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Case report

Iliac artery-enteric fistula developed during bevacizumab-containing chemotherapy for recurrent cervical cancer: A case report and literature review

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ABSTRACT

An arterioenteric fistula is a devastating and life-threatening condition. As patients often present in extremis from hemorrhage shock, an early diagnosis and prompt life-saving interventions have to be performed. In this report, we describe a case of a 38-year-old Japanese woman who presented with hematochezia that rapidly progressed to hemorrhagic shock secondary to an iliac artery-enteric fistula that developed during bevacizumab-containing chemotherapy for recurrent cervical cancer. The patient underwent successful endovascular treatment with a covered stent-graft as a bridge to definitive open surgery.

1. Introduction

An iliac artery-enteric fistula (IEF) is a rare but life-threatening condition that requires urgent treatment. Most IEFs arise de novo, and known predisposing factors include a male gender and history of pelvic surgery, pelvic malignancy, or pelvic radiotherapy (Vetto et al., 1987; Policha et al., 2015). Bevacizumab, a monoclonal antibody against VEGF, is an anti-angiogenic agent that demonstrated a significant clinical activity against cervical cancer (Tewari et al., 2014). Despite its significant contribution to improve survival, the use of bevacizumab has been associated with the development of perforations or fistulas in the gastrointestinal (GI) tract or genitourinary (GU) system (Tewari et al., 2014; Mabuchi et al., 2021). However, to our knowledge, a bevacizumab-associated arterioenteric fistula has never been reported.

We herein describe the first case of IEF that developed during bevacizumab-containing chemotherapy for recurrent cervical cancer that was successfully treated with endovascular stent grafting. We also summarize, through literature review, the current knowledge about the predisposing factors and the management of IEFs.

2. Case report

A 38-year-old Japanese woman (gravida 0) had undergone chemotherapy with bevacizumab (15 mg/kg), carboplatin (AUC5), and paclitaxel (175 mg/kg) for her recurrent cervical cancer. On the 17th day of her 3rd cycle of chemotherapy, the patient presented with hematochezia lasting for 7 days. Her past surgical and medical history was unremarkable except for a FIGO stage IB2 cervical cancer (squamous cell carcinoma) treated with radical hysterectomy with pelvic lymphadenectomy and adjuvant pelvic radiotherapy two years prior.

On evaluation, she did not have a fever or abdominal pain, and no hematemesis or hematuria was reported. Her vital signs were stable: a blood pressure of 123/75 mmHg; heart rate, 78 bpm; breathing, 18 cpm; and body temperature, 36.4°C. Laboratory work-up revealed a hemoglobin level of 8.0 g/dL, white blood cell (WBC) count of 5,230 cells/mm^3, platelet count of 255,000 cells/mm^3, and a serum-creatinine 0.52 mg/dL. Contrast computed tomography (CT) of the abdomen revealed no pathological findings except for the recurrent cervical cancer in the right pelvic sidewall. The patient was diagnosed with chemotherapy-related anemia, admitted and received a blood transfusion of 2 units

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of packed red blood cells.

Six hours after the transfusion, the patient developed massive hematochezia and lost consciousness. As the patient had no palpable pulse then, she was diagnosed with hemorrhagic shock, and was transferred to the intensive care unit. She was appropriately resuscitated with 26 units of red blood cells, 20 units of fresh frozen plasma (FFP), and 20 units of platelet concentrate (PC). Contrast CT of the abdomen revealed a 2.3 cm pelvic mass involving the right external iliac artery and ileum, the recurrent cervical cancer, and necrotic tissue with a collection of gas bubbles in it, which was suspected as an IEF formation. A CT-angiography could not confirm extravasation, but the images showed an irregular arterial wall in the right external iliac artery, which was suggestive of an arterio-enteric fistula. A digital subtraction angiography performed by vascular surgeons demonstrated an extravasation from the right iliac artery into the ileum, and a diagnosis of a fistula formation between the external iliac artery and the ileum was confirmed. The vascular surgeons performed an endovascular repair with percutaneous placement of a self-expanding covered stent (8 mm × 100 mm, Viabahn®, W.L. Gore, Flagstaff, AZ, USA), and broad spectrum antibiotics were initiated (see Fig. 1). Subsequently, to exclude the possibility of a recurrent infection or new fistulization, surgery with the aim of resecting the involved bowel segments en bloc with the iliac covered stent, anastomosis of the small bowel, and extra-anatomic right-to-left iliofemoral arterial bypass was planned. Nineteen days after the placement of the covered stent (37 days after the previous bevacizumab administration), explorative laparotomy was performed that revealed a 5 cm lesion suggestive of a fistula formation between the ileum and the external iliac artery, which was connected to the recurrent cervical cancer. Due to the highly adhesive, hard, and fibrotic tissue around the involved lesion presumably because of a previous surgery, irradiation, the ongoing inflammation, and the recurrent cervical cancer, the plan for an iliac arterial bypass and an anastomosis of the small bowel was abandoned. The formation of a mucous fistula (cutaneous stoma for the excluded ileum and ascending colon segments) and an ileo-ascending colon anastomosis (about 230 cm from the Treitz ligament) was performed. The decision was made to continue the intravenous antibiotics (Cefmetazole) for a total duration of 4 weeks. The patient had an uneventful postoperative course and was discharged on the 27th postoperative day. She restarted chemotherapy with irinotecan plus cisplatin for her recurrent cervical cancer 1 month after surgery, and is currently alive 2 years after the development of the IEF.

3. Discussion

In this report, we described a case of IEF that developed during bevacizumab-containing chemotherapy for recurrent cervical cancer, which resulted in a catastrophic hemorrhage. To our knowledge, this is the first report of a bevacizumab-associated arterioenteric fistula (AEF).

AEFs are a rare life-threatening condition, with a reported incidence of less than 1%. An IEF represents an uncommon variant of AEFs as most AEFs involve the proximal anastomotic site at the abdominal aorta. IEFs are an extremely rare condition, comprising less than 0.1% of all AEFs (Franchin et al., 2011). In contrast to aortoenteric fistulas, which are predominantly secondary fistulas that classically develop after abdominal aortic aneurysm repair, most of the AEFs have not been associated with prior vascular surgery and have been primary fistulas that developed in patients without prior vascular intervention. According to a review of IEFs, the predisposing factors include a male gender, pelvic surgery, pelvic malignancy, pelvic radiotherapy, and infection (Vetto et al., 1987; Policha et al., 2015). AEFs most commonly involve the colon, followed by the small bowel and the rectum. Almost all the patients with IEFs presented with lower gastrointestinal bleeding, and the reported 30-day mortality rate was 26% (Vetto et al., 1987; Policha et al., 2015).

Our patient had a history of prior pelvic surgery and adjuvant pelvic radiotherapy as risk factors for IEF development. In addition to these, bevacizumab might also have contributed to the development of IEF in this patient. According to the results from the GOG240 study and a retrospective investigation conducted in Japan, 10%–15% of cervical cancer patients experienced GI/GU perforations or fistulas during or after receiving bevacizumab-containing chemotherapies (Tewari et al., 2014; Mabuchi et al., 2021). More importantly, both studies demonstrated that prior radiotherapy was a risk factor of bevacizumab-associated GI/GU events (Tewari et al., 2014; Mabuchi et al., 2021). The mechanisms responsible for the pathogenesis of bevacizumab-associated GI/GU perforations/fistulas have not been fully investigated. However, the possible mechanisms are as follows (Mabuchi et al., 2021; Kamba and McDonald, 2007): First, the reduction in the vascular density or the arterial thromboembolic events induced by bevacizumab, which may lead to ischemic perforations/fistulas. Second, as tumors that invaded the GI serosa or smooth muscle may provide some stability to the GI/GU organ structures, the regression and subsequent necrosis of the tumors in response to bevacizumab treatment will be a cause of GI/

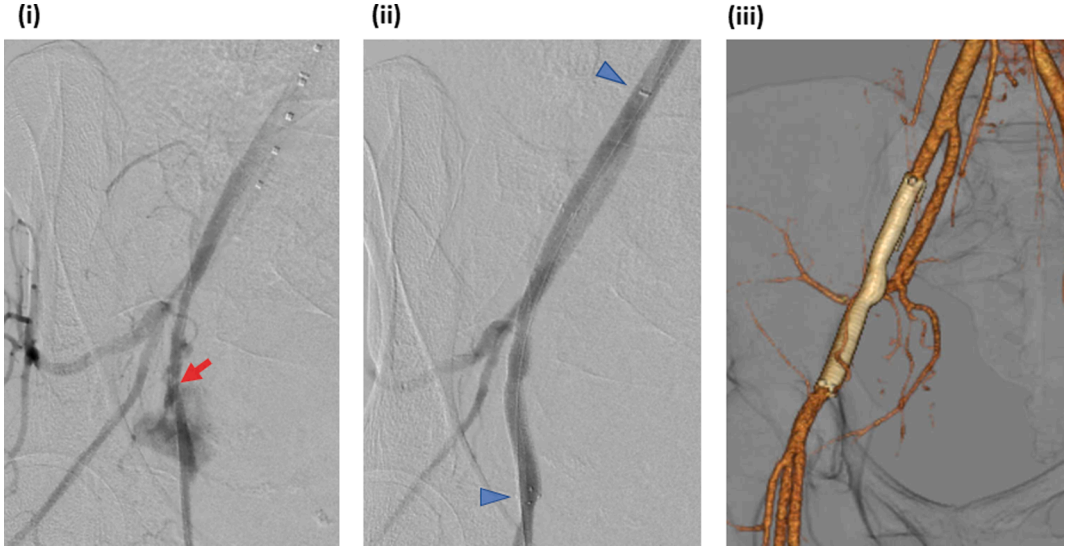

Fig. 1. An angiogram of the right external iliac artery. (i) Contrast extravasation into the ileum (arrow), suggesting a fistula formation between the ileum and the external iliac artery. (ii) the right external iliac artery after the application of an 8 mm wide, 10 cm long covered stent-graft. (iii) A CT-angiography image after the application of the covered stent-graft.

GU events. Third, bevacizumab might prevent the healing of GI ulcers, colonic diverticulitis, or colitis, which could subsequently develop into GI/GU events. In the present case, the recurrent tumors were observed close to the IEF. Moreover, as the patient had been previously treated with pelvic radiotherapy, the patient might have suffered from radiation-induced colonic enterocolitis. Thus, these multiple factors might have contributed significantly in the development of IEF.

The treatment algorithm for IEF should include prompt diagnosis, patient resuscitation, and definitive surgical management. However, an open surgical repair in the acute setting is associated with significant morbidity and mortality. In a study of AEFs conducted by Kakkos et al., a perioperative morbidity of 77% and an in-hospital mortality rate of 35% after open repair have been reported (Kakkos et al., 2011). Thus, endovascular treatment with placement of a covered stent has been preferably employed as a bridge to open surgery under a more controlled, healthier, and elective circumstances. In a study of AEFs, a perioperative morbidity of 25% and no in-hospital deaths were observed in patients who underwent endovascular treatment (Kakkos et al., 2011). In the present case, an IEF was successfully controlled with endovascular stent grafting. As the secondary surgery aimed at resecting the involved bowel segments en bloc with the iliac covered stent had been abandoned, the endovascular treatment resulted in the definitive management for IEF in this case. Fortunately, her postoperative course was uneventful without causing covered stent infection.

Based on the result from a randomized controlled study conducted in the United States (GOG240), bevacizumab in combination with platinum-based chemotherapy has now become one of standard regimens for recurrent cervical cancer (Tewari et al., 2014). We believe that the present case will help physicians and cervical cancer patients to understand the risk of life-threatening fistula formation during bevacizumab-containing chemotherapy.

4. Conclusion

IEF is an extremely rare condition. Early diagnosis and urgent treatment are required because it causes catastrophic hemorrhage. When a recurrent cervical cancer patient presents with sudden onset hematochezia after pelvic lymphadenectomy, radiotherapy, or bevacizumab treatment, IEF should be a part of the differential diagnoses.

Consent

Written consent was obtained from the patient herself.

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Author Contribution section

Seiji Mabuchi made contributions to conceptualization, supervision and drafting the manuscript. Fuminori Kitada and Yuri Matsumoto made contributions to supervision, patient care, and reviewing the report. Masahiko Umemoto, Risa Atsumi, Ayako Miyazaki, Ayako Watnabe and Ryoko Okura made contributions to patient care. Kosuke Sakurai made contributions to interpretation of CT images, Takashi Shibuya made contributions to endovascular treatment of the patient. Yuki Karasawa made contributions to data collection, patient care, and drafting the report.

All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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