CASE REPORT

Double Perforation after Colorectal Cancer Surgery During Bevacizumab Treatment

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Abstract

Bevacizumab is a monoclonal antibody which has shown promising results in the treatment of varied malignant pathology, including metastasized colorectal cancer. It acts by inhibiting VEGF (vascular endothelial growth factor), and one of its most cited complications is intestinal perforation, by mechanisms which are not yet fully understood. We present the case of a 68 year old patient, operated for metastasized colorectal cancer, which underwent chemotherapy with Bevacizumab, and shortly after initiating therapy developed fistula of low colorectal anastomosis, followed by ischemic perforation of the small intestine.

Keywords: Bevacizumab, metastasized colorectal cancer, ischemic perforation.

Rezumat

Bevacizumab-ul este un anticorp monoclonal ce a arătat rezultate promițătoare în tratamentul diverselor patologii neoplazice, printre care și cancerul colorectal metastazat. Acesta acționează prin inhibiția VEGF-ului (factor de crestere vascular endotelial), iar una din complicațiile cele mai citate o reprezintă perforațiile intestinale, a cărei mecanism nu este pe deplin elucidat. Prezentăm cazul unui pacient de 68 de ani, operat pentru cancer colorectal metastazat, pentru care a urmat chimioterapie cu Bevacizumab, iar la scurt timp după inițierea terapiei a dezvoltat inițial fistulă de anastomoză colorectală joasă, apoi perforație ischemică de ansă ileală.

Cuvinte cheie: Bevacizumab, cancer colo-rectal metastazat, perforație ischemică.

INTRODUCTION

Bevacizumab (Avastin) is used in the treatment of metastasized colorectal cancers. Other malignant pathologies in which it is used are renal and pulmonary carcinoma, relapsed glioblastoma and metastasized breast cancer[1,2]. The mechanism by which Bevacizumab acts is the inhibition of VEGF, reducing the process of tumoral angiogenesis[3]. Its most cited side effects are proteinuria, thrombosis/thromboembolism, hypertension and gastrointestinal perforation[4,5]. The incidence of intestinal perforations cited by clinical studies was of about 2%[6,7].

CASE PRESENTATION

We present the case of a 68 year old patient, with history of resected prostate cancer followed by hormone

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therapy, hepatitis C related liver cirrhosis (score Child A), diagnosed with rectal cancer at 6cm from the anal verge. In January 2016 a colostomy for initiating radiotherapy was performed, and after undergoing neoadjuvant radiotherapy, a low anterior resection with colo-anal anastomosis and diverting loop ileostomy was performed (March 2016). Histological examination of the resected specimen revealed moderately differentiated adenocarcinoma, G2, yRpT3N1b. The patient underwent adjuvant chemotherapy - 6 months of FOLFOX (folinic acid, fluorouracil, oxaliplatin), then had an ileostomy reversal procedure (June 2016). In March 2018, the patient underwent colonoscopy, which detects normal anastomosis at 3 cm from the anal verge. The follow up CT scan detects bilateral pulmonary metastases. Testing of the paraffin blocks for RAS mutation was performed, which concluded the patient was positive for All-RAS mutation. From March 2018, palliative chemotherapy with CAPOX (capecitabin, oxaliplatin) is initiated, until May 2018, when after multiple hypersensitivity type II reactions to Oxaliplatin, it is changed with CAPIRI (capecitabin, irinotecan). In July and August 2018, two series of Bevacizumab and CAPIRI are administered, with relatively good tolerance. Another follow up CT scan done in August 2018 detects newly developed multiple bilateral lung metastasis. A multidisciplinary team meeting considered the pathology is progressive, and decided on continuing treatment with Bevacizumab and CAPIRI.

In September 2018, the patient is hospitalized with pelvic pain and bowel disorder. CT scan shows anorectal collection, secondary to fistula of low coloanal anastomosis (Figure 1). Biopsies collected at that level exclude tumoral recurrence.

The patient underwent surgery for intestinal obstruction by stenosis and fistula of low coloanal anastomosis, peritoneal adhesions, for which a loop colostomy and adhesion dissection is performed. After surgery, the patient develops bronchopneumonia, which under specific conservative treatment is remitted. 7 days after the surgery, fecal liquid is observed in the drainage tube in the Douglas pouch. Emergency surgery is performed. Intraoperative diagnosis is peritonitis through segmental small bowel necrosis with ischemic perforation. Segmental enterectomy with double-barrel ileostomy is performed, with favorable postoperative evolution. The histological examination of the resected intestine showed area of total necrosis, with acute inflammatory cell infiltration, and hemorrhagic areas through the entire intestinal wall (Figure 2).

DISCUSSION

The exact mechanism through which the perforation occurs is not entirely known, but there are a series of hypothesis that have been cited.

One of them implies the lesion of the intestinal mucosa by altering its protection factors, such as prostacyclin and nitric oxide, that are both dependent on VEGF. Lowering of prostacyclin levels has been associated with lowering of gastric protection factors, which can cause intestinal perforations, especially if they are associated with NSAIDs[8,1].

Another theory implies the damaging of mucosal micro vascularization through thrombosis. By inhibiting VEGF, bevacizumab also inhibits the function of some coagulation factors (von Willebrand factor, factor III), resulting in thrombosis and obstruction of the splanchnic vascularization, which in turn leads to ischemia and perforation of the intestines[9,1].

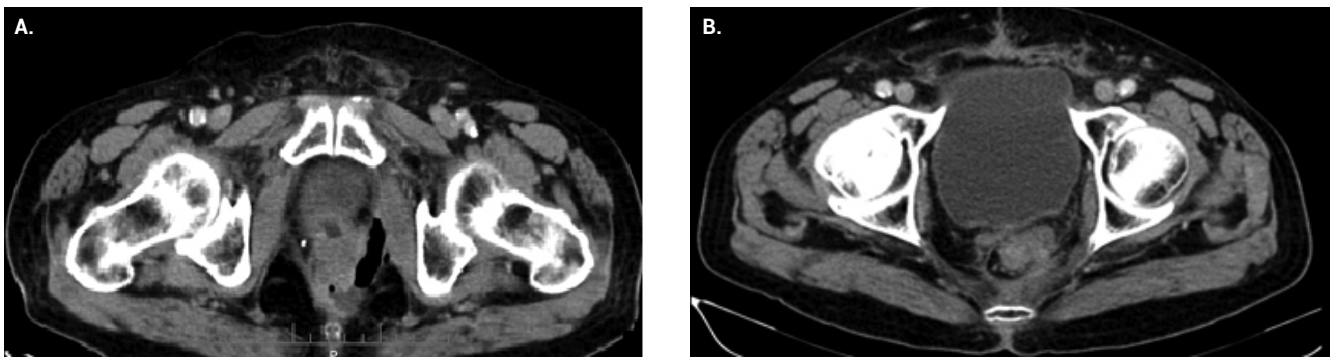

Figure 1. Rectal collection with mixed content (fluid and gaseous), on the left posterior-lateral wall of the rectum, in contact with the left internal obturator muscle, aspect suggesting perianastomotic accumulation secondary to fistula.

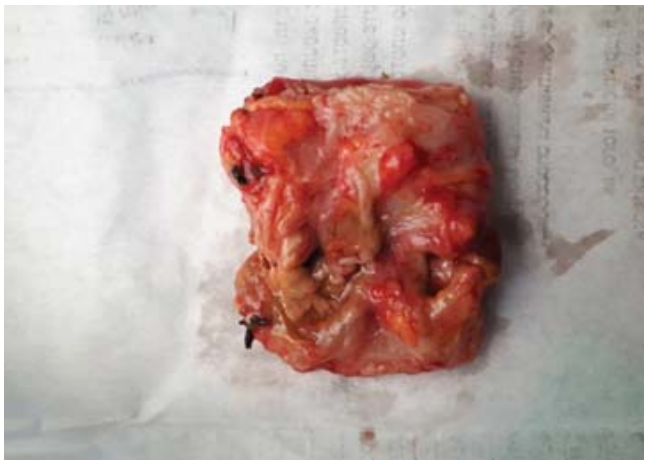

Figure 2. Segmental enterectomy (of aproximately 4 cm), with ischemic perforation of about 8 mm.

Another possible mechanism is perforation secondary to tumoral necrosis and regression, due to the lowered permeability and pressure in the interstitial space, which leads to lesions in the intestinal wall and perforation[10].

Studies have shown a number of factors which raise the risk of intestinal perforation. They are regarding the type of malignant pathology, associated medical history and various therapeutic conducts applied secondary to chemotherapy.

Regarding the types of cancer, most perforations have been reported in cancer of the pancreas, ovary, gastroesophageal, colorectal and renal[11]. Other factors that have been cited in raising the risk of perforation were history of ulcer or diverticulitis, pelvi-abdominal radiotherapy, endoscopies done 1 month prior chemotherapy and the administration of NSAIDs[12-14].

In our case, the time between initiating chemotherapy and occurrence of the perforation was approximately one month. There is a study in which a patient was operated for ascending colon cancer (colon resection and anastomosis), and underwent chemotherapy with Bevacizumab, Irinotecan and Fluorouracil 8 months after surgery because of newly developed metastasis. Emergency surgery was required 2 months after chemotherapy for ischemic intestinal perforation[15]. There are also 2 studies published in which intestinal perforation occurred 7 days after chemotherapy[16].

From the risk factors mentioned before, the patient underwent preoperative radiotherapy and colonoscopy prior to surgical intervention. Another risk factor for both perforations and anastomotic fistula is liver cirrhosis. Patient has history of hepatitis C related liver cirrhosis score Child A. Regarding anastomotic fistula, a study was conducted on 1875 patients with colorectal anastomosis, of which 24 had liver cirrhosis or severe fibrosis. It was shown that fistula occurrence rate was 12.5% in patients with cirrhosis, and 2.5% in those without[17]. Studies have shown that the location of intestinal perforation in patients with cirrhosis is predominantly at the first portion of the duodenum, one study having cited a perforation at the duodeno-jejunal flexure[18].

CONCLUSIONS

It has been demonstrated that associating Bevacizumab in the chemotherapy of metastasized colorectal cancer improves survival and response rate[19]. Intestinal perforation is a complication which must be considered after administrating Bevacizumab. The period of time between chemotherapy administration and the occurrence of perforation is variable, and thus early surveillance of signs and symptoms of intestinal perforation is recommended after administering Bevacizumab.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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