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**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 83354

**Manuscript Type:** CASE REPORT

**Successful treatment of breast metastasis from primary transverse colon cancer: A case report**

Treatment of breast metastasis from colon cancer

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## **Abstract**

### **BACKGROUND**

The incidence of colon cancer is increasing worldwide. Treatment includes surgery and surgery combined with chemotherapy and radiotherapy, but the median survival rate is still poor. Colon cancer most commonly metastasizes to lymph nodes, lungs, liver, [peritoneum](#), and brain, but breast metastasis is rare. There is no agreement on treatment. We found breast metastasis after four cycles of chemotherapy following transverse colectomy. Postoperative chemotherapy and targeted therapy are effective for treatment of breast metastasis of colon cancer.

### **CASE SUMMARY**

A 23-year-old woman was admitted to our hospital for further treatment with a history of acute abdominal pain, nausea and vomiting. Her physical examination and computed tomography (CT) revealed an abdominal tumor. Transverse colectomy was successfully performed. Histopathological examination revealed that the tumor was a mucosecretory adenocarcinoma with signet ring cells. The patient inadvertently found a mass in the outer upper quadrant of the right breast after four cycles of XELOX chemotherapy (oxaliplatin 130 mg/m<sup>2</sup>, d1, intravenous (iv) drip for 2 h; capecitabine 1000 mg/m<sup>2</sup>, po, bid, d1–d14). After discussion with the patient, we performed a lumpectomy and frozen biopsy. The latter revealed that the breast tumor was intestinal metastasis. Genetic testing showed wild-type *RAS* and *BRAF*. So we replaced the original chemotherapy with FOLFIRI [irinotecan 180 mg/m<sup>2</sup>, d1, iv drip for 3–90 min; leucovorin 400 mg/m<sup>2</sup>, d1, iv drip for 2 h; 5-fluorouracil (5-FU) 400 mg/m<sup>2</sup>, d1 and 5-FU 1200 mg/(m<sup>2</sup> d) × 2 d, continuous iv drip for 46–48 h] + cetuximab (500 mg/m<sup>2</sup>, d1, iv drip for 2 h). Serum tumor markers level returned to normal after several treatment cycles, and there was no evidence of tumor recurrence or metastasis.

### **CONCLUSION**

Breast metastasis from colon cancer is rare. Radical breast surgery should be avoided unless needed for palliation. Chemotherapy combined with targeted therapy should be the first choice.

**Key Words:** Colon cancer; Breast metastasis; Tumor markers; FOLFIRI; Cetuximab; Prognosis; Case report

Jiao X, Xing F, Zhai M, Sun P. Successful treatment of breast metastasis from primary transverse colon cancer: A case report. *World J Clin Cases* 2023; In press

**Core Tip:** Breast metastasis from colon cancer is rare. The prognosis is poor and conservative treatment is mainly adopted. We present a rare case of breast metastasis from colon cancer in a young patient who received chemotherapy (FOLFIRI) combined with targeted therapy (cetuximab) after undergoing transverse colectomy and lumpectomy. There was no recurrence or metastasis during the 16-mo follow-up after lumpectomy, and the treatment effect was good.

## INTRODUCTION

Colon cancer<sup>5</sup> is the third most common type of cancer worldwide and the fourth leading cause of cancer mortality<sup>[1]</sup>. Approximately 25% of patients with colon cancer have been diagnosed as stage IV cancer, and<sup>9</sup> the five-year survival rate for patients with stage IV tumors is less than 10%<sup>[2]</sup>. The metastatic pathways of colon cancer are similar to those of other malignancies, and include lymphatic, hematogenous and distant metastases. Breast metastasis is rare, with an incidence of 0.5%–3%<sup>[3]</sup>, and is especially rare from colon carcinoma. Since the first case in 1976<sup>[4]</sup>, only no more than 30 cases have been reported<sup>[5,6]</sup>. Tien-Chan Hsieh et al<sup>[7]</sup> summarized 45 cases that were previously reported, and we found that about 60 studies have reported this rare case so far by searching literatures<sup>2</sup> in the Reference Citation Analysis (RCA) database, PubMed and Embase. Prognosis is poor because it is usually indicative of

disseminated disease. It is important to distinguish breast metastasis from primary breast carcinoma in order to plan the most suitable treatment<sup>[8]</sup>. Treatment experience is uncomfortable due to the rarity of the metastatic pattern. We report a new case of breast metastasis from colon carcinoma.

## **CASE PRESENTATION**

### ***Chief complaints***

A 23-year-old woman was admitted to our hospital in February 2021 for further treatment with a history of acute abdominal pain, nausea and vomiting.

### ***History of present illness***

She suddenly suffered from abdominal pain, nausea and vomiting, without fever, chills, fatigue, melena, haematemesis, hematochezia or other discomforts.

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### ***History of past illness***

The patient had no previous medical history.

### ***Personal and family history***

There was no personal or family history of acute or chronic disease. There was no family history of tumors.

### ***Physical examination***

Physical examination revealed abdominal tension, pressing pain, and rebound pain. There was a large abdominal mass with hard texture, unclear boundary and uncertain size, and tenderness of the left abdomen.

### ***Laboratory examinations***

Laboratory examination showed significant increases in serum tumor markers: carcinoembryonic antigen (CEA): 697.90 ng/mL (normal range 0–10 ng/mL),

carbohydrate antigen (CA)125: 104.20 U/mL (normal range 0–35 U/mL), CA72-4: > 300.0 U/mL (normal range 0–6.9 U/mL). The level of CA19-9 (3.49 U/mL) was normal (normal range 0–27 U/mL).

### ***Imaging examinations***

Computed tomography (CT) and abdominal enhanced CT showed that the abdominal tumor measured 7.5 cm × 10.9 cm, with uneven density, and unclear boundary between the tumor and surrounding tissues (Figure 1A). There were swollen lymph nodes in the mesentery. Abdominal enhanced CT was highly suspicious for gastrointestinal stromal tumors, and abdominal and retroperitoneal lymph nodes were swollen. Preoperative chest CT showed no abnormalities.

### ***Surgical exploration and pathological diagnosis***

We performed exploratory laparotomy. A tumor with hard texture was located in the middle of the transverse colon, causing peritonitis because of perforation. The diameter of the tumor was ~10 cm. Transverse colectomy was successfully performed. The lymph nodes around the transverse colon were cleared, but the retroperitoneal lymph nodes could not be removed. The favorable recovery period for the patient was ~2 wk. Histopathological examination revealed that the tumor was a mucosecretory adenocarcinoma with signet ring cells (Figure 2D, E). Immunohistochemistry was negative for CD20 and CD117, and positive for CK20, CDX-2 (caudal-related homeobox transcription factor 2) (Figure 2A), villin (Figure 2C), mucin 2 (Figure 2B), Dog-1 (Delay of Germination 1), LCA (Leukocyte Common Antigen) and CD3. Lymph node metastasis was evident (of the 24 detected lymph nodes, 23 were metastatic lymph nodes), but no distant metastasis was detected. The pathological stage was IIIC.

### ***Disease evolution***

The patient received chemotherapy according to the National Comprehensive Cancer Network guidelines for colorectal cancer. We retested the serum tumor markers after

surgery in March 2021, which revealed significant changes: CEA: 44.65 ng/mL (normal range 0–10 ng/mL), CA125: 7.33 U/mL (normal range 0–35 U/mL), CA72-4: 68.0 U/mL (normal range 0–6.9 U/mL). The level of CA19-9 was normal (< 0.6 U/mL, normal range 0–27 U/mL). The effect of tumor resection was remarkable. The patient inadvertently found a mass in the outer upper quadrant of the right breast after receiving four cycles of chemotherapy (XELOX: oxaliplatin 130mg/m<sup>2</sup>, d1, ivdrip for 2 h; capecitabine 1000 mg/m<sup>2</sup>, po, bid, d1–d14). Physical examination revealed that the breast mass was 1.5 cm × 2 cm, with hard texture, and clear boundary between the mass and surrounding tissues. Further examination was performed. Breast ultrasound showed a tumor of 2.1 cm × 1.5 cm × 1.3 cm, with unclear boundary and echo heterogeneity. Color Doppler flow imaging showed blood flow signal (Figure 1B). Axillary lymph nodes were normal. It was not clear whether the breast tumor was a primary cancer or metastasis from colon cancer. There were slight elevations in serum tumor markers: CEA: 76.7 ng/mL (normal range 0–10 ng/mL), CA125: 7.66 U/mL (normal range 0–35 U/mL), and CA72-4: 43.20 U/mL (normal range 0–6.9 U/mL). The level of CA19-9 (8.83 U/mL, normal range 0–27 U/mL) was still normal. After discussion with the patient, we decided to perform a lumpectomy and frozen biopsy in June 2021. Frozen biopsy revealed that the breast tumor was intestinal metastasis. Routine hematoxylin and eosin staining of breast tumor revealed breast metastasis from mucosecretory adenocarcinoma possibly of colonic origin (Figure 2G, H). The tumor was negative for estrogen receptor, progesterone receptor, GATA binding protein-3 (GATA3) (Figure 2F), gross cystic disease fluid protein (GCDFP), Her-2 and CK7, and positive for CDX-2, villin and SATB. GATA3 is an important indicator of primary breast cancer; however, CDX-2, villin and SATB are important indicators of enterogenous breast cancer. The disease was considered to be disseminated.

### **FINAL DIAGNOSIS**

Based on the pathological findings and clinical results, the final diagnosis was breast metastasis from transverse colon carcinoma.



## **TREATMENT**

Genetic testing showed that *RAS* and *BRAF* were wild type. According to the treatment guidelines for distant metastasis of colon cancer, we replaced the original chemotherapy with FOLFIRI + cetuximab [irinotecan 180 mg/m<sup>2</sup>, d1, iv drip for 30–90 min; leucovorin 400 mg/m<sup>2</sup>, d1, iv drip for 2 h; 5-fluorouracil (5-FU) 400 mg/m<sup>2</sup>, d1 and, 5-FU 1200 mg/(m<sup>2</sup> d) × 2 d, continuous iv drip for 46–48 h; cetuximab 500 mg/m<sup>2</sup>, d1, iv drip for 2 h]. The level of serum tumor markers was significantly reduced in July 2021 after one treatment cycle: CEA: 26.20 ng/mL (normal range 0–10 ng/mL), CA125: 2.84U/mL (normal range 0–35 U/mL), and CA72-4: 5.96 U/mL (normal range 0–6.9 U/mL). The level of CA19-9 (7.76 U/mL, normal range 0–27 U/mL) was still normal. The patient received 10 cycles of FOLFIRI + cetuximab. The level of serum tumor markers (CEA, CA12-5, CA72-4 and CA19-9) was normal, and there was no evidence of tumor recurrence or metastasis. The patient has been reviewed regularly without further treatment.

## **OUTCOME AND FOLLOW-UP**

The patient did not receive further treatment after 10 cycles of FOLFIRI + cetuximab. During the whole treatment process, the patient underwent chest and abdominal CT examinations every 3 mo, and there was no evidence of distant metastasis. The level of serum tumor markers CEA, CA12-5, CA72-4 and CA19-9) was normal (Figure 3). The patient is in no evidence of disease (NED) state.

## **DISCUSSION**

Breast metastasis from colon cancer without liver metastasis, lung metastasis or peritoneal dissemination is extremely rare. The prognosis for metastatic breast cancer remains poor overall, due to disseminated disease. The breast lump can be mistaken for primary breast cancer<sup>[9]</sup>. Histopathological examination revealed that the tumor in the present case was a mucosecretory adenocarcinoma with signet ring cells, which is a



type of colon cancer with poor prognosis. In addition, there was a large number of lymph node metastases. Metastatic breast cancer appears about 4 mo after surgery.

In the present case, rapid growth of the breast mass indicated high malignancy of the colon tumor. Signet ring cells were found in the colon and breast tumors. Typically, colorectal carcinoma is positive for CK20, whereas this is exceptional in primary breast carcinoma. Metastatic breast cancer is usually negative for estrogen and progesterone receptors. Aspiration and excision biopsies are feasible for diagnosis of breast metastases. Previously, authors have advised against extensive resection of metastatic breast tumor<sup>[5]</sup>. Thus, surgical treatment of metastatic breast tumor should be both diagnostic and palliative. However, when the tumor is large or painful, mastectomy is sometimes required.

Breast metastasis from colon cancer should be considered as systemic metastasis, although the metastatic pathway is not clear. The most common forms of metastasis of colon cancer are lymph node and hematogenous metastases<sup>[10]</sup>. The lymphatic network of the breast is rich, with a large distribution of lymph flowing to the axillary lymph nodes. The lymphatic drainage of the breast can flow to the parasternal lymphatic vessels through the intercostal lymphatic vessels, or it can flow back to the abdominal organs along the rectus abdominis sheath<sup>[11]</sup>. Therefore, we consider that there may be two possible pathways for metastasis to the breast from colon carcinoma. The first possibility is that colon cancer cells invade the blood circulation, and tumor cells are planted in the breast and grow into a mass similar to primary breast cancer. Another possibility is that colon cancer cells invade the lymphatic vessels of the abdominal wall and communicate with the lymphatic vessels of the breast along the intercostal lymphatic vessels or along the rectus abdominis sheath. In the present case, we prefer the second explanation. Previous reports have hardly mentioned the route of breast metastasis of colon cancer.

Because of early diagnosis and new therapeutic methods, the overall incidence and mortality of colorectal cancer have declined significantly<sup>[12,13]</sup>. However, metastasis remains a significant challenge in prolonging survival. In particular, we have no

experience in the treatment of breast metastasis from colon cancer, and there is no clear statement in the relevant guidelines. For the treatment of metastatic colorectal cancer, KRAS, NRAS, RAS and BRAF should be tested first by genetic testing, which is the basis for treatment with cetuximab or bevacizumab. We selected cetuximab according to the results of genetic testing (wild-type KRAS, NRAS, RAS and BRAF). After we replaced FOLFIRI + cetuximab with XELOX, the level of CEA, CA125 and CA72-4 decreased dramatically. According to the treatment guidelines for distant metastasis of colon cancer, there is no mistake in giving chemotherapy and targeted treatment. Diagnosis of breast metastasis from colon cancer has been reported, but there are few reports on treatment and metastasis route<sup>[14-15]</sup>. The prognosis of patients is poor. Barthelmes reported a case of breast metastasis from colon cancer who died 4 mo later from advanced intra-abdominal carcinomatosis<sup>[5]</sup>. In our case, the patient survived for 16 mo after receiving lumpectomy, which was due to the application of chemotherapeutic and targeted drugs, especially cetuximab. Cetuximab is used for the treatment of metastatic colorectal cancer with overexpression of epidermal growth factor (EGF) receptor and resistance to irinotecan-based chemotherapy. Cetuximab is an IgG1 monoclonal antibody against EGF receptor. After specific binding, the two antibodies block the intracellular signal transduction pathway by inhibiting tyrosine kinase binding to EGF receptor, resulting in inhibition of proliferation of cancer cells, inducing apoptosis of cancer cells, and reducing the production of matrix metalloproteinase and vascular endothelial growth factor<sup>[16]</sup>. Wang X et al<sup>[6]</sup> performed XELOX chemotherapy regimen combination with bevacizumab to a patient with breast metastasis from colon cancer for 8 cycles, increasing successful treatment experience for patients with this rare metastasis. This is similar to our research. In addition, most of the other reports only reported the diagnosis of this rare metastasis. The average survival time is 14.9 mo by searching literature<sup>[6]</sup>. Only one case had a more than five-year overall survival with colon cancer metastasis to breast<sup>[6]</sup>. The patient had 16-mo disease-free in our case, which has exceeded the average level, indicating that our treatment is effective.

Our patient received chemotherapy and targeted therapy after surgery. At the same time, the patient was regularly reviewed, including chest and abdominal CT, gastrointestinal tumor markers. The dramatic decrease in tumor markers (CEA, CA125 and CA72-4) was due to the removal of colon tumor after transverse colectomy. When breast metastasis occurs, tumor markers begin to increase. However, in our case, the level of tumor markers (CEA, CA125 and CA72-4) decreased and remained within the normal range after treatment with FOLFIRI + cetuximab. CEA is usually highly expressed in digestive system tumors, especially in some patients with advanced gastric cancer and colorectal cancer<sup>[17]</sup>. As a specific tumor marker, CA72-4 is used to monitor the recurrence and prognosis of gastric cancer. CA125 is a sensitive marker for ovarian cancer<sup>[18]</sup>, and is also elevated in gastrointestinal tumors. CA125 seems to be a better tumor marker than CEA for predicting progressive disease in colorectal cancer in men and women<sup>[19]</sup>. The changes of CEA, CA125 and CA72-4 reflected disease progression and effect of treatment in our patient. These three tumor markers play an important role in evaluating disease status, tumor recurrence, tumor metastasis and prognosis of gastrointestinal cancer patients. They also indicate postoperative follow-up of patients with gastrointestinal tumors. We will continue to evaluate the condition of the patient by paying attention to the level of tumor markers and CT changes, which are beneficial for treatment planning.

Breast metastasis from colon cancer is a manifestation of advanced cancer. There are a variety of treatment methods, but they are complex and difficult. In addition to chemotherapy and targeted therapy, immunotherapy may also become a new choice, which needs further clinical research. For this patient, we will observe the effect of treatment by follow-up and deciding whether to give further treatment according to the review results.

## **CONCLUSION**

Breast metastasis from colon cancer is rare. Typically, it has poor prognosis because it is associated with disseminated metastatic disease. Radical breast surgery should be

avoided unless needed for palliation. The surgical treatment of a metastatic breast tumor should be both diagnostic and palliative. Chemotherapy combined with targeted therapy should be the first choice. The mechanism of metastasis and better treatment need to be studied.

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