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CASE REPORT

A case report of rectal perforation associated with bevacizumab treatment after carbon ion radiotherapy for recurrent rectal cancer

Takahito Okuda · Hideki Tsuji · Satoshi Kitagawa · Shigeru Yamada

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Abstract Bevacizumab, an antibody that targets vascular endothelial growth factor, is commonly used in the treatment of unresectable or recurrent colorectal cancer in combination with 5-fluorouracil-based chemotherapy. Clinical studies have shown, however, that bevacizumab administration can give rise to a number of adverse events including hypertension, proteinuria, bleeding, gastrointestinal perforation, thrombosis, and wound-healing complications. Among these, potentially fatal gastrointestinal perforations occur in 1–3 % of patients. A possible risk factor for this particular adverse event is a recent history of abdominal/pelvic irradiation. Carbon ion radiotherapy for recurrent rectal cancer is safer and results in better local control than conventional radiotherapy. This might be an even more effective option if followed by 5-fluorouracil-based chemotherapy and bevacizumab administration, although this is yet to be definitively demonstrated. Here, we report a case of rectal perforation in a patient treated with bevacizumab subsequent to carbon ion beam therapy for recurrent rectal cancer. Histological evaluation of bowel biopsies revealed inflammation similar to that associated with X-ray irradiation. In conclusion, just as with conventional abdominal/pelvic irradiation, it is important to consider the possibility of gastrointestinal perforation during bevacizumab treatment following carbon ion beam therapy.

T. Okuda (✉) · H. Tsuji · S. Kitagawa
Department of Radiology, Toyota Memorial Hospital, 1-1 Heiwa-cho, Toyota, Aichi 471-8513, Japan
e-mail: takahito_okuda@mail.toyota.co.jp

S. Yamada
Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

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Introduction

Bevacizumab (BV), an angiogenic inhibitor, produces good therapeutic outcomes when used in combination with standard chemotherapy for unresectable advanced or recurrent colorectal cancer [1–4]. However, its use has led to a number of adverse events that are not generally associated with conventional cytotoxic agents [1–4]. Of particular concern are potentially fatal gastrointestinal perforations (GIPs), which have occurred in 1–3 % of patients treated with BV [5–8]. A possible risk factor for this event is a recent history of abdominal/pelvic irradiation [3, 5, 9].

Carbon ion radiotherapy (CIR) shows promise as a salvage treatment for inoperable local recurrent rectal cancer, yielding results comparable to those of surgical therapy [10, 11], and its combination with a 5-fluorouracil (FU)-based regimen plus BV as an adjuvant chemotherapy may yield even better results in the future. However, whether X-ray irradiation and CIR combined with BV cause GIPs through the same mechanism is still unclear. Here, we report the case of a patient with recurrent rectal cancer who developed rectal perforation on BV administration after CIR.

Case report

A 54-year old man with rectal cancer underwent low anterior resection followed by adjuvant chemotherapy (tegafur, uracil, and leucovorin) for 3 months from March

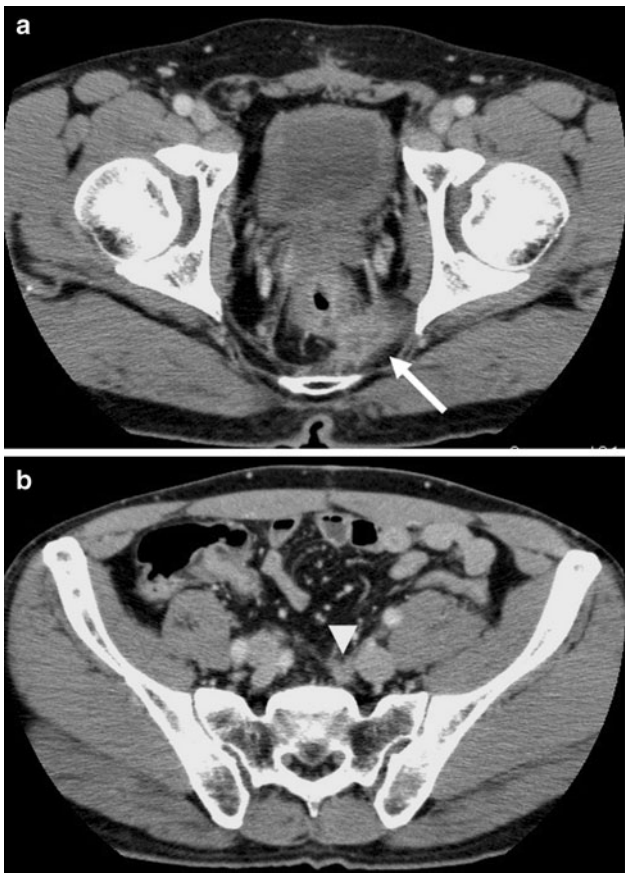

Fig. 1 A pelvic CT scan showing **a** a local recurrence beneath the anastomosis (*white arrow*) and **b** a lymph node metastasis medial to the left common iliac vein (*white arrow head*)

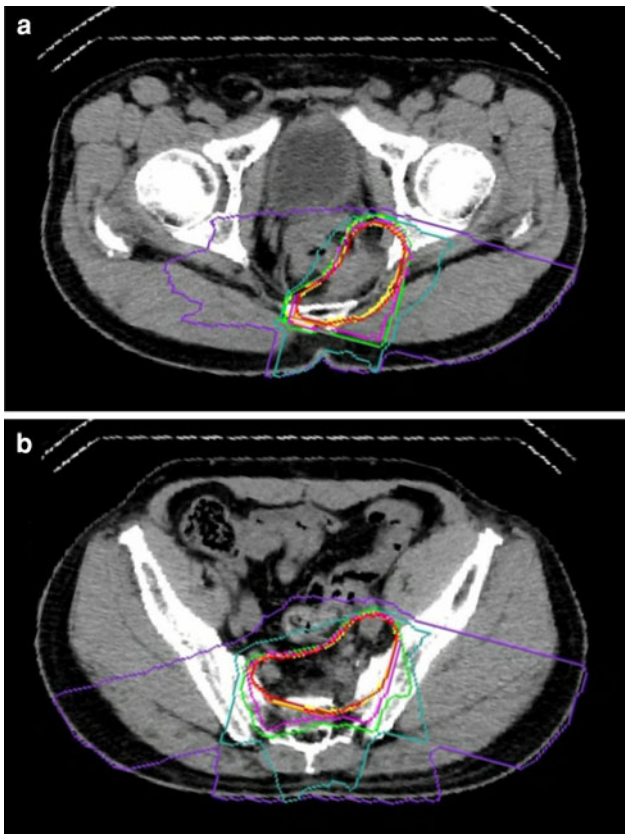

Fig. 2 Carbon ion irradiation fields in the pelvis containing the local recurrence (**a**) and common iliac lymph node region (**b**). Areas encircled by *red*, *orange*, *magenta*, *green*, *dark marine*, and *violet lines* receive over 95, 90, 70, 50, 30, and 10 % of the total dose, respectively. The *yellow line* indicates the planned target area

2007. In September 2007, a fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan revealed local recurrence at the anastomotic site (Fig. 1a) and left common iliac lymph node metastasis (Fig. 1b). In June 2008, treatment for local recurrence and lymph node metastasis using CIR was started, with a total dose of 73.6 GyE for 4 weeks at 4.6 GyE/Fr (Fig. 2a), followed by 50.4 GyE for 3 weeks at 4.2 GyE/Fr (Fig. 2b), resulting in local control at all sites. In April 2009, a computed tomography (CT) scan revealed brain, lung, and para-aortic lymph node metastases, and therefore, modified 5-FU, leucovorin, and oxaliplatin (mFOLFOX) therapy was administered. The disease remained stable for 10 months, after which, in February 2010, a CT scan revealed multiple bone metastases. In July 2010, the patient was treated with palliative radiation therapy for multiple bone metastases followed by 5-FU and leucovorin (5-FU/LV) in combination with 5 mg/kg BV every other week. Five months later, in December 2010, he suddenly developed a fever and acute hip pain and was emergently hospitalized. A CT scan showed the presence of free air in the pelvis (Fig. 3a, b). Endoscopy showed a large ulceration with fistulas on the left rectal wall 5 cm from the anal verge (Fig. 4). Multiple biopsies revealed no malignancy, and the specimens were consistent with only inflammatory change (Fig. 5a, b). A diagnosis of rectal perforation at the anastomotic site and subcutaneous abscess due to an anastomotic ulcer was made. An emergency operation was performed, and drainage and colostomy were performed, but the patient suffered a subcutaneous abscess and subsequently developed multiple metastases. He died in May 2011.

Discussion

To our knowledge, this is the first reported case of a patient with recurrent rectal cancer in which prior CIR was a risk factor for GIPs during the use of BV.

Approximately 50 % of GIPs associated with BV occur in or close to the primary lesion [12], and indeed, in this case, the GIP developed near the anastomosis site. Furthermore, GIP has previously been reported to develop within 6 months of starting BV [8], which was also true in

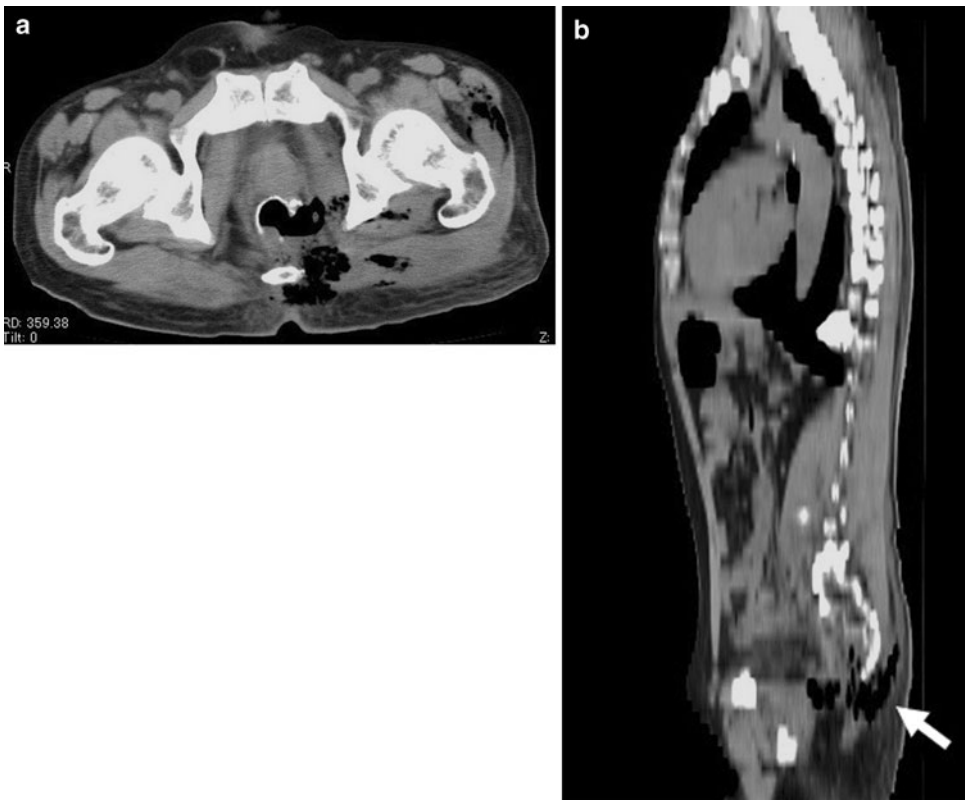

Fig. 3 A pelvic CT scan (**a**) and a reconstructive sagittal view (**b**) showing a rectal perforation within the field of the CIR and empty spaces around muscles and fat tissues

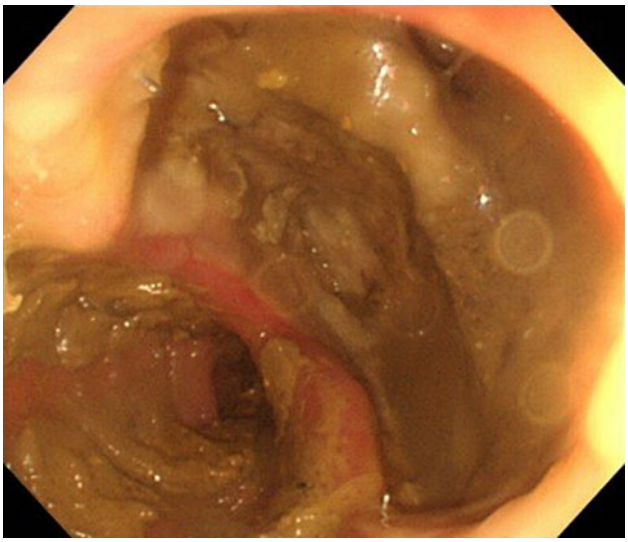

Fig. 4 Endoscopy showing deep colonic ulcers

the current case—GIP occurred 5 months after starting BV. Other potential risk factors for bowel perforation are acute diverticulitis, intraperitoneal abscess, bowel obstruction, residual tumor, carcinomatous peritonitis, and surgery in the 60 days preceding BV treatment [6–8], but none of these risk factors were noted in this case, making CIR the most likely cause.

In the current case, therapy included irradiation with 73.6 GyE delivered to the local recurrent rectal cancer. Doses in excess of 70 GyE delivered by CIR to treat uterine cancer significantly increase the risk of perforation [13]. The incident rate of late perforation has been reported to be 9.6 % for uterine cancer patients treated with CIR, and the estimated radiation dose to the intestines was at least 69 GyE [13].

CIR doses used in local recurrent rectal cancer were determined on the basis of phase I/II dose escalation study findings [11]. Accordingly, the maximum recommended dose was 73.6 GyE per fraction. This dose restriction resulted in a good safety profile, with none of the 112 patients experiencing National Cancer Criteria grade 3–5 acute reactions. Two cases of abscess formation caused by tumor necrosis and one of gastrointestinal ulceration were seen as late adverse events, but no GIPs were reported.

The perforation site in this case was adjacent to the irradiated field, and based on the radiotherapy plan, it would have received the full dose. However, the perforated rectal wall was covered by only 30–50 % of the energy accumulation area in the treatment field, actually resulting in an estimated dose of no more than 36.8 GyE. These doses were extremely low, even when compared with the reported maximum tolerated dose, and therefore, CIR was unlikely to have been the direct cause of GIP.

Histological analysis of the perforated area showed an ischemic change resulting from vascular damage, but no thrombotic changes were noted in the feeding artery around

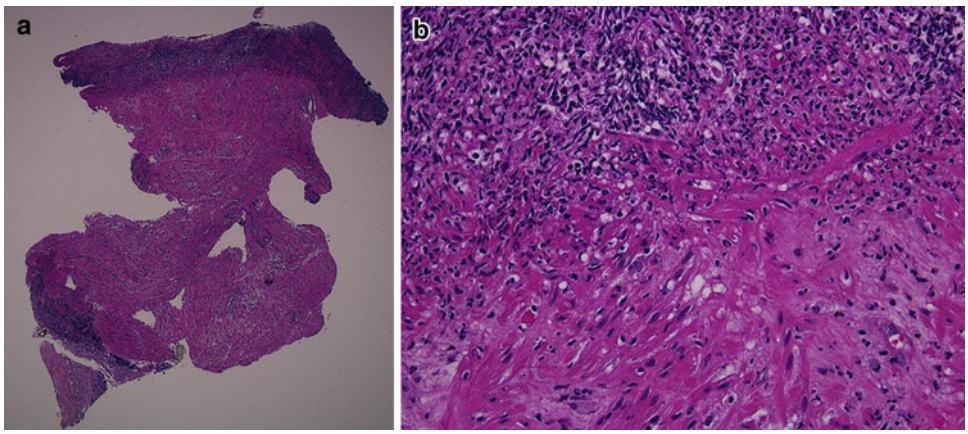

Fig. 5 Rectal mucosal biopsy specimen showing fibrosis and necrosis, findings consistent with ischemic damage (H&E stain; original magnification **a** ×20, **b** ×100)

the rectal perforation site. Thus, we cannot be sure that the ischemic change was due to the thrombotic effect of BV. Similarly, the feeding arteries around the perforation site were not sufficiently well represented by the endoscopic biopsy samples, and it was thus difficult to pathologically determine whether CIR or BV caused these ischemic changes via vascular damage.

CIR was suspected to be a risk factor for GIP in this case, as is abdominal/pelvic irradiation, However, further studies are required before concluding that CIR followed by BV administration is a risk factor for GIP. It is still unclear how CIR and BV interact, and a better understanding of this may help in the increasingly important goal of identifying high-risk groups for GIP and the establishment of safety administration schedules for combined BV and CIR.

Conflict of interest All authors of this manuscript have no conflict of interest.

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