Case Report

Extensive bowel necrosis related to bevacizumab in metastatic rectal cancer patient: a case report and review of literature

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Abstract

Recently, bevacizumab has become a key drug for treatment of metastatic colorectal cancer. Molecularly targeted agents such as bevacizumab can cause life-threatening adverse effects, though they are generally considered less toxic than cytotoxic drugs. Here, we review the case of a 76-year-old male rectal cancer patient with liver metastasis who suffered extensive bowel necrosis after administration of 5-fluorouracil-based chemotherapy with bevacizumab, and required a subtotal colectomy and end-ileostomy. Microscopic findings revealed extensive mucosal necrosis in the resected colon specimen and necrosis at the muscularis propria of the descending colon. Pathological findings suggested that the mucosal damage induced by chemotherapy may be exacerbated by treatment with bevacizumab, resulting in extensive necrosis.

Key words: bevacizumab, intestinal perforation, necrosis, metastatic colorectal cancer, 5-fluorouracil

Introduction

Vascular endothelial growth factor (VEGF) plays an important role in tumor proliferation, invasion and metastasis, by promoting angiogenesis. Bevacizumab is a recombinant, humanized monoclonal antibody against VEGF. It is one of the most important and well-studied molecularly targeted, anti-angiogenic agents. A combination of cytotoxic agents and bevacizumab is the most frequently used regimen for treatment of advanced metastatic colorectal cancer (mCRC) (1). Combination therapy for mCRC improves response rates to chemotherapy, progression-free survival (PFS) and overall survival (OS) compared with treatment with cytotoxic agents alone (2,3). The United States Food and Drug Administration (FDA) approved bevacizumab as a first-line treatment for mCRC in February 2004. They subsequently approved a regimen of bevacizumab combined with 5-fluorouracil (5-FU), leucovorin and oxaliplatin (FOLFOX4) as a second-line treatment for mCRC in June 2006 (4). Continuous use of bevacizumab after first-line treatment improved PFS and OS compared with chemotherapy alone (5). Thus, bevacizumab has been accepted as a standard drug for the management of mCRC.

Molecularly targeted agents are generally less toxic than cytotoxic agents; however, they can have life-threatening adverse effects, including post-operative bleeding, thromboembolic events and bowel perforation. Here, we review a case of extensive bowel necrosis after combined treatment of a patient with rectal cancer with 5-FU-based chemotherapy and bevacizumab. The detailed mechanisms by which the bowel becomes necrotic are not yet clear. This case may be the first report of extensive bevacizumab-related bowel necrosis. We review the
literature concerning bevacizumab-related gastrointestinal necrosis or perforation, and discuss the characteristics of several important cases.

Case presentations
A 76-year-old man diagnosed with rectal cancer with multiple liver metastases, underwent an anterior resection with primary anastomosis in April 2012 to relieve a bowel obstruction. He also had a history of diabetes mellitus, hypertension and prostate cancer. He underwent a total prostatectomy and orchietomy 12 years ago and was continually treated with 10 mg of prednisolone for >10 years for biochemical recurrence of prostate cancer. He also took calcium polystyrene sulfonate (CPS) for hyperkalemia caused by chronic kidney disease. Following surgery for primary rectal cancer, he received eight courses of modified FOLFOX6 (mFOLFOX6) with bevacizumab (7.5 mg/kg) therapy for every 3 weeks to target the liver metastases. He developed mild diarrhea during initial chemotherapy. Oxaliplatin was removed from the additional six courses because the patient developed Grade 3 neuropathy.

The liver metastases showed a partial response to the combination therapy. Twelve days after the last treatment, the patient complained of sudden-onset lower abdominal pain accompanied by vomiting and was hospitalized. His blood pressure was 100/69 mmHg, his heart rate was steady and 100 beats/min, his respiratory rate was 24 breaths/min and his body temperature was 34°C with diaphoresis. He was presented with generalized abdominal tenderness and muscular guarding. Laboratory tests revealed an elevated white blood cell count of 14.8 x 10^3 cells/μl, a CRP level of 0.30 mg/dl which is within the standard range and elevated blood urea nitrogen level of 22.4 mg/dl, a creatinine level of 1.32 mg/dl, a glutamic oxaloacetic transaminase level of 55 U/l, an lactate dehydrogenase level of 325 U/l and a signifi- cantly elevated D-dimer level of 9.1 μg/ml. Enhanced abdominal computed tomography revealed distension of the colon in full length and an enhanced mesentery around the descending colon (Fig. 1a and b). Although neither free air nor vascular thrombosis was detected, the clinical course strongly suggested a lower bowel perforation. Explorative laparotomy revealed that the colon was totally enlarged and had a necrotic appearance. We performed a Hartmann procedure and resected from the cecum to the descending colon (sub-total colectomy) with end-ileostomy. After rehabilitation and a stoma care program, he was discharged from the hospital 42 days after the emergency surgery. Chemotherapy was not re-introduced and he died of disease progression 8 months post-surgery.

Discussion
In the case presented here, extensive acute bowel necrosis developed 12 days after the last treatment with chemotherapy and bevacizumab. Pathological findings included diffuse necrosis and hypoplasia of the crypts in the mucosa, consistent with chemotherapy-induced, severe mucositis. Given that bevacizumab can impair wound healing, it may contribute to cytotoxic necrosis that progress from the mucosa through the full layers of the bowel wall.

Chemotherapy-induced mucositis is recognized as one of the major adverse effects caused by cytotoxic agents. Anticancer drugs that inhibit mitosis affect the proliferative zone of the mucosa and stimulate apoptosis (6). Milles et al. (7) reported colonic histological

Figure 1. Enhanced abdominal computed tomography (CT) scan. (a) The colon was distended (arrows). (b) The mesentery showed contrast enhancement (arrows).

Macroscopic examination of the resected colon indicated bowel enlargement and edematous changes. The mucosa exhibited gross necrotic changes in all areas (Fig. 2). Histological analysis revealed mucosal necrosis over the entire resected colon. Necrosis was extended from the mucosa to the muscularis propria in the descending colon. Inflammatory cells were observed infiltrating all layers of the bowel wall (Fig. 3a). Finally, the crypts of the mucosa were either absent or hypoplastic (Fig. 3b). There was no visible vascular occlusion, vasculitis or perforation.
changes induced by 5-FU. Early changes usually occurred between the fourth and ninth days post-chemotherapy, with lymphocyte infiltration in the lamina propria, atrophic changes of glands and decreasing numbers of goblet cells. Mucositis gradually spread to diffuse areas and necrosis led to desquamation of superficial areas, with vascular congestion and bleeding in advanced cases. After mucosal healing, an abnormal histological appearance persisted for as long as 18 days after the onset of treatment (7). They also reported that some patients showed marked histologic alterations in colonic mucosa without manifestation of toxicity (7). In this case, the patient did not complain of diarrhea or other abdominal discomfort, but he may have had asymptomatic 5-FU-induced mucositis. These changes are usually reversible but frequent administration of cytotoxic agents could result in accumulation of damage to the bowel.

Bevacizumab acts to inhibit VEGF-mediated angiogenesis and to promote tumor regression and necrosis. It stabilizes the tumor vasculature, decreasing vascular permeability and interstitial pressure. This results in more effective delivery of chemotherapy (8). Life-threatening adverse effects caused by bevacizumab treatment however are well known and include gastrointestinal perforation caused by transmural necrosis (a serious condition induced by the progression of mucosal damage). In a meta-analysis of 17 randomized, controlled trials the incidence of gastrointestinal perforation was 0.9% (95% CI 0.7–1.2) among patients receiving bevacizumab; a two-fold increased risk compared with control treatment alone, and the mortality was 21.7% (95% CI 11.5–37.0) (9). Patients at risk for gastrointestinal perforation associated with bevacizumab therapy include those with intact primary tumors, a history of colonoscopy within 1 month of initiating bevacizumab therapy, a history of previous adjuvant radiotherapy (10), and those that receive a higher dose of bevacizumab (5 mg/kg per week) (9).

A review of the literature allowed identification of 14 cases from 9 reports (11–19) of bevacizumab-related gastrointestinal necrosis or perforation between 2000 and 2013 which are summarized in Table 1. Surgical treatments were performed in 10 cases, drainage was performed in one case, and conservative therapies were used in three cases. Pathological findings were obtained in 6 of 14 cases. Two of the six cases were associated with small bowel metastases from lung and breast cancer, and two other cases had bowel ischemia with microvascular thrombosis. The cause of bowel perforation was not accounted for in the remaining two cases.

Detailed mechanisms of bevacizumab-related gastrointestinal perforation remain unclear. The most likely etiologies are tumor invasion or ischemia, and some possible mechanisms have been suggested. Firstly, tumor invasion into the gastrointestinal serosa with subsequent necrosis may result in bowel perforation (9). Secondly, bevacizumab might damage the structure and function of the gastrointestinal vasculature, resulting in ischemic perforation of the normal bowel or anastomotic site (9). Inhibition of VEGF in mice was reported to reduce the vascular density in the small intestinal villi as well as in other organs (20). Another report suggests thirdly that inhibition of VEGF-mediated release of nitric oxide might lead to vasoconstriction (21). Thus, bevacizumab has the potential to cause gastrointestinal tract ischemia.

We have described the first report of bevacizumab-related, extensive bowel necrosis. However, the etiology of bowel necrosis is still unclear. In the present case, none of the three mechanisms described above can explain the observed findings. Therefore, we might hypothesize as the fourth mechanism that the insufficient bloody supply caused by anti-angiogenic treatment might lead the delay for healing process in severe mucositis, followed by bowel necrosis. However, the effect of bevacizumab to this adverse event may not be definitive. Other reasons than bevacizumab or 5-FU might explain this adverse effect. One possibility is ischemic colitis, but in this case, there were no signs of mesenteric artery and vein thrombosis or vasoconstriction identified in imaging studies or operative findings. Pathological findings of the resected specimens also did not show microvessel occlusion or primary arteritis. The histopathological findings in the present case showed inflammatory infiltration, degeneration of crypts and submucosal bleeding, which were similar to those in the ischemic colitis. However, other important findings for ischemic colitis including ulcerated area or partially destroyed crypts so called ’ghost like appearance’ were not observed. Otherwise, prednisolone or CPS, both of which were taken long-term by this patient, might cause bowel damage. Schellhaas et al. (16) reported that diffuse thrombus formation led to perforation of the normal colon, but the present case exhibited diffuse mucosal damage without thrombus. Taken together, it would be more convincing to assume that bevacizumab and/or 5-FU are related to this extensive bowel necrosis. 5-FU-based chemotherapy combined with bevacizumab might exacerbate inflammatory changes in the mucosa due to cytotoxic chemotherapy that result in necrotic changes to all layers of the bowel wall. Although bevacizumab-related

![Figure 3. Histological analysis of the resected colon.](image-url)

(a) Mucosal necrosis was observed in the entire resected colon. Necrosis partially ranged over the muscularis propria at the descending colon. Tissue sections were stained with Hematoxylin and Eosin (H&E). Magnification x100. Scale bar: 100 μm. (b) Hypoplasia and the absence of bowel crypts were observed at the mucosa in the specimen. H&E staining. Magnification x400. Scale bar: 20 μm.
<table>
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<tr>
<th>Author</th>
<th>Age</th>
<th>Gender</th>
<th>Primary tumor</th>
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<th>Perfusion site</th>
<th>Intervention</th>
<th>5-FU based chemotherapy</th>
<th>Total length of bevacizumab therapy (weeks)</th>
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APR, abdominoperineal resection; LAR, low anterior resection; RHC, right hemicolecotomy; LHC, left hemicolecotomy; HAR, high anterior resection; NA, not available.

aPresent case.
gastrointestinal perforation has been reported in several clinical trials and in post-marketing surveillance, elaborated discussion for pathogenesis was not referred clearly in all cases. Similar mechanism might have occurred in previous cases in which patients developed a gastrointestinal perforation from an unknown cause following treatment with bevacizumab.

Conclusions
We documented a case of extensive bowel necrosis following treatment of a rectal cancer patient with 5-FU-based chemotherapy and bevacizumab, and bevacizumab was considered to be associated with the etiology. Given these findings, it is important to consider that life-threatening gastrointestinal complications may develop with bevacizumab treatment.

Conflict of interest statement
None declared.

References