Extensive Colonic Ischemia Following Treatment with Bevacizumab, Fluouracil and CPT-11 in a Young Patient with Advanced Adenocarcinoma of the Rectum

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Key words: adenocarcinoma of the rectum, colonic ischemia, bevacizumab

IMAJ 2007;9:488–489

Bevecizumab (Avastin®) is a monoclonal antibody against vascular endothelial growth factor, an important element in tumor angiogenesis. Although a good safety profile in combination with standard chemotherapy has been demonstrated, specific side effects were reported including arterial thromboembolism and gastrointestinal perforations [1]. We present a young patient treated with bevacizumab added to 5-fluorouracil and irinotecan, who developed colonic ischemia 10 days after the treatment.

Patient Description

A 20 year old male was diagnosed with carcinoma of the rectum, which presented as anemia, diarrhea and bloody discharge per rectum. A non-obstructing adenocarcinoma was found on colonoscopy, beginning at 10 cm and reaching 15 cm from the anal verge. The rest of the colon was normal and no other polyps were found. His mother died 5 years previously at the age of 42 from carcinoma of the breast. No other family members with cancer are known.

Computerized tomography and ultrasound did not reveal liver metastasis, but mesenteric lymph nodes were enlarged. Exploratory laparoscopy demonstrated multiple tumor implants on the peritoneal surface in the lower abdomen and pelvis, and in the omentum. No implants were seen on the small intestine or the colon, but the cecum was adherent to the tumoral mass in the pelvis. Due to the diffuse spread of the tumor, the resection plan was aborted, and the patient was referred to chemotherapy without any resection or even manipulation of the bowel.

He started chemotherapy 7 days after the operation. Bevacizumab (Avastin®) 300 mg (5 mg/kg body weight), irinotecan (Campto®) 180 mg, fluorouracil 200 mg and leukoverin 700 mg were administered (according to the FOLFIRI protocol). On the third day, an additional infusion of irinotecan 180 mg was given.

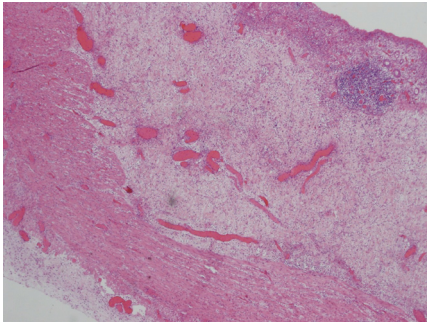
Three days after the treatment the patient was admitted to the hospital for observation due to diffuse abdominal pain and diarrhea. On admission he had diffuse abdominal tenderness and distension but no signs of peritoneal irritation. The leukocyte count was 7.18/µl (75% neutrophils), platelets 255/µl, and hemoglobin 8.6 g/dl. An abdominal CT scan showed dilatation of the small and large bowel but no signs of intestinal obstruction consistent with paralytic ileus. No free air or signs of perforation were noted. He was treated with intravenous fluids and supportive care, but the abdominal distension worsened despite continuous diarrhea. An abdominal plain film 2 days later showed severe dilatation of the small and large bowels. He became lethargic and developed signs of peritoneal irritation.

Laparotomy demonstrated diffuse dilatation of the large bowel. At the transverse colon a 2 cm area of discoloration was found, which rapidly spread to almost the entire transverse colon and within minutes most of the transverse colon appeared ischemic. Blood pressure values were normal at the time and after a period of local warming of the bowel with warm saline, the transverse colon seemed irreversibly ischemic. It should be noted that the pulse at the middle colic arcade was normal. The transverse colon was resected and a right colon colostomy and a left colon mucus fistula were created. After the operation the patient recovered slowly due to impaired wound healing, manifested by partial would dehiscence. The mucosa of the stomas appeared ischemic but gradually became viable over the next 8 days.

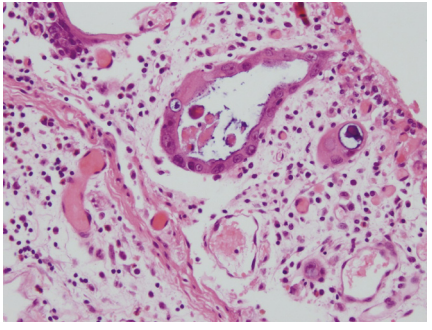
The histopathological examination of the specimen showed that the entire mucosa was necrotic, with edema and vascular distension [Figure A]. The remaining crypts had severe cytologic atypia consistent with cytotoxic effect [Figure B]. Diffuse histiocytic infiltration was apparent through all the layers of the bowel. At the mesocolon severe dilatation and edema of the blood vessels was noted but with no thrombosis. Mesenteric lymph nodes were enlarged but with no evidence of malignant cells.

Comment

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor combined with standard chemotherapy for colorectal cancer, was shown to confer a significant survival advantage as first-line and second-line treatment of colorectal cancer [2,3]. The reported side effects associated with bevacizumab therapy were hypertension, proteinuria, arterial thrombosis, minor bleeding events from mucosal surfaces, and delayed wound healing. Potentially fatal gastrointestinal perforations were reported in up to 2% of the cases but its etiology is not yet understood. The perforation events were sometimes associated with a preexisting inflammation such as gastric ulcer



[A] Large bowel showing that the entire mucosa is necrotic, with edema and vascular distension. (Hematoxylin and eosin. x 40)



[B] The remaining crypts of the bowel wall showing severe cytologic atypia consistent with cytotoxic effect. Diffuse histiocytic infiltration is also apparent through all the layers of the bowel. (Hematoxylin and eosin. x 200)

and diverticulosis, but in other patients perforations occurred in areas with no preexisting pathologies like the ileum and the transverse colon [4]. Moreover, a recent study reported severe ischemic colitis following treatment with bevacizumab in three patients after irradiation to the pelvis [5].

Although an increased risk of arterial thrombo-embolic events was found in patients receiving bevacizumab, in the patient described here it was highly improbable due to his young age, the anatomic pattern of the ischemic colon and the histological findings. The mechanism of colonic ischemia in this patient remains elusive, because unlike the reported cases of ischemia our patient was not irradiated. We hypothesize that bevacizumab could have caused critical injury in addition to the chemotherapy-induced damage. Since vascular endothelial growth factor is a blood vessel stabilizer as well as a growth factor, it is possible that vessels at the capillary level were the site of injury.

Based on the reported cases of unexplained colonic perforations, ileal necrosis, ischemic colitis following pelvic irradiation, and on the case presented here, caution should be exercised when adding bevacizumab to chemotherapy, and a high index of suspicion is necessary with any case of abdominal symptoms.

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