to identify appropriate treatment, particularly in

case one (preoperative histological examination of the sigmoid colon tumor did not lead to a diagnosis); and iii) cytoreductive surgery is associated with improvement of overall survival in patients with widespread metastases of colorectal cancer (20). A number of cases of synchronous ovarian metastasis from colorectal cancer also exhibit distant metastasis and/or peritoneal dissemination (6,7), therefore, the prognosis is generally poor. Jiang *et al* (21) reported that the median survival in patients with residual disease after metastasectomy is 10 months. However, as a result of marked improvement in systemic chemotherapy treatment for advanced colorectal cancer, it has been estimated that the median survival time of the patients may improve to >20 months following the administration of FOLFOX or 5-FU, leucovorin and irinotecan combination chemotherapy plus bevacizumab or anti-epidermal growth factor receptor monoclonal antibody (22-25).

In conclusion, ovarian metastases from primary colorectal cancer may present as pelvic tumors, thus, preoperative examination of the gastrointestinal tract and excision of the ovarian tumor are required to establish a histological diagnosis for the selection of appropriate treatment strategies.

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