Case Report

Successful Management of Bowel Perforation from Bevacizumab for the Treatment of Metastatic Colorectal Cancer: Three Case Reports and Literature Review

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Bevacizumab is a monoclonal antibody that deactivates the vascular endothelial growth factor leading to disruption of vital cancer-signaling pathways and inhibition of angiogenesis, which results in its anti-tumor activity. The use of bevacizumab increases survival in patients with metastatic colorectal cancer (mCRC), but serious adverse effects of bevacizumab have been reported. Among them, the incidence of bowel perforation is relatively rare, approximately 0.3% to 2.4%, but is an often fatal event. Mortality rates have been reported as high as 15%. We reviewed three cases of bowel perforation from 135 mCRC patients with bevacizumab treatment in one single institute. The incidence of bowel perforation was 2.22% (3/135) from the current study; however, no mortality was found after our early diagnosis and palliative operation as stoma creation, intra-abdominal drain and empiric antibiotics would probably reduce the mortality and morbidity from our limited experience.
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Key Words
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Bevacizumab is a monoclonal antibody targeting the vascular endothelial growth factor (VEGF) and was approved by the Federal Drug Administration for first-line treatment in metastatic colorectal cancer (mCRC) patients in 2004. In a phase III trial of patients with mCRC, bevacizumab in combination with the standard chemotherapy (IFL) consisting of irinotecan (CPT-11), 5-fluorouracil (5-FU), and leucovorin showed a 30% significant increase in overall survival (OS) compared with IFL alone (20.3 months vs 15.6 months, $p < 0.001$) and progression-free survival (PFS) by 71% (from 6.2 to 10.6 months, $p < 0.001$).[1] Bevacizumab is the first anti-angiogenesis biologic used in mCRC. With increased use of bevacizumab, serious adverse effects are being reported more frequently, including hypertension, proteinuria, hemorrhage, thrombosis, fistula formation, and bowel perforation.[2,3] The reported incidence of bowel perforation has ranged from 0.3% to 2.4% in the clinical trials.[4] The mortality rates have been reported as high as 15%.[5] Four possible mechanisms of action have been described: (1) the inhibition of VEGF by bevacizumab could cause thrombosis of smaller splanchnic or mesenteric vessels, leading to bowel ischemia and ultimately bowel perforation;[6,7] (2) bowel wall proliferation and healing are dependent on microcirculation, protection with nitrous oxide, prostacyclin, and normal platelet function, all of which depend on VEGF; (3) the intestinal mucosa could be susceptible to ulcers and even perforation as a result of VEGF inhibition by bevacizumab;[8] and (4) tumor structure may provide some stability to the intestinal wall itself, and tumor death creates an area of disruption susceptible to perforation.[6,7,9] The regression of normal blood vessels is observed in animal models, and thereafter increases the possibility of damage, necrosis, and perforation of bowel.[10] The risk factors for bevacizumab-associated perforation remain unclear, but possibilities identified in previous studies include colon surgery within 2 months, history of peptic ulcer disease, partial or complete disease response to treatment, intact primary tumor, endoscopy within 1 month of treatment, prior adjuvant radiotherapy, tumor at the site of perforation, obstruction, intra-abdominal abscess, carcinomatosis, regular NSAID use, and acute diverticulitis.[1,7,11-13] Herein, we reported three cases of bowel perforation associated with bevacizumab treatment of mCRC disease in one single institute.

Case Presentations

Case 1

A 64-year-old male patient had symptoms and signs of bloody stool, small stool caliber, tenesmus and body weight loss. Rectosigmoid colon adenocarcinoma with partial obstruction and liver metastasis (cT3N1M1a) was diagnosed by abdominal- computed tomography (CT) and colonoscopic biopsy (Fig. 1 A-C). After lower anterior resection, he received chemotherapy with FOLFIRI and bevacizumab 36 days after the operation. After the 4th cycle of treatment with FOLFIRI plus bevacizumab, he suffered from sudden onset of fever, perianal pain and lower abdominal pain. The period of this episode occurred 10 weeks after the first bevacizumab administration. The abdominal CT scan showed rectal perforation with abscess formation (Fig. 1D & E). Then, we performed transverse colostomy immediately and drainage of the abscess combined with antibiotics treatment. After conservative treatment, he recovered uneventfully.

Case 2

A 73-year-old female patient had a history of hepatitis C carrier and ovarian cancer following operation with radiotherapy and chemotherapy. Sigmoid colon cancer was found incidentally during healthy examination. Abdominal CT revealed this was accompanied with liver metastasis (cT3N2M1a) (Fig. 2A & B). She received neoadjuvant chemotherapy with FOLFIRI and bevacizumab for mCRC. After the third cycle of FOLFIRI plus the second cycle of bevacizumab, she suffered from sudden onset of abdominal fullness, nausea, and vomiting about 4 weeks after the first administration of bevacizumab. An abdominal CT scan showed mechanical ileus due to acute obstruction, and suspected microperforation of the tumor site (Fig. 2C & D). Accordingly, under the

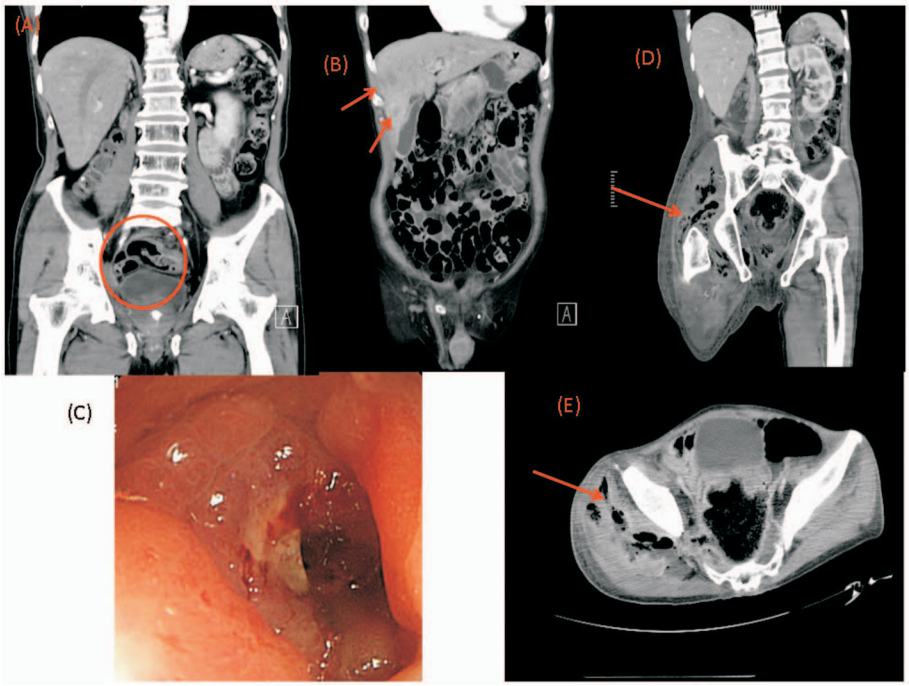

Fig. 1. (A) & (B) Rectosigmoid colon cancer with liver metastasis; (C) colonoscopy; (D) & (E) colonic perforation with abscess formation.

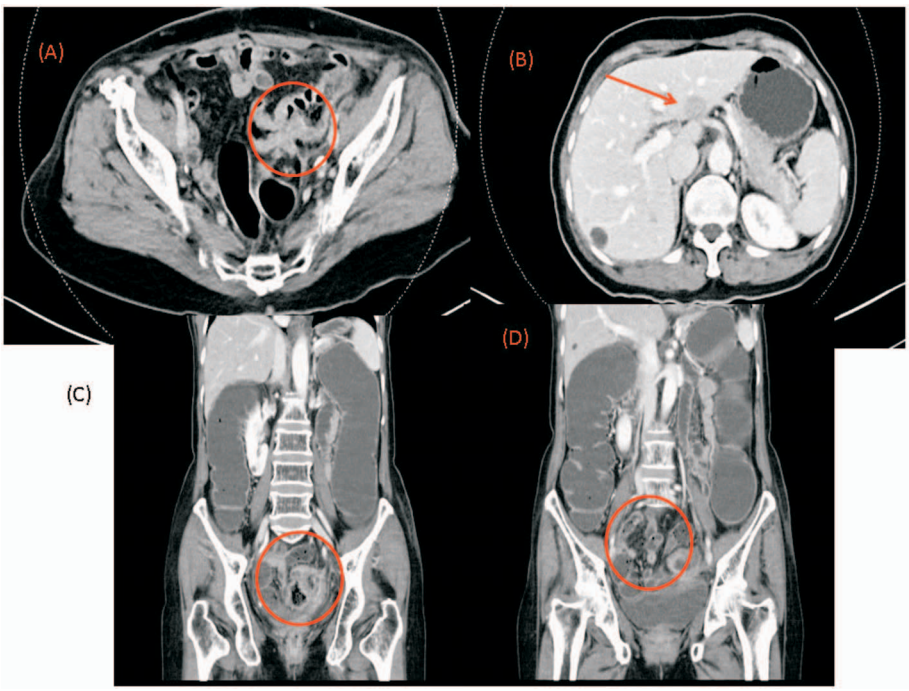

Fig. 2. (A) & (B) Sigmoid colon cancer with liver metastasis; (C) & (D) mechanical ileus due to acute obstruction, suspect microperforation of colon.

impression of bevacizumab-associated bowel perforation, we performed transverse colostomy and combined antibiotics treatment. She also recovered from this episode uneventfully.

Case 3

A 46-year-old female patient was a victim of hepatitis B carrier. She had a hypoechoic nodule found by abdominal sonography incidentally. The colonoscopy revealed that a polypoid mass was located at 20 cm from anal verge and biopsy showed adenocarcinoma. Abdominal CT was performed and revealed sigmoid colon cancer with liver metastasis (cT2N1M1a) (Fig. 3A & B). She received neoadjuvant chemotherapeutic regimen of FOLFIRI plus bevacizumab. After the third cycle of FOLFIRI and the second cycle of bevacizumab, she suffered from sudden onset of fever and lower abdominal pain. This episode occurred after 6 weeks after the first bevacizumab administration. The abdominal CT demonstrated pneumoperitoneum and suspected hollow organ perforation. An accompanying finding was prominent shrinkage of the primary sigmoid colon cancer. She also received transverse colostomy and draining of intra-abdominal abscess and combined antibiotics treatment. Fortunately, she completely recovered from this episode.

Discussion

In this study, we demonstrated that bevacizumab treatment could induce anastomotic delayed leakage or tumor perforation preoperatively. For those who undergoing bevacizumab theraphy, abdominal CT could be a useful tool for diagnosis of bowel perforation. If gastrointestinal (GI) tract perforation with pneumoperitoneum was diagnosed, we performed stoma creation combined with drainage of intra-abdominal abscess and antibiotic treatment for infection control immediately. Neither mortality nor serious complications were noted in our cases after management. After analyzing our three perforated cases complicated with bevacizumab, we suggest that: (1) the bowel surgery before administering of bevacizumab; (2) possible bowel obstruction; (3) previous abdominal radiation; and (4) rapid shrinkage of primary tu-

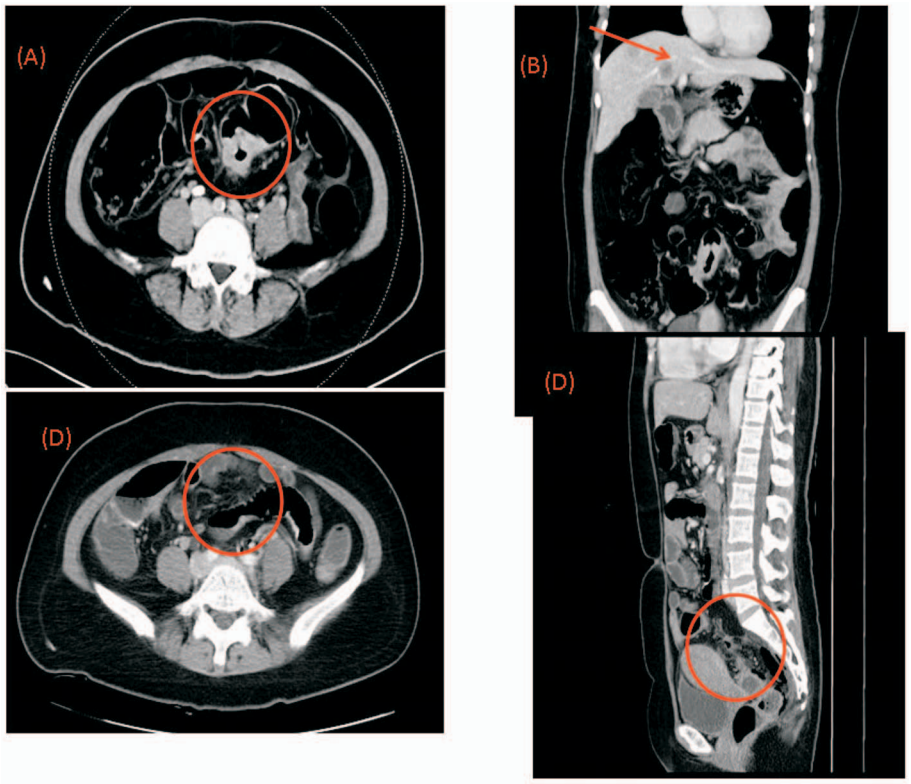

Fig. 3. (A) & (B) Sigmoid colon cancer with liver metastasis; (C) & (D) Pneumoperitoneum and prominent shrinkage of primary sigmoid colon cancer.

mor, were all factors potentially associated with GI tract perforation resulting from bevacizumab administration. On the other hand, the perforation rates of our cases with bevacizumab treatment were 2.22%. The incidence was similar to previous reports.[4]

Preliminary data sets from 1367 patients using bevacizumab with chemotherapy as the first-line treatment for various cancers demonstrate that bowel perforation occurs approximately 1.6% of the time after treatment.[1] Though several mechanisms of bevacizumab causing bowel perforation have been described but not established, a physician must have the highest suspicion for bowel perforation and lower threshold for ordering diagnostic imaging. CT sacn should be considered the diagnostic study of choice because it may reveal pneumoperitoneum, small bowel loops caused by obstruction, or even pneumatosis intestinalis.[14,15] Therefore, the best approach to bowel perforation in patients with bevacizumab is suggested to be early surveillance, prompt diagnosis and surgical intervention. In our presented cases, we used the abdominal CT scan for accurate diagnosis and immediate management with palliative operation as stoma creation can significantly reduce the mortality and morbidity.

Once bowel perforation does occur in patients receiving bevacizumab, the perforation is managed conservatively or surgically. The decision regarding treatment can be complicated because patients typically have a terminal illness and are administrated with bevacizumab that might cause poor wound healing and dysfunctional platelets. In the study by Badgwell et al. with 24 patients, 4 patients were treated surgically and 20 were treated conservatively. No patients expired after surgery. However, in the conservative group, 3 patients died within 30 days after bowel perforation and 6 died within 60 days after perforation. However, it should be noted that the 3 patients who died during the first 3 months after bowel perforation were deemed nonoperative due to advanced carcinomatosis.[11] A study by Scappaticci et al. showed that cancer patients who underwent emergency surgery while on bevacizumab were at higher risk for wound healing complications such as fascial dehiscence, cellulitis, intra-abdominal and cutaneous fistulae, anastomotic leak, intra-abdominal bleeding, hemothorax and bowel perforation.[16] Whether conservative management or surgical intervention is the best approach remains to be determined.

In conclusion, bevacizumab has been demonstrated as an effective biologic for patients with mCRC. Bevacizumab may result in severe complications as bowel perforation and physicians must have a suspicion of bowel perforation when acute abdomen occurred. Palliative operation as stoma creation, intra-abdominal drain and empiric antibiotics would probably reduce the mortality and morbidity from our limited experience.

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病例報告

成功治療因使用癌思停 (Bevacizumab) 治療轉移性結直腸癌導致之腸穿孔：三例病例報告與文獻綜述

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Bevacizumab (商品名：Avastin 中文名：癌思停) 是一種血管內皮增生因子的單株抗體，它會破壞重要的癌症信號通路和抑制血管生成，因而造成抗腫瘤作用。使用 Bevacizumab 治療轉移性結腸直腸癌提高了存活率，但仍有一系列之副作用被報導，其中腸穿孔發生率雖然相對較低，大約 0.3% 到 2.4%，但卻是致命的，死亡率高達 15%。我們回顧了單一機構使用 Bevacizumab 治療轉移性大腸直腸癌之 135 位病患，其中 3 位發生腸穿孔，腸穿孔的發生率為 2.22%，然而在我們的早期診斷與腸造口之保守手術及抗生素治療後能降低併發症且目前並無死亡之病例。

關鍵詞 腸穿孔、轉移性結直腸癌、化療、Bevacizumab。