Recurrent Cervical Cancer with Intestinal Perforation That Was Related to Bevacizumab after Long-term NSAIDs Administration and Was Treated with Laparoscopy-assisted Anastomosis

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Bevacizumab is an effective drug for recurrent/advanced cervical cancer. A 59-year-old patient diagnosed with FIGO stage I B2 squamous cell carcinoma of the cervix at our hospital was treated with concurrent chemoradiotherapy as initial treatment. The outcome was judged as close to CR. Local recurrence in the irradiation field and paraaortic lymph node metastasis were noted 2 months after completion of this treatment. Chemotherapy of bevacizumab combined with paclitaxel plus carboplatin (TC) was initiated for recurrent cervical cancer. At 17 days after the 4th cycle, abdominal pain suddenly developed, and a close examination detected free air on abdominal CT, based on which intestinal perforation was diagnosed. Laparoscopic surgery performed to investigate the intraabdominal cavity showed that the small intestine was perforated at 2 sites. These were treated with laparoscopy-assisted partial resection of the small intestine and functional end-to-end anastomosis. Drug therapy for the recurrent cervical cancer was considered, but the primary disease rapidly aggravated and the patient died of the primary disease 11 months after completion of the initial treatment.

Key words: Cervical cancer, Bevacizumab, Intestinal perforation, Case report

INTRODUCTION

Bevacizumab is established as the standard treatment for initial and recurrent ovarian cancers in Japan. The indication has been expanded to cervical cancer and the drug is used for advanced or recurrent cervical cancer at many institutions [1, 2]. However, gastrointestinal perforation, hypertension, proteinuria, thromboembolism, delayed wound healing, congestive heart failure, fistula, interstitial pneumonia, and thrombotic microangiopathy have been reported as adverse events after administration of bevacizumab. Gastrointestinal perforation is a particularly characteristic adverse event of this drug [3–5] that varies in grade from mild to severe, and may lead to death in some cases. This makes careful observation of symptoms necessary during treatment with bevacizumab. We encountered a patient with recurrent cervical cancer after initial radiotherapy in whom small intestinal perforation occurred in treatment with bevacizumab and was subsequently treated with laparoscopy-assisted repair.

CASE REPORT

The patient was a 59-year-old 1 gravida 1 para woman. She visited a physician for abnormal genital bleeding, and a mass of about 4 cm was detected in the uterine cervix by transvaginal ultrasonography. The patient was referred to our department for suspected cervical cancer. On the first examination in our department, a hemorrhagic mass was observed in the anterior wall of the uterine cervix and was clearly invasive cancer macroscopically. Squamous cell carcinoma (SCC) was detected in cervical cytology, and the histological diagnosis was squamous cell carcinoma, keratinizing type of the cervix.

On magnetic resonance imaging (MRI), a 4.5 × 3.3-cm mass was present on the ventral side of the cervix and pale high and low intensities were heterogeneously mixed on T2-weighted imaging (Fig. 1). T1-weighted imaging revealed a lobular mass with gadolinium (Gd) enhancement mainly in the margin. On computed tomography (CT), lymph node enlargement was present in the left internal iliac region. No distant metastasis was observed. The tumor markers were SCC, 2.2 ng/mL.

Based on the diagnosis of stage I B2 cervical cancer,

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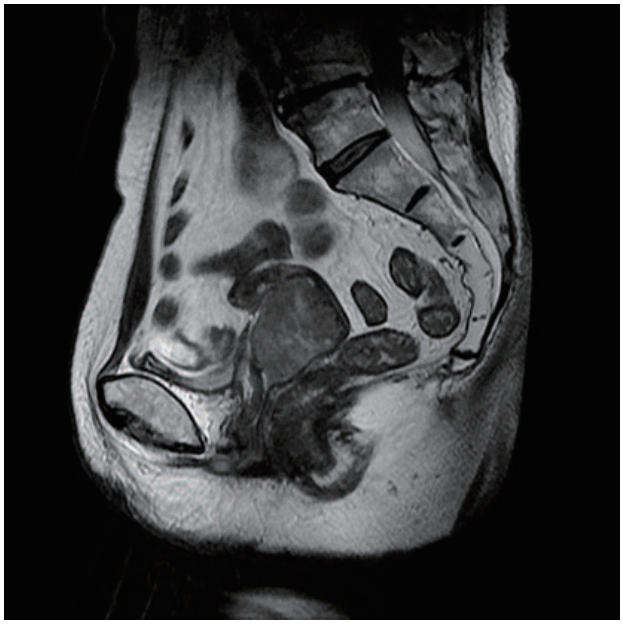

Fig. 1 MRI findings. A 4.5 × 3.3-cm primary mass was present on the ventral side of the cervix on the first MRI examination.

surgery and radiotherapy were considered. The patient selected the latter and concurrent chemoradiotherapy (CCRT) was initiated as the initial treatment. Whole-pelvis radiation therapy (WPRT) was applied at 50.0 Gy in 25 fractions, and additional irradiation was applied at 10.0 Gy in five fractions to the left internal lymph node area (Fig. 2a, b, c), followed by intracavitary brachytherapy (ICBT) at 20.0 Gy in 4 fractions. In addition, 5 cycles of cisplatin (CDDP) (40 mg/m^2) were administered. Immediately after completion of this treatment, cytological diagnosis in the cervix was negative for intraepithelial lesion or malignancy (NILM), indicating that radiation was effective.

At one month after completion of the initial treatment, the primary tumor had disappeared macroscopically on examination. Size reduction of the primary tumor was noted on CT, without a new finding of metastasis. At 2 months after completion of the initial treatment, cancerous invasion of the vaginal wall and left parametrial induration were observed on internal examination. The histological diagnosis was squamous cell carcinoma of the cervix with inflammation.

On CT, regrowth of the primary tumor and enlargement of the paraaortic lymph node were apparent. Moreover, separately from the primary lesion, a recurrent mass was present on the left dorsal side of the cervix on pelvic MRI (Fig. 3). Based on these findings, the patient was diagnosed with local recurrence and paraaortic lymph node metastasis after treatment of cervical cancer, and paclitaxel plus carboplatin (TC) and bevacizumab therapy was initiated.

Abdominal pain suddenly developed 17 days after completion of the 4th cycle of TC + bevacizumab and the patient was transported to our hospital. On arrival, her consciousness level was alert, and blood pressure was 140/100 mmHg with a pulse of 118/min. Contrast-enhanced CT showed accumulation of ascites, and features of free air were noted at several sites in the abdominal cavity, based on which gastrointestinal perforation was diagnosed. A gastrointestinal series

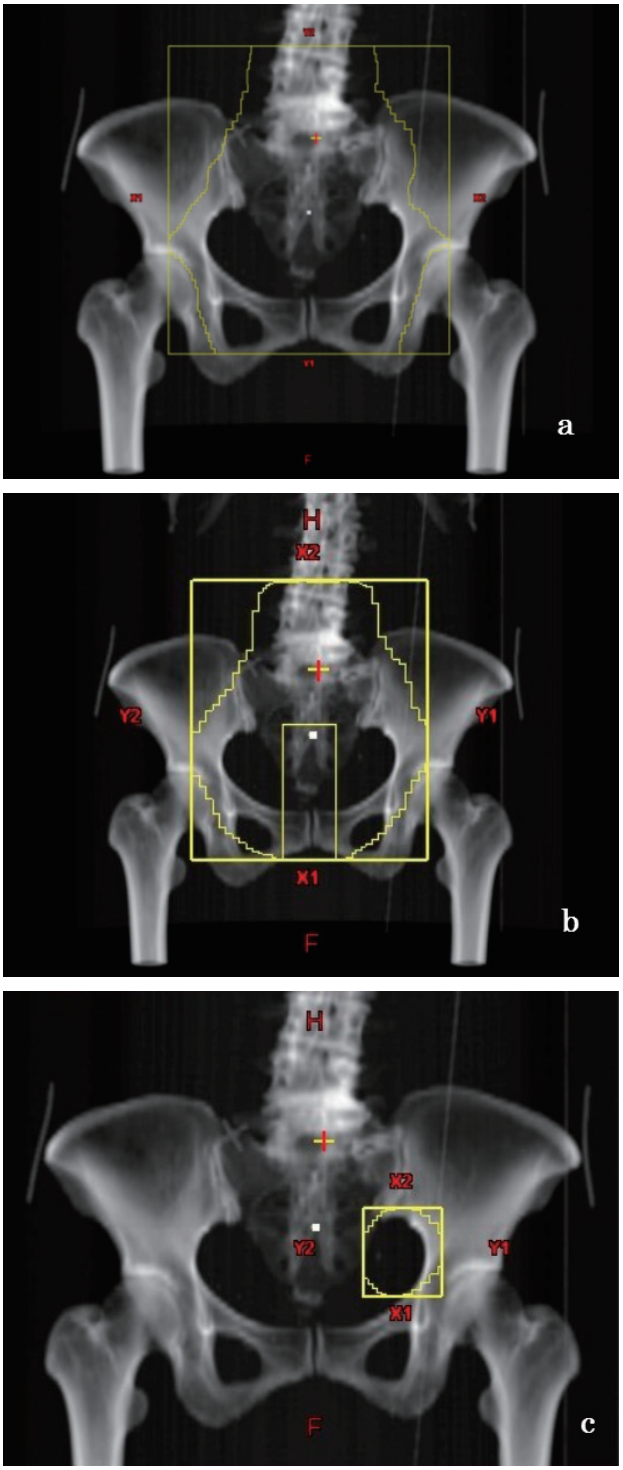

Fig. 2 Simulation chart for irradiation. a) Whole-pelvis radiation therapy (WPRT) was applied at a total of 50.0 Gy in 25 fractions. b) Center block was combined in the latter 20.0 Gy of irradiation of WPRT. c) Additional irradiation was performed to the left internal lymph node area at 10.0 Gy in five fractions.

was performed after consultation with the Department of Gastrointestinal Surgery, but the perforated regions were unclear. Therefore, we decided to perform a search of the abdominal cavity using laparoscopy.

A 12-mm camera port was inserted through the umbilical region, pneumoperitoneum was applied, 5-mm ports were inserted into the bilateral lower abdominal regions, and the search was initiated. Two perforated regions were found in the small intestine, although nei-

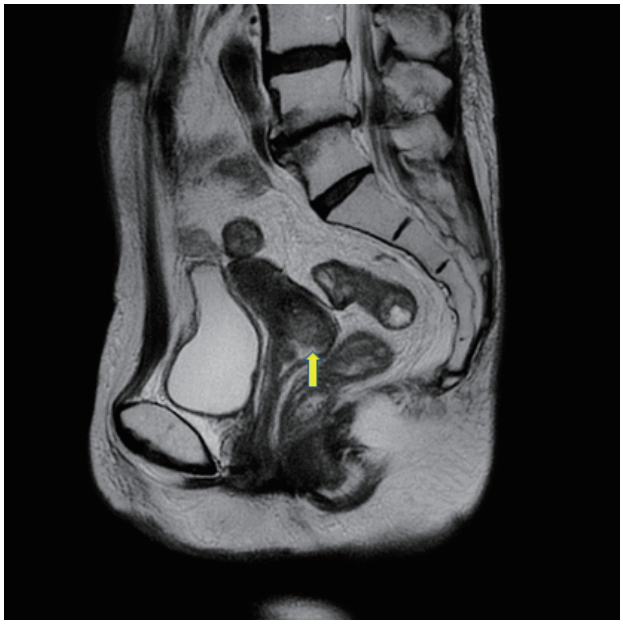

Fig. 3 MRI findings. A recurrent mass was present on the left dorsal side of the cervix on MRI performed at the time of recurrence.

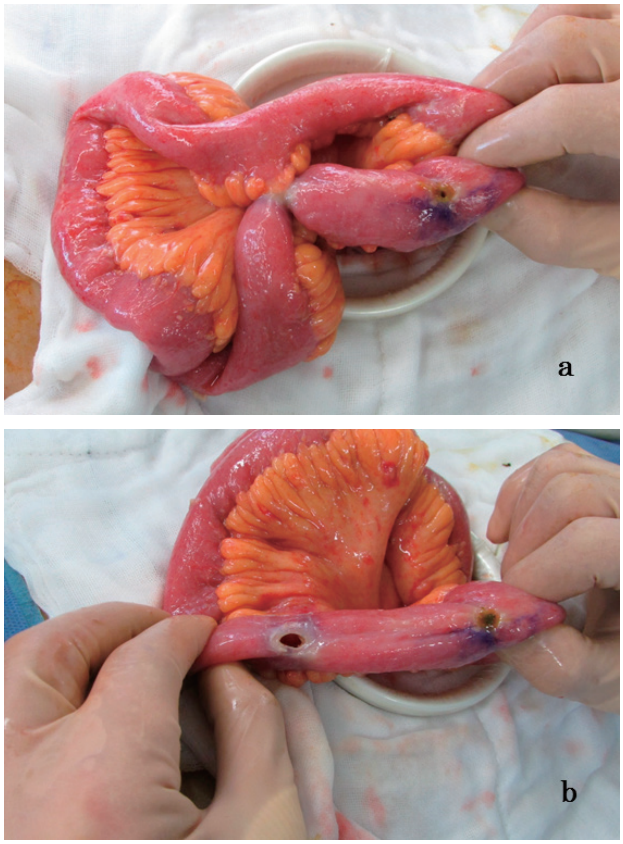

Fig. 4 Intraoperative findings. a) The small intestine was perforated and part of the intestine was twitched by adherence. b) Perforation of the small intestine was clearly noted at two sites, but no disseminating lesion was present around either of these regions.

ther clear peritoneal dissemination nor irradiation-related edema was observed in the whole intestine (Fig. 4a, b) [6], and the incision of the umbilical port was extended. A small size Alexis wound retractor (Applied Medical, Rancho Santa Margarita, CA, USA) was attached, and the small intestine was guided out of the

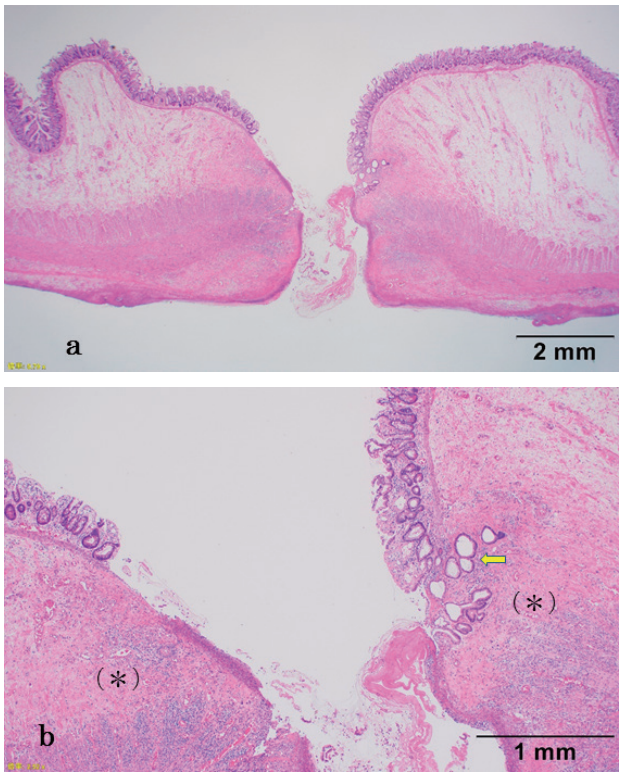

Fig. 5 Histopathological findings. a) Only findings of peritonitis were noted in the perforated regions in the resected intestine under a loupe and no carcinomatous dissemination or intestinal invasion was found. b) No finding suggesting peritoneal dissemination was noted in the perforated regions of the intestine. Fibrotic regions (*) and aberrant non-atypical ductal structures (yellow arrow) were present in the intestinal muscle layer.

body. The part of the small intestine containing the perforated regions was resected and then reconstructed by functional end-to-end anastomosis. Information drains were placed in the bilateral subphrenic regions and Douglas pouch, and surgery was completed. There was no malignant finding in cytology of the collected ascites. The postoperative course was favorable and the patient was discharged 12 days after surgery.

On pathological examination of the excised intestinal specimen, inflammatory cells, such as macrophages and neutrophils, were found to have accumulated around the perforated regions, but there was no finding of carcinomatous peritoneal dissemination, including in the perforated regions (Fig. 5a, b). The influence of bevacizumab may have been a cause of intestinal perforation, but the patient had also taken oral NSAIDs for a long time for tumor invasion-induced visceral pain. The patient had taken loxoprofen sodium at 180 mg per day for about 1 month, and the possibility of an association with perforation cannot be ruled out; i.e., together with the histopathological findings of the perforated regions, perforation due to NSAID-related ulcer may also have been a cause.

In the later course, the recurrent mass in the pelvis grew, cancer pain aggravated, multiple pulmonary metastases developed, and treatment changed to palliative care. The general condition gradually aggravated and the patient died of the primary disease 11 months after completion of the initial treatment.

DISCUSSION

During bevacizumab administration, careful attention to symptoms is required for appropriate diagnosis of gastrointestinal perforation. Patients not meeting exclusion criteria (symptoms of intestinal obstruction, previous radiotherapy of the abdominal and pelvic regions, abscess, surgery within 28 days, hemorrhagic tendency, uncontrollable hypertension), those with little previous chemotherapy, and those with no gastrointestinal complication need to be carefully selected, with appropriate monitoring of adverse events [7, 8].

The time to intestinal perforation from initiation of bevacizumab varies among reports from early after initiation to late onset, with no consistency, but it has been reported that 70% of cases with perforation develop within 6 months after the initial administration, with a median onset time of 3.35 months (0.39–37.32 months) [9]. In addition, perforation is more likely to develop in cases with tumorous and disseminating lesions directly invading the intestinal wall, internal intestinal pressure elevation due to these lesions, intestinal obstruction, or gastrointestinal organ disorders associated with previous irradiation [10]. Bevacizumab is contraindicated for these patients as a rule, and these conditions were included in the exclusion criteria in previous clinical studies [11–14].

The present case was treated with CCRT as the initial treatment. However, on imaging at the time of recurrence, there was no tumorous lesion invading the intestine and no irradiation-associated symptoms, such as radiation enteritis and intestinal obstruction. Thus, bevacizumab-combined chemotherapy was initiated. Intestinal perforation was suspected during bevacizumab treatment, but based on consultation with the Department of Gastrointestinal Surgery, a laparoscopic search was first initiated to examine the abdominal cavity. Despite this being performed after irradiation, no intestinal edema or tissue hardening impairing peristalsis was noted. Thus, there was no difficulty in identifying the perforated regions, and surgery could be completed with laparoscopic assistance throughout the procedure from partial resection of the intestine, to reconstruction anastomosis.

On histological examination of the perforated regions, there was no finding suggesting cancer invasion, and inflammatory cells, such as macrophages and neutrophils, had accumulated around existing gastrointestinal mucosal injuries. These findings are similar to the features of perforation of a peptic ulcer. Therefore, the intraoperative abdominal cavity findings, macroscopic and histological findings of the perforated regions, and long-term oral ingestion of NSAIDs suggested that asymptomatic ulcers were affected by bevacizumab and resulted in the intestinal perforations. This is consistent with a report showing that the inhibitory effect of bevacizumab on angiogenesis delays healing of gastric ulcers [15]. Previous oral ingestion of NSAIDs has also been reported to be a risk factor for bevacizumab-induced intestinal perforation [16]. This suggests that the content and history of medication should be carefully considered in management of a malignant tumor in a case with long-term treatment. In the future, long-term oral ingestion of NSAIDs may be viewed as an exclusion criteria in considering the indication for bevacizumab.

In a case with suspected bevacizumab-induced intestinal perforation, laparotomic surgical treatment is often considered on the assumption of peritoneal dissemination and invasion of the intestinal wall by a mesentery mass. However, in our patient, laparoscopic surgery was first selected for examination, and laparoscopy-assisted treatment could be carried out from identification of the perforated regions of the intestine to resection of these regions and reconstruction anastomosis. This was made possible through findings of an absence of a dissemination lesion and a small influence of irradiation on the abdominal cavity.

When such severe adverse disorders as those in this case are suspected, an accurate diagnosis of the pathological condition and initiation of treatment as soon as possible are clearly beneficial. When intestinal perforation is suspected and a search in the abdominal cavity is required to make a definite diagnosis, performance of exploratory laparotomy or laparoscopic surgery depends on the capability of each facility. However, if the conditions are met, it is preferable to use a method that is low-invasive for the patient [17, 18]. Also, when a diagnosis can be made and repair of the intestine can subsequently be carried out laparoscopically, treatment previously performed by laparotomy in many cases can be performed with laparoscopy, which leads to early recovery of general conditions after surgery and subsequently an early restart of tumor treatment. Our case suggests that laparoscopic surgery may also be useful for bevacizumab-induced intestinal perforation associated with an NSAIDs-related ulcer.

Intestinal perforation after treatment with bevacizumab is a pathological condition encountered at a certain frequency in treatment of advanced/recurrent gynecological cancers. When this condition develops, accurate and rapid diagnosis and treatment are necessary, with attention to the history of medication, particularly for NSAIDs. Use of a low-invasive procedure such as laparoscopic surgery shortens the time required for treatment of the adverse reaction and permits continuation of tumor treatment with minimal interruption; however, careful selection of patients who do not meet exclusion criteria is important.

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