

# World Journal of *Clinical Cases*

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## Isolated metachronous splenic multiple metastases after colon cancer surgery: A case report and literature review

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**Author contributions:** Hu L and Yan ZL designed the manuscript and performed the surgery; Zhu JY reviewed the literature and contributed to drafting the manuscript; Fang L performed the radiology analyses; Yu XC performed the pathology analyses; Hu L wrote the manuscript; all authors have read and approved the final manuscript.

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### Abstract

#### BACKGROUND

Isolated splenic metastasis is a rare clinical entity. Multiple metastases in the spleen after radical colon resection in a patient who subsequently underwent a second local resection for isolated metachronous splenic metastasis are exceedingly rare.

#### CASE SUMMARY

We report a colon cancer patient who underwent laparoscopic radical colon resection 14 mo previously, and subsequently underwent a second local resection due to local recurrence detected by elevated serum carcinoembryonic antigen (CEA) and positron emission tomography (PET). However, multiple metastases in the spleen were found 7 mo later by elevated serum CEA and PET-magnetic resonance imaging. Then the patient underwent total laparoscopic splenectomy. Local tumor recurrence and splenic metastasis from colorectal cancer (CRC) were found by postoperative pathology. Genetic analysis of these recurrent and metastatic tissues showed KRAS exon2, APC exon16 and TP53 exon6 missense mutations, but no mutations of NRAS, KRAF, EGFR, ERBB2, MET, MLH1, MSH2 and MSH6 were detected. Chemotherapy and target therapy were administered after multiple disciplinary team (MDT) consultation, and no tumor recurrence has been observed to date. We also reviewed the literature by conducting a search of the PubMed database using the following key words: CRC, splenic metastasis, isolated, and review. We identified 34 relevant papers, which included 28 cases of metachronous metastasis and 6 cases of simultaneous metastasis.

#### CONCLUSION

Close monitoring of serum CEA levels is crucial for the detection of isolated splenic metastases after colon surgery. In terms of overall survival and progression-free survival, MDT plays an important role in the entire process of disease management.

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**Core tip:** Isolated splenic metastasis is a rare clinical entity. We report a case of 48-year-old woman with isolated splenic metastasis 21 mo after radical colon adenocarcinoma resection. Close monitoring of serum carcinoembryonic antigen levels is crucial after colon adenocarcinoma surgery. Splenectomy seems to be the preferred treatment and multiple disciplinary team plays an important role in the entire process of disease management.

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## INTRODUCTION

Splenic metastases in patients with malignant tumors generally indicate multiple metastases<sup>[1,2]</sup>. Isolated splenic metastasis after radical colon adenocarcinoma resection is a rare clinical entity<sup>[3]</sup>. The mechanism of their rarity is unknown and many theories have focused on anatomical and histological aspects. We report a case of isolated splenic metastasis 21 mo after radical colon adenocarcinoma resection, which was successfully treated by totally laparoscopic splenectomy. We discuss the clinical and pathological aspects of the case, and consider the diagnostic and therapeutic options based on our observation of the case. We also reviewed the literature and identified 34 relevant papers, including 28 cases of metachronous metastasis and 6 cases of simultaneous metastasis.

## CASE PRESENTATION

### Chief complaints

A 48-year-old female patient was admitted to our hospital with elevated serum carcinoembryonic antigen (CEA). The patient had no symptoms of abdominal pain, diarrhea or bloody stools.

### History of present illness

The patient underwent laparoscopic radical colon resection 14 mo previously and subsequently underwent a second local resection due to local recurrence detected by elevated serum CEA and positron emission tomography (PET). However, multiple metastases in the spleen were found 7 mo later by elevated serum CEA and PET-magnetic resonance imaging. The patient then underwent a totally laparoscopic splenectomy. Local tumor recurrence and splenic metastasis from the colorectal cancer (CRC) were found by postoperative pathology.

### History of past illness

The patient denied a history of hypertension, diabetes, and other relevant illnesses.

### Family history

The patient did not have a family history of cancer.

### Physical examination upon admission

Physical examination was normal.

### Laboratory examinations

Complete blood count, liver and renal function tests, and alpha fetoprotein, carbohydrate antigen 19-9 (CA19-9), cancer antigen 125 (CA125), and CA153 were within normal limits, except for CEA which was 12.41 ng/mL (normal range 0-5.0 ng/mL), 51.49 ng/mL and 206.89 ng/mL, respectively.

### Endoscopy

The first endoscopy revealed a sigmoid colon mass. The second and third endoscopies were normal.

### Imaging examinations

A sigmoid colon mass was found by abdomen enhanced computed tomography (CT) (Figure 1A). Local recurrence in the descending colon was found by positron emission tomography (PET)-CT (Figure 1B) and lymph nodes showed no high metabolic shadow. Isolated splenic metastasis was found by PET-magnetic resonance imaging (MRI) (Figure 1C) and lymph nodes also showed no high metabolic shadow.

### Interventions

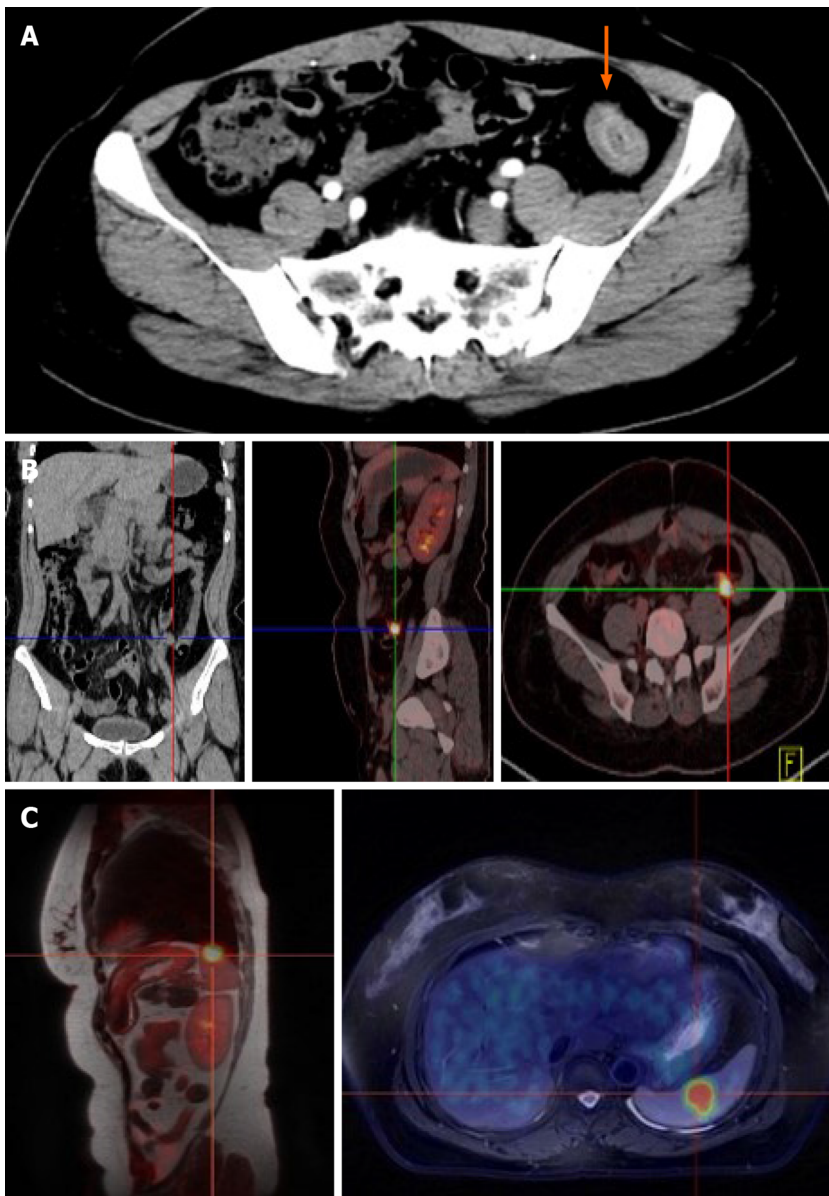
The clinical stage assessed by enhanced CT before surgery was cT4aN0M0 and postoperative pathological stage was pT4aN2M0 after laparoscopic radical resection of sigmoid adenocarcinoma and one-stage anastomosis. The patient received chemotherapy (Xelox regimen, capecitabine 1000 mg/m<sup>2</sup>) for 3 wk with a total of 8 treatment courses. However, the CEA level gradually increased 14 mo after surgery, and PET-CT showing a high metabolic shadow in the descending colon. Following MDT consultation, a second laparoscopic exploration was performed. The extent of local resection based on a laparoscopic exploration and no other recurrences were found. Local resection of the recurrence in the intestinal tract and one-stage anastomosis were carried out during surgery. The tumor edge is 5 cm away from the proximal and distal margin. Postoperative pathology confirmed a poorly differentiated colon adenocarcinoma (with extra-serosal and muscular invasion). The circumferential, proximal, and distal margins were negative. Xelox chemotherapy was again administered for 3 wk per treatment course for almost 3 mo. At a subsequent examination, the CEA level had gradually increased over the 7-mo period after the second operation. After the second MDT consultation, laparoscopic exploration was performed, and no peritoneal metastases were observed and the spleen was removed *via* laparoscopy. The surgical specimen displayed multiple metastases (Figure 2). Chemotherapy with FOLFIRI (irinotecan 180 mg/m<sup>2</sup> + 5-FU 400 mg/m<sup>2</sup> d1, injection, +2400 mg/m<sup>2</sup>, injection, every 2 wk) and bevacizumab (5 mg/kg drop every 2 wk) was administered for 2 wk following the suggestions by a third MDT consultation.

### Pathology

The first postoperative pathology indicated a poorly differentiated adenocarcinoma; 4 of 15 perirectal lymph nodes harvested were positive; and circumferential, proximal, and distal margins were negative. The second postoperative pathology showed the same results. The last postoperative pathology indicated multiple metastatic moderately differentiated adenocarcinoma of the spleen, with tumor sizes ranging from 0.4 to 3.0 cm, and originating from CRC *via* hematoxylin and eosin staining and immunohistochemistry (Figure 3). Genetic analysis of local recurrence and splenic metastasis showed KRAS exon2, APC exon16, and TP53 exon6 missense mutations, while no mutations of NRAS, KRAF, EGFR, ERBB2, MET, MLH1, MSH2 and MSH6 were detected.

## FINAL DIAGNOSIS

The diagnosis of postoperative isolated metachronous splenic metastasis of CRC requires clear imaging, which can be obtained by CT examinations, and sometimes ultrasonography and PET are required. In our case, PET-CT was performed due to an elevated CEA level, which only revealed local colon cancer and not splenic metastasis (Figure 1B), and subsequent PET-MRI detected isolated splenic metastasis (Figure 1C). Pathological stage I was found in the primary focus in only 1 case (3.4%), stage II in 7 cases (24.1%), stage III in 18 cases (62.1%), and the stage in 3 cases (10.4%) could not be determined. Higher pathological staging suggests the possibility of splenic metastasis. However, stage I CRC can also metastasize to the spleen. Pathological biopsy was



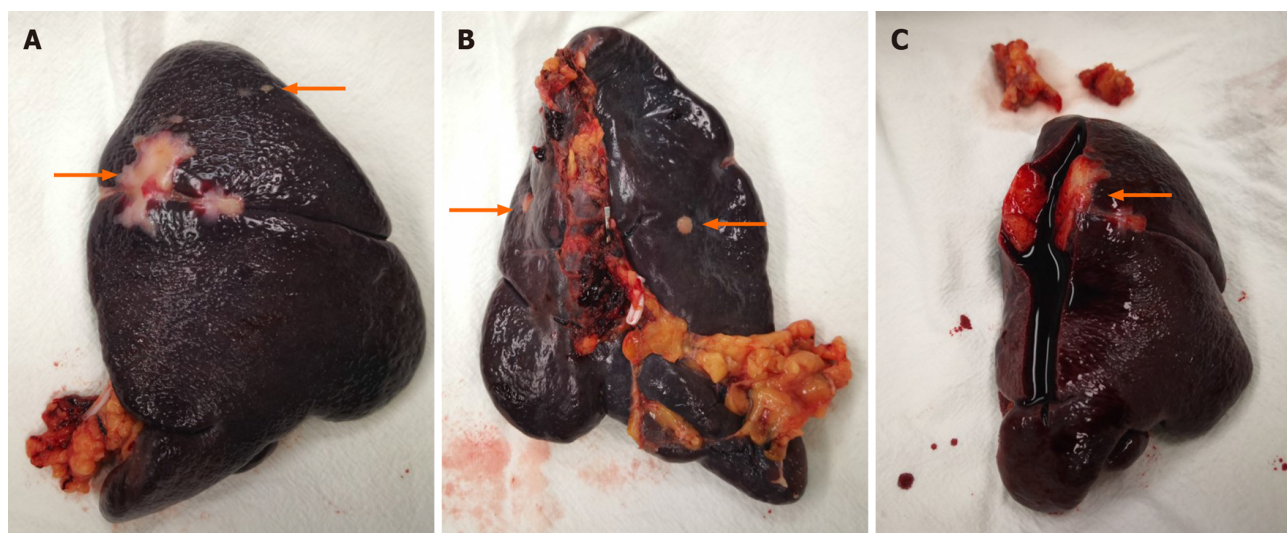
**Figure 1** Imaging examinations of the colon. A: Initial contrast-enhanced computed tomography (CT) of abdomen showed slight enhancement of the wall of sigmoid colon and a mass (arrow); B: Positron emission tomography (PET)-CT showed a high metabolic shadow in the descending colon, suggesting metastasis, but no such shadow was seen in the spleen; C: PET-magnetic resonance imaging revealed a high metabolic shadow, suggesting metastasis.

needed for the final diagnosis of postoperative splenic metastasis of CRC, 2 cases were confirmed by fine needle biopsy, and the others by postoperative pathology.

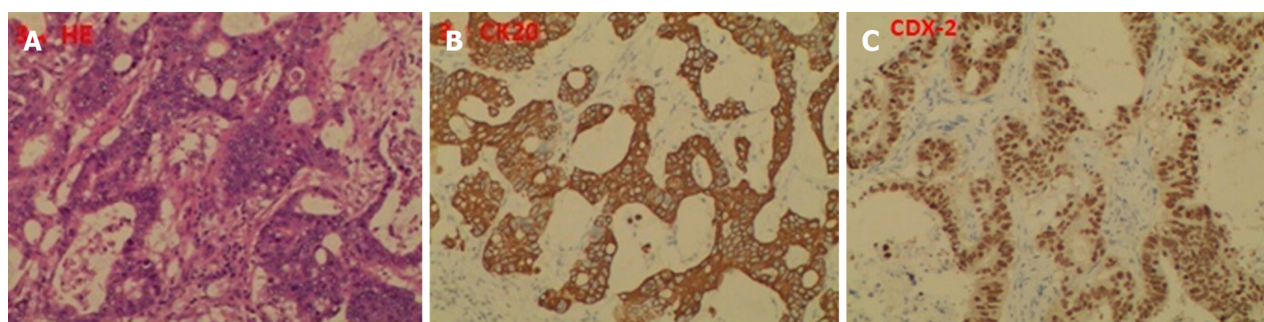
## TREATMENT

The treatment of postoperative isolated metachronous splenic metastasis of CRC includes surgery, chemotherapy combined with targeted therapy or radiotherapy. Surgery was performed in all cases, 2 cases underwent totally laparoscopic splenectomy (including our case), and the remaining cases underwent open total splenectomy. Laparoscopic resection of a splenic malignancy is controversial due to potential cancer cell implantation during laparoscopic surgery. Lopez Monclova *et al*<sup>[4]</sup> reported 6 cases of laparoscopic metastasis splenectomy, all of which had no postoperative complication and the total survival time ranged from 2 mo to 11 years<sup>[4,5]</sup>. In terms of abdominal organ malignancy, laparoscopic surgery does not result in higher surgical complications than traditional laparotomy<sup>[6]</sup>. Therefore, laparoscopic total splenectomy is safe, reproducible and results in a faster postoperative recovery than traditional surgery. Our patient underwent three surgeries, all conducted under laparoscopy, and no postoperative complications were





**Figure 2** The surgical specimen displayed multiple metastases (A-C).



**Figure 3** The postoperative pathology (100 ×). A: Postoperative pathology with hematoxylin and eosin staining indicated multiple metastatic moderately differentiated adenocarcinoma of the spleen; B and C: Immunohistochemistry, cytokeratin 20 (+++), and caudal type homeobox 2 (+++) suggested metastatic adenocarcinoma.

observed. Chemotherapy is considered a priority treatment for distant metastasis. However, only 4 patients received perioperative chemotherapy and 1 received targeted therapy after splenectomy of metastatic tumors, as shown in Table 1. It is possible to reach a state of No Evidence of Disease after excision of an isolated metastasis and most cases require continuous observation. The time to disease recurrence after splenectomy ranged from 3 to 84 mo (median time 18.0 mo) in these patients. Although few patients were treated with chemotherapy and targeted therapy, systemic chemotherapy still provides an essential contribution to the overall survival rate in the presence of distant metastasis. No relevant literature was identified on the use of radiotherapy in combination with chemotherapy. In our case, patient received chemotherapy combined with targeted therapy after splenectomy, following the suggestions of the MDT. The time without disease recurrence remains to be defined in this patient.

## FOLLOW-UP AND OUTCOME

No sign of tumor recurrence or metastasis was observed 7 mo after totally laparoscopic splenectomy.

## DISCUSSION

The most common metastatic organ of CRC is the liver, and it has been reported that almost 50% of patients diagnosed with CRC experienced simultaneous or



Table 1 Cases of isolated splenic metastasis after colorectal cancer surgery from PubMed

No.	Age/sex	Primary	Stage	Size in cm	SO/M	CEA in ng/mL	Imaging	Treatment	1 <sup>st</sup> DFI in mo	2 <sup>nd</sup> DFI in mo	Ref.
1	78/F	Rectum	III	18	SO	64	CT	S	48	84	[13]
2	72/M	Sigmoid	III	9	SO	106	LSS	S	48	6	[14]
3	81/M	Cecum	III	NA	SO	7.5	LSS	S	30	12	[15]
4	51/F	Rectum	II	NA	SO	13.5	CT	S	51	14	[16]
5	72/F	Descending	II	3	SO	223	CT	S	144	12	[17]
6	62/F	Descending	III	4	SO	High	CT	S	42	12	[18]
7	74/M	Sigmoid	II	9.5	SO	23.4	CT	S	24	24	[19]
8	52/M	Ascending	NA	NA	SO	NA	US and CT	S	12	6	[20]
9	48/M	Ascending	NA	NA	SO	NA	US and CT	S	24	3	[20]
10	33/F	Sigmoid	III	3.5	SO	9	CT and MRI	S	3	12	[21]
11	65/M	Ascending	III	5	SO	14.9	CT	S	36	18	[22]
12	60/F	NA	NA	NA	SO	High	CT	S	108	5	[23]
13	51/M	Sigmoid	III	13	SO	N	CT	S	72	6	[24]
14	62/M	Sigmoid	III	3	SO	N	US and CT	S	24	23	[25]
15	55/F	Sigmoid	III	3	SO	N	PET-CT	S	21	12	[26]
16	52/F	Sigmoid	II	13	SO	7.2	US and CT	Cmt, S	108	22	[27]
17	76/M	Descending	III	6.5	SO	High	PET-CT	S, Cmt	17	12	[28]
18	72/M	Rectum	III	NA	SO	High	CT	S	18	NL	[29]
19	69/F	Sigmoid	II	4	SO	High	CT	S	24	60	[30]
20	52/F	Descending	III	4.5	SO	High	PET	S	36	NL	[31]
21	80/F	Transverse	III	8	SO	52	CT	S, TT	9	6	[32]
22	73/M	Hepatic flexure	II	1.5	SO	High	CT, PET	S	60	40	[33]
23	70/M	Splenic flexure	III	8	SO	High	CT, US	S	24	12	[34]
24	59/M	Ascending	III	4	SO	37	CT	S	15	24	[35]
25	58/M	NA	II	3.5	SO	N	CT	S, Cmt	20	11	[36]
26	78/M	Cecum	III	7	SO	38.6	CT, PET	Cmt, S	37	9	[37]
27	64/F	Cecum	I	4.9	SO	38	CT	S	16	6	[2]
28	76/F	Descending	III	1.6	SO	N	PET	S, Cmt	24	21	[6]
29	46/F	Sigmoid	III	0.4-3	M	206.8	PET-CT/MRI	S, Cmt, TT	21 (14, 7)	7	Our case

1<sup>st</sup> DFI between treatment of the primary tumor and diagnosis of splenic metastasis; 2<sup>nd</sup> DFI after splenectomy. CEA: Carcinoembryonic antigen; SO/M: Solitary/multiple; DFI: Disease-free interval; US: Ultrasonography; LSS: Liver splenic scintigraphy; CT: Computed tomography; PET: Positron emission tomography; MRI: Magnetic resonance imaging; N: Normal; NA: Not available; NL: Not listed; S: Surgery; Cmt: Chemotherapy; TT: Target therapy.

heterogeneous liver metastases<sup>[3,7]</sup>. Splenic metastases in patients with malignant tumors generally indicate multiple metastases<sup>[1,2]</sup>. A splenic primary tumor or metastasis a rare disease, and the most common sources of splenic metastasis are melanoma (34%), breast cancer (12%), ovarian cancer (12%), CRC (10%), and lung cancer (9%)<sup>[8,9]</sup>. However, isolated splenic metastasis is even rarer. Berge *et al*<sup>[1]</sup> found that the splenic metastases accounted for 4.4% in 7165 cadaver reports, of which 1.6% were from colon cancer, and isolated splenic metastases in colon cancer was not mentioned in their paper<sup>[1,10]</sup>. Another global study showed that up to 2012, less than 100 cases of isolated splenic metastases from colon cancer had been recorded<sup>[11]</sup>.

Splenic metastases are clinically infrequent; thus, the mechanism of their formation is unknown and many theories have focused on anatomical and histological aspects.

With regard to the anatomy of the metachronous metastasis pathway, the splenic artery and abdominal cavity are formed at acute angles and the rhythmic contraction of the spleen<sup>[12]</sup> prevents tumor cells from remaining and growing in the spleen. Other researchers have proposed that tumor cells from the inferior mesenteric vein flow back into the splenic vein and reverse flow into the spleen, resulting in intra-splenic metastasis. With regard to lymphatic metastasis, there is no direct lymphatic input to the spleen, but there are lymphatic systems in the portal vein, subcapsule and trabeculae of the spleen. Tumor cells entering the spleen through these lymphatic systems may also explain the fact that these tumor cells are limited to the subcapsular membrane and thus form isolated lesions. Histologically, the spleen is the second largest lymphatic reticuloendothelial organ in the body. It is composed of a large number of monocytes, Kupffer cells, immunoglobulins and opsonins, which have a high phagocytic activity. In addition, studies have shown that tumor cells entering the spleen will be destroyed by splenic lymphatic reticuloendothelial cells, preventing tumor implantation. Research has also determined that adenocarcinoma cells flow into the liver faster than they flow into the spleen<sup>[1,2,9]</sup>. This might indicate that the spleen may generate anti-tumor fixations and reproductive factors. Possible causes of rare metastatic tumors of the spleen are summarized in [Table 2](#).

We identified 34 cases of isolated splenic metastasis after CRC surgery from the PubMed database (28 cases of metachronous metastasis and 6 cases of simultaneous metastasis, shown in [Table 1](#)). We report the 28<sup>th</sup> case of solitary metachronous splenic metastasis in this study. Our case was characterized by a solitary splenic metastasis during the second surgical procedure, followed by multiple metastases in the spleen, which was different from previous reports. It can be seen from [Table 1](#) that the 15 male and 14 female cases were aged between 33 years and 81 years, with a median age of 63.5 years. The majority of cases presented with an increased CEA level (85.7%) and plasma CEA level ranged from 7.2 to 223 ng/mL, while the CEA level in our case reached a maximum of 206.8 ng/mL. The first disease-free interval in these cases ranged from 3 to 144 mo and the first local colon recurrence in our case was observed 14 mo after the first surgery, and the second splenic metastasis was observed 7 mo later. The diameter of the tumors ranged from 1.5 to 18 cm, all of which were a single metastasis, including 6 cases not mentioned in the reports, and our patient had multiple metastases, which ranged from 0.4 to 3.0 cm in diameter ([Figure 2](#)). Primary lesions were found in the right hemi-colon in 8 cases (3 cases in the cecum, 4 cases in the ascending colon and 1 case in the colonic liver curvature), accounting for 27.6%. The primary tumor was found in the transverse colon in 1 patient (3.4%), and in 18 cases the tumor was found in the left hemi-colon (1 case in the colonic splenic curvature, 4 cases in the descending colon, 9 cases in the sigmoid colon and 3 cases in the rectum), accounting for 62.1%. The tumor site was not mentioned in 2 cases. The high proportion originating from the left hemi-colon also supports the hypothesis that tumor cells have the trait of a counter current to the spleen *via* the inferior mesenteric vein.

## CONCLUSION

We report, for the first time, the occurrence of multiple metastases in the spleen during the second postoperative progression of colon cancer. Our findings enrich the data on metastases of the spleen and provide experience in the management of this disease. Close monitoring of serum CEA levels plays a crucial role in the postoperative follow-up of these patients ([Figure 4](#)). Otherwise, the patient may have multiple organ metastases and lose the opportunity of a second or third operation. Surgical removal of the tumor is just part of the treatment regimen, and postoperative chemotherapy, radiation therapy, targeted therapy, immune therapy and follow-up are also important. Appropriate treatment strategies based on MDT consultation is conducive to improving cancer patients' overall survival and progression-free survival.

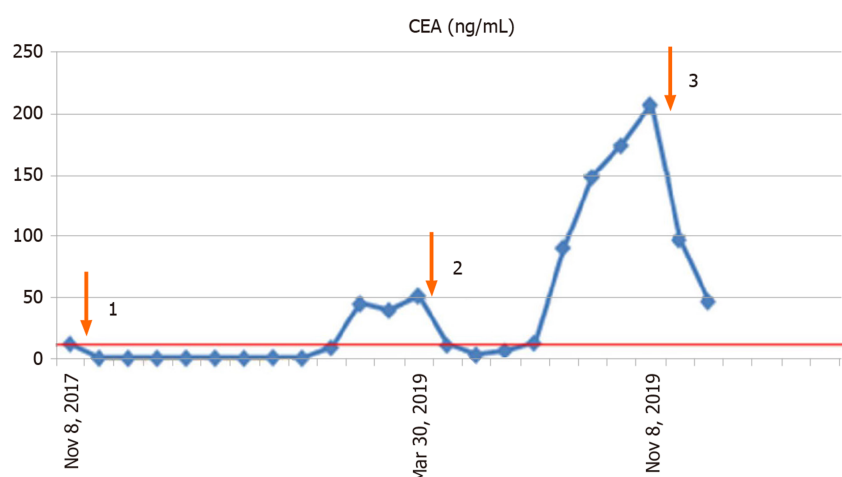
**Table 2 Possible causes of splenic metastasis****Possible causes of splenic metastasis****Anatomical causes**

Blood metastasis: The splenic artery and abdominal cavity are formed at acute angles; rhythmic contraction of the spleen; tumor cells from the inferior mesenteric vein flow back into the splenic vein and reverse flow into the spleen

Lymphatic metastasis: No direct lymphatic input to the spleen; lymphatic systems are present in the portal vein, subcapsule and trabeculae of the spleen

**Histological causes**

The spleen is the second largest lymphatic reticuloendothelial organ in the body; Monocytes, Kupffer cells, immunoglobulins and opsonins have a high phagocytic activity; Anti-tumor fixations and reproductive factors



**Figure 4** Changes in carcinoembryonic antigen level in the reported patients. Three operations were performed as indicated by the arrows. CEA: Carcinoembryonic antigen.

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