



Case report

Recurrent colon perforation after discontinuation of bevacizumab for ovarian cancer



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ABSTRACT

Bevacizumab (Bev) is an antiangiogenic drug used to treat various malignancies, including ovarian cancer (OC). Bev is generally well-tolerated; however, it has a characteristic toxicity profile. In particular, gastrointestinal perforation (GIP) is a rare but serious side effect that can be lethal. A 55-year-old woman with recurrent OC had an episode of GIP during third-line chemotherapy comprising Bev and topotecan (TPT). Bev was discontinued while TPT was continued as monotherapy. Three months after discontinuation of Bev, the patient presented with left lower abdominal pain and was diagnosed with a second GIP. She had emergent surgery. One year later, she is still alive and healthy, and is continuing TPT. This is the first report of recurrent GIP after discontinuation of Bev. Our case suggests that physicians should be aware of GIP even after the discontinuation of Bev.

1. Introduction

Bevacizumab (Bev) is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF)-A, which is a growth factor that stimulates angiogenesis in various cancers. Bev possesses anti-tumor effects through inhibition of angiogenesis and is used widely for treating malignancies such as colorectal, lung, kidney, and ovarian cancers (Roviello et al., 2017; Sato and Itamochi, 2012). The efficacy of the combined use of Bev and cytotoxic agents in the treatment of platinum-resistant recurrent ovarian cancer (ROC) has been confirmed, and its applications have expanded over the past decade (McClung and Wenham, 2016).

Although Bev is generally well-tolerated, it has a characteristic toxicity profile (Geiger-Gritsch et al., 2010) including hypertension, proteinuria, and bleeding. In addition, gastrointestinal perforation (GIP) and thrombosis are relatively rare but serious adverse events (AEs) associated with the use of Bev. GIP is particularly difficult to prevent and can be lethal (Wu et al., 2017). Generally, once GIP occurs, administration of Bev is permanently discontinued to avoid further AEs. Here, we report a rare case wherein Bev-associated GIP occurred, not only during the Bev treatment but also after discontinuation of Bev during salvage chemotherapy for ROC.

2. Case presentation

Using staging laparotomy, a 55-year-old woman was diagnosed with International Federation of Gynecology and Obstetrics stage IIC ovarian clear cell carcinoma. She underwent modified radical hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, appendectomy, and pelvic and para-aortic lymphadenectomy. No macroscopic residual disease was observed. She received six cycles of adjuvant chemotherapy comprising paclitaxel (PTX, 175 mg/m²) and carboplatin [area under the curve (AUC) 5] every three weeks. Although there were no symptoms, computed tomography (CT) at 11 months after the end of primary treatment revealed recurrent disease involving the mediastinal lymph nodes. As second-line treatment, she underwent three cycles of pegylated liposomal doxorubicin (PLD, 30 mg/m²) plus carboplatin (AUC 5) every four weeks; however, her disease still progressed. Because recurrence occurred only in the mediastinal lymph nodes, and because no dissemination or intestinal obstruction was observed in the peritoneal cavity, we chose to administer PTX (80 mg/m² on day 1, 8, and 15) plus Bev (15 mg/kg on day 1) every four weeks as third-line chemotherapy following the receipt of informed consent. This regimen suppressed tumor growth over 25 weeks (26 cycles); however, the tumor eventually reached the progressive disease state, we therefore changed the regimen to topotecan (TPT, 1.25 mg/m² on days 1–5) plus Bev (15 mg/kg on day 1) every three weeks as fourth-line therapy. On day 6 of the

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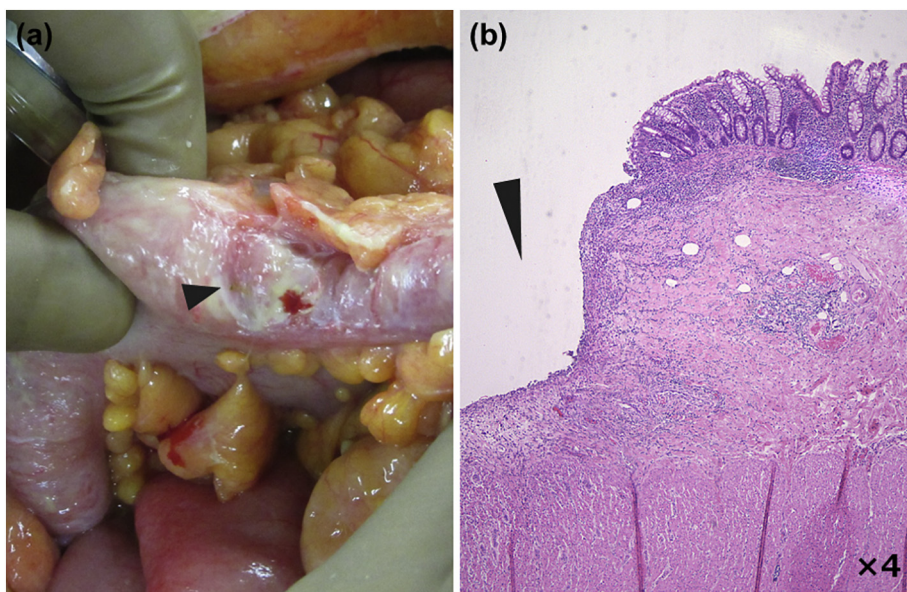


Fig. 1. (a) A pin-hole perforation (arrow) was intraoperatively observed on the transverse colon. No peritoneal dissemination or obvious thinning of the intestinal wall was observed. (b) Histological findings of the perforation site are shown. The surface of the wedge was sharp and smooth. Malignant cells, abscess, or micro thrombosis were not detected near this site. (Original magnification: 40×)

third cycle, the patient suddenly complained of pain in the lower right abdomen. Abdominal X-ray showed no evidence of free air or air-fluid levels. As the abdominal pain persisted and serum level of C-reactive protein was increased, CT was performed which revealed free air around the transverse colon. Emergency laparotomy was performed under a preoperative diagnosis of colon perforation. A pin-hole perforation was confirmed on the right side of the transverse colon (Fig. 1a). The margin of the perforation showed neither abdominal dissemination nor thinning of the intestinal wall. After trimming of the margin of the perforation, closure of the hole by suturing was performed. Pathological examination showed neither malignant findings nor abscess formation at the perforation site (Fig. 1b).

Consequently, Bev was discontinued and TPT was carefully continued as salvage chemotherapy. On day 5 of the fourth cycle of TPT (three months after discontinuation of Bev), the patient was admitted to our hospital with mild lower left abdominal pain. Because she had a history of perforation associated with Bev, we immediately performed CT, which revealed perforation of the colon. Laparotomy revealed a perforation with a diameter of 1 cm at the left colon flexure (Fig. 2a)

and thinning of the intestinal serosa over a range of approximately 5 cm on the oral side from the perforated area. The surgeon performed simple closure of the hole and the thinned site. The histological findings confirmed a ghost-like appearance of the crypt as a consequence of dropping-off of the epithelium (Fig. 2b), which suggested an ischemic change. No metastatic lesion or thrombosis was observed. TPT monotherapy was restarted 3 weeks after the second perforation. We continued her treatment for 20 months, and she had stable disease without experiencing any severe adverse effect.

3. Discussion

The latest meta-analysis clearly showed that Bev extends survival for patients with ROC (Wu et al., 2017). ROC is difficult to cure, and it is inappropriate to exclude treatment options that involve the use of Bev for ROC patients. The incidence of GIP in patients with ROC treated with Bev is remarkably higher than that observed in patients with other malignancies, which range from 0% to 11.4% (Hapani et al., 2009; Wright et al., 2006; Badgwell et al., 2008). Therefore, it is important to

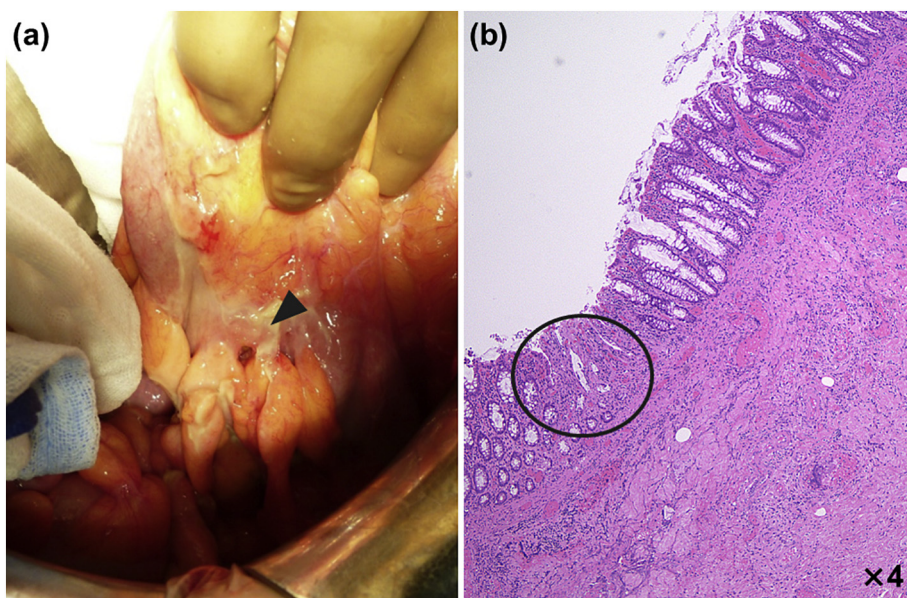


Fig. 2. Intraoperative findings of the second surgery are shown. A perforation hole with a diameter of 1 cm was detected on the left side of the transverse colon (arrow). Histological examination around the perforation site indicated a “ghost-like appearance (round),” which suggested an ischemic mucosal change. (Original magnification: 40×).

ensure patient safety when using Bev. According to previous reports, there are two main causes of Bev-associated GIP. The first is necrosis of the tumor that is penetrating the gastrointestinal wall caused by the antitumor effects of Bev, and the second is necrosis because of intestinal mucosal ischemia caused by inhibition of angiogenesis secondary to Bev. Clinically, these two mechanisms can be present in the same patient. In ovarian cancer, the presence of intraperitoneal dissemination and the tumor in the pouch of Douglas are high risk factors for the first mechanism. Bowel obstruction, bowel wall thickening or suspected bowel involvement, inflammatory bowel disease, and prior bowel surgery are high risk factors for the second mechanism (Han and Monk, 2007; Randall and Monk, 2010). These were noted as patient exclusion criteria in recent clinical trials of Bev. In the present case, no recurrent lesions were observed in the abdominal cavity. Therefore, one possible explanation for the development of the second GIP is intestinal ischemia caused by the anti-angiogenic effect of Bev. The half-life of Bev is reported to be 20 (11–50) days (Avastin [package insert], 2004). In general, the time taken by the body to eliminate the drug is approximately five times the half-life, and in the case of Bev, it is approximately 3 months. Thus, possible contribution of residual Bev to the second GIP cannot be excluded.

The number of treatment regimens received by patients that qualifies them for Bev treatment is controversial. Cannistra et al. reported the highest rate of perforation (11.4%) among studies, which resulted in early termination of their clinical trial. In their study, GIP occurred in 23.8% of patients who received more than three chemotherapy regimens, but it did not occur in patients who received up to two regimens (Cannistra et al., 2007). In congruence with their finding, the US Food and Drug Administration restricted the use of Bev to patients with a treatment history of only two regimens. However, Martin et al. reported that it could be safely used in patients who had received more than three regimens (Martin et al., 2016). Furthermore, a retrospective study reported that GIP during Bev therapy could be prevented by carefully excluding patients with clinical symptoms of bowel obstruction, evidence of rectosigmoid involvement on pelvic exam, and bowel involvement on CT scan, even in heavily treated patients (Simpkins et al., 2007). In our case, Bev was initiated as tertiary chemotherapy. However, the first GIP occurred during the fourth chemotherapy. Therefore, the total dose of Bev may be more important for GIP development than the number of treatment regimens comprising cytotoxic agents.

There have been no reports indicating that the combination of Bev and cytotoxic drugs is more likely to cause GIP. The FDA approves TPT, PTX, and PLD for use as combination drugs with Bev. Among these, PTX is well known to have an antitumor effect by inhibiting angiogenesis like Bev (Bocci et al., 2013). Our patient had been treated with long-term combination chemotherapy using Bev and PTX. The synergistic effect of Bev and PTX on angiogenesis inhibition may have caused clinically unrecognizable intestinal ischemia. The combination of TPT and Bev may have enhanced the antiangiogenic effect of Bev, thereby increasing the risk of GIP. Further research is needed to clarify whether the risk of GIP differs for each Bev-related regimen.

GIP is a rare but potentially life-threatening complication of Bev. Early diagnosis of GIP is crucial to prevent death or septic shock. Bev treatment should be performed at a facility capable of comprehensive management, including early detection of GIP using CT and surgical treatment in ROC patients with high risk factors. In our case, the attending physician was aware of Bev-associated GIP and was therefore able to prevent septic peritonitis by promptly ordering a CT scan and making an early diagnosis. Most importantly, our case suggests that GIP

may occur not only during Bev treatment but also within three months after discontinuation of Bev in patients receiving cytotoxic chemotherapies. To our knowledge, this is the first report on recurrence of GIP after discontinuation of Bev in patients with ROC.

Disclosure

There are no conflicts of interest to declare.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors' contributors

Michiko Nonaka designed the study, and wrote the initial draft of the manuscript. Seiya Sato contributed to analysis and interpretation of data, and assisted in the preparation of manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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