A case of rectal cancer in which the administration of mFOLFOX6 plus cetuximab might have caused duodenal perforation

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ABSTRACT

Although cetuximab-containing chemotherapies are effective treatments for unresectable advanced colorectal cancer, characteristic side effects have been reported. Here, we report a case of rectal cancer in which duodenal perforation is likely to have occurred during the administration of mFOLFOX6 plus cetuximab as first-line chemotherapy. A 55-year-old woman complained of abdominal pain for several months. She was diagnosed with advanced rectal cancer and unresectable multiple liver and lung metastases. We initiated first-line chemotherapy with mFOLFOX6 plus cetuximab, which was administered with the expectation of early tumor shrinkage and consequent reductions in her abdominal pain. After 2 courses of chemotherapy, her abdominal symptom improved. However, after 4 courses of chemotherapy, she suddenly reported severe abdominal pain and was conveyed to our department. Abdominal computed tomography revealed intraabdominal free air, which we suspected was caused by gastrointestinal perforation. Urgent laparotomy was performed. We identified the perforation at the anterior wall of the duodenal bulb, closed the perforated site, and covered it with the omentum. In general, it has been reported that chemotherapy with cetuximab regimen is associated with some adverse events such as hematotoxicity, acne-like rash and hypersensitivity reaction. This time, we experienced a rare case of duodenal perforation that might have been associated with mFOLFOX6 plus cetuximab. We suggest that bowel perforation should be considered if a patient experiences sudden abdominal pain when receiving chemotherapy. *Ryukyu Med. J., 37 (1~4) 97~104, 2018*

Key words: Unresectable rectal cancer; Duodenal perforation; mFOLFOX6 plus Cetuximab

INTRODUCTION

Colorectal cancer is a common malignant disease worldwide and the fourth-leading cause of cancer death in the Western world[1]. Its prevalence and incidence have recently been increasing in Japan[2]. The standard treatments for unresectable colorectal cancer are generally defined as surgical intervention, radiotherapy, and chemotherapy. There have been improved in chemotherapy for unresectable colorectal cancer, as a consequence of the development of molecular-targeted drugs such as anti-vascular endothelial growth factor (VEGF) antibody and anti-epithelial growth factor receptor (EGFR) antibodies[3, 4]. For instance, the anti-EGFR monoclonal antibody cetuximab has improved overall and progression-free survival for patients with unresectable colorectal cancer, and has helped to preserve quality of life (QOL) by tumor shrink consequence to the relevance of symptom in patients with KRAS wild-type tumors compared with the supportive care patients.[5, 6].

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Adding cetuximab to FOLFIRI (irinotecan and infusional fluorouracil and leucovorin) was associated with higher tumor response irrespective of patients' baseline symptomatic status, and enhanced symptom relief from baseline in those whose tumors had responded. So cetuximab plus chemotherapy improved patients' QOL associated with tumor response and survival[7]. Recently, the evaluation of mutation in exon 2, 3 and 4 of KRAS and NRAS (extended RAS analysis) is important for the treatment of unresectable colorectal cancer, so the anti-EGFR monoclonal antibody should be administered for patients with RAS wild-type[4]. On the other hand, it has generally been reported that cetuximab is associated with some adverse events and side effects, such as acne-like rash, hypomagnesemia, and hypersensitivity reaction[5, 8]. In particularly, care for skin toxicity is needed when administering cetuximab, we routinely administrate moisturizing agent, topical steroids, and antibiotics. Here, we report a rare case of duodenal perforation that might have been associated with cetuximab-containing first-line chemotherapy.

CASE REPORT

A 55-year-old woman had complained intermittently of right hypochondrial dull pain for several months, and lost 5 kilograms over 6 months. She went to a nearby hospital to be examined closely, and was diagnosed with multiple liver tumor and rectal tumor. She was referred to our hospital for additional examinations and treatments. Her laboratory examination revealed increasing levels of carcinoembryonic antigen (CEA) (1856ng/mL; normal: <5.0ng/mL) and carbohydrate (CA) 19-9 (4905U/mL; normal: <37.0U/mL). Further, deteriorations of liver and biliary tract enzymes were noted with elevated aspartate aminotransferase (88IU/L; normal: <40IU/L), alanine aminotransaminase (71IU/L; normal: <40IU/L), lactate dehydrogenase (2813IU/L; normal: <245IU/L), and alkaline phosphatase (1256IU/L; normal: <360IU/L) levels. Colonoscopic findings revealed an advanced rectal tumor of type 1 (Fig. 1). The histological analysis of the colonoscopy biopsies revealed Group 5 expression as malignant cells. Further cytological examination of the biopsy specimen revealed atypical cells, which indicated well-differentiated adenocarcinoma, and malignant cells were positive for expression of EGFR protein. The *KRAS* status was wild type.

We can check the RAS status now, but the mutation of RAS could not be examined at that time. A contrast-enhanced thoracoabdominal computed tomography (CT) scan indicated multiple unresectable lung and liver metastases (Fig. 2). Esophagogastro-

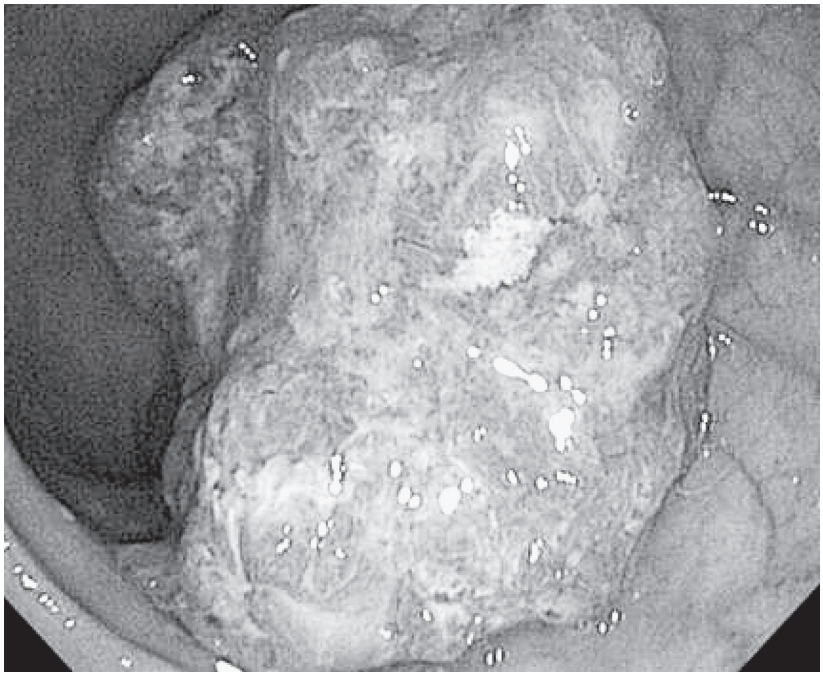

Fig. 1 **Colonoscopic findings revealed an advanced rectal tumor of type 1**

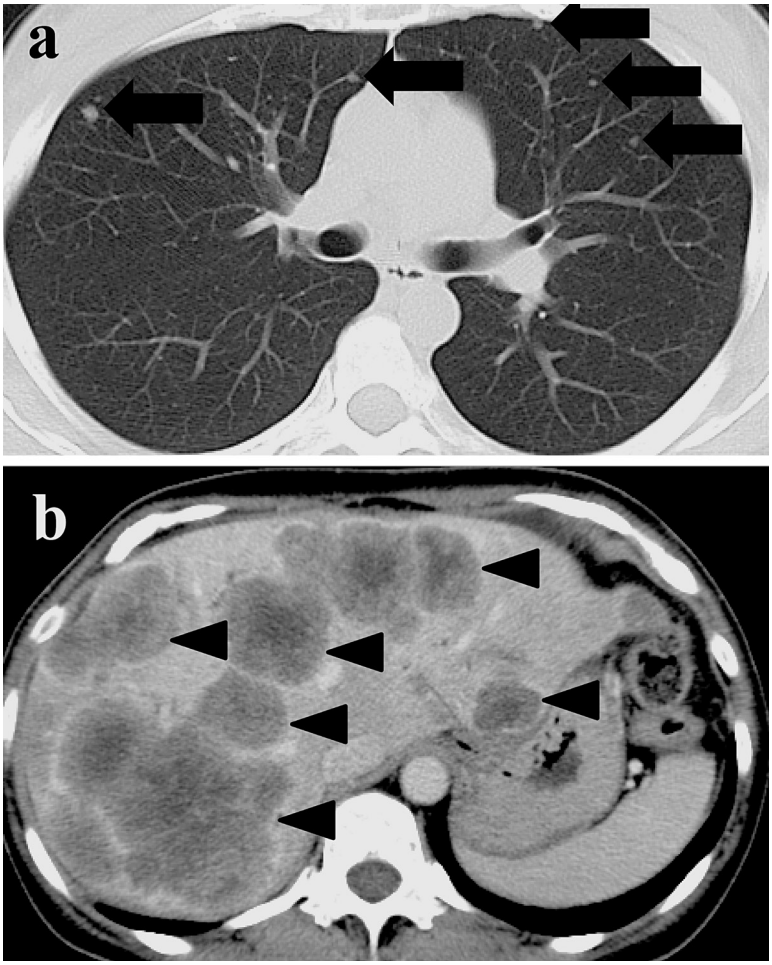

Fig. 2 **A contrast-enhanced abdominal computed tomography scan showed multiple small lung tumors(arrows) (a) and multiple large liver tumors (arrowheads) (b)**

duodenoscopy (EGD) revealed only atrophic gastritis without the abnormality findings of duodenum in the examination for hypochondrial pain. Her past history such as peptic ulcer, enteritis, diverticulitis, abdominal irradiation therapy was not pointed out, and she did not take the administration of NSAIDs and steroids so far.

Her abdominal dull pain seemed to derive from an enlarged liver by metastases and gradually deteriorated. We therefore initiated first-line chemotherapy with cetuximab (initially 400mg/m^2, followed by weekly infusions of 250mg/m^2) plus modified oxaliplatin (85mg/m^2), folinic acid (200mg/m^2), and 5-fluorouracil (5-FU) (400mg/m^2) bolus on day 1, followed by continuous infusion of 5-FU (2400mg/m^2) over the next 46 hours (mFOLFOX6) in an expectation of early tumor shrinkage[9]. After 2 courses of chemotherapy, she presented with improvements in her abdominal symptom. However, after 4 courses of chemotherapy, she suddenly complained of severe abdominal pain and was promptly conveyed to our department. Physical examination showed mainly upper abdominal pain and rebound tenderness.

An abdominal computed tomography scan showed intraabdominal free air (Fig. 3), which we suspected had resulted from gastrointestinal perforation. Urgent laparotomy was performed, we identified a small hole of perforation (4×6mm) at the anterior wall of the duodenal bulb (Fig. 4). The perforated site was closed via suturing and covered with the omentum. Although she experienced a postoperative intraabdominal abscess under the incised wound, it was treated successfully by the administration of antibiotics. She was discharged with no complications on postoperative day 16. In this case, tumor maker levels decreased that CEA was from 1856 to 86 (ng/mL) and CA19-9 was from

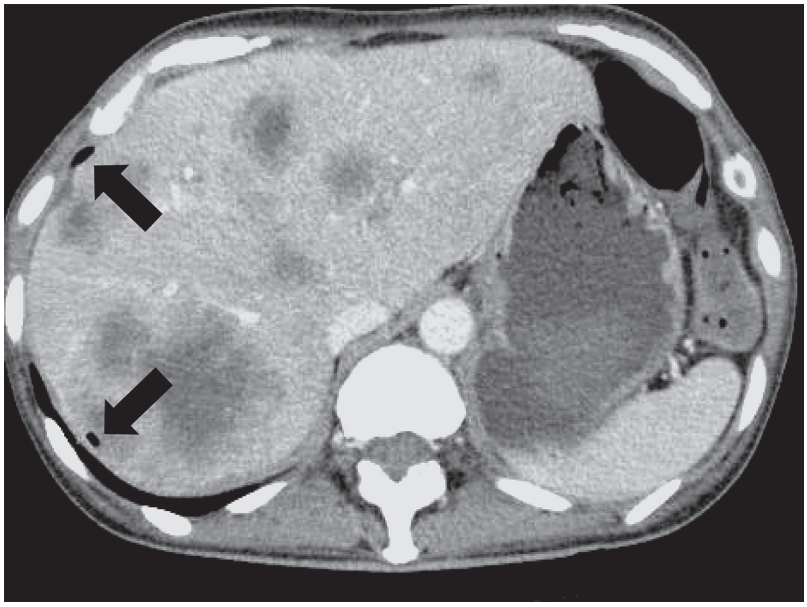

Fig.3 **An abdominal computed tomography scan showed intraabdominal free air (arrows)**

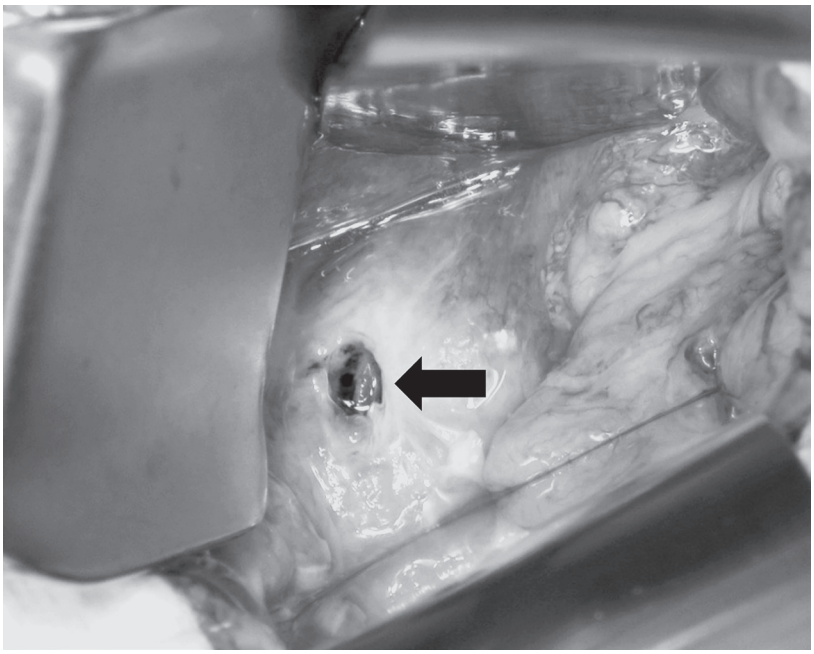

Fig.4 **A small hole of perforation was observed at the anterior wall of the duodenal bulb (arrow)**

4905 to 232 (U/mL), respectively, after 4 courses of chemotherapy. Moreover the liver metastatic tumor shrank sufficiently (Fig. 3) without the enough contraction of lung metastatic tumor, indicating the efficacy of cetuximab in combination with mFOLFOX6. We discussed continuing chemotherapy with her informed consent, and she strongly desired to continue the same chemotherapeutic regimen. Re-starting the dose of chemotherapeutic ragents was the same as first-line administrated chemotherapy dose, after we confirmed the healing of duodenal perforation with EGD.

She received an additional 8 courses of chemotherapy until tumor progression. Throughout the courses of chemotherapy, there were several moderate adverse events (hematotoxicities and non-hematotoxicities, both of grade 2 or less), but there was no recurrence of the gastrointestinal perforation (grade 4).

DISCUSSION

Recently, pharmacotherapy-based treatments for unresectable metastatic colorectal cancer (mCRC) have improved substantially with the development of new cytotoxic drugs, such as oxaliplatin and irinotecan, and molecular-targeted agents, such as anti-VEGF and anti-EGFR antibody[3, 4]. Studies have reported that these chemotherapies are effective, and have improved the survival of patients with unresectable mCRC[10, 11].

Expression of EGFR has been observed in the human colon[12]. Some populations of colorectal cancer overexpress EGFR, which activates cellular signaling, migration, and proliferation[13]. Cetuximab is a monoclonal antibody that inhibits EGFR, blocks cancer cell growth, and induces apoptosis. Cetuximab-containing chemotherapy has improved overall and progression-free survival for patients with unresectable colorectal cancer[5, 6]. The CRYSTAL (Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) and OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) clinical trials demonstrated that adding cetuximab to first-line chemotherapy in patients with KRAS wild-type mCRC improved the treatment outcome compared with chemotherapy alone. The addition of cetuximab to chemotherapy resulted in the improvement in overall survival (OS) and progression-free survival (PFS) and overall response rate (ORR) compared with chemotherapy alone, median OS was 23.5 months and 19.5 months, median PFS was 9.6 months and 7.6 months, ORR was 57.3% and 38.5%, respectively[14].

Moreover, it has been reported that early tumor shrinkage due to the administration of cetuximab is a predictive maker for favorable treatment outcomes[9, 15]. Chemotherapy with cetuximab regimen was indicated to relieve patients' symptoms such as pain, fatigue, appetite loss with higher tumor response of the treatments[7]. Therefore, the administration of cetuximab-containing chemotherapy is thought to be useful as a means of achieving early tumor shrinkage for select patients with paraneoplastic abnormality findings derived from the liver metastases, such as our patient. Indeed, our patient's abdominal pain related to liver metastasis had improved after 2 courses of cetuximab plus mFOLFOX6, and her liver metastatic tumor had shrunk sufficiently.

On the other hand, there are several reported side effects and adverse events related to molecular-targeted agents. Cetuximab is also reportedly associated with various side effects, such as skin rash, hypomagnesemia, hypersensitivity reaction[5, 8]. Therefore, the above-mentioned care is warranted when administering cetuximab for mCRC. Notably, one of the harmful events is gastrointestinal perforation, which is reported to have a frequency of approximately 1% during the administration of bevacizumab, an anti-VEGR antibody[16, 17]. It has been reported that the frequency of gastrointestinal perforation occurred by chemotherapy alone for colorectal cancer was reported to be 0.13%[18], but the precise frequency of bowel perforation by cetuximab regimen could not be found out.

There has been only two reports of bowel perforation following cetuximab with the exception of pneumatosis cases undergoing cetuximab treatment for mCRC[13, 19]. The exact mechanism of cetuximab-containing chemotherapy associated bowel perforation was unknown, except for the tumor mass involving the bowel wall and peritoneal carcinomatosis[17, 19]. Ozturk et al reported that cetuximab might cause bowel perforation by reducing VEGF levels or causing mucositis[13] and Bruns CJ et al also reported to decrease the production of VEGF[20], but we could not mention more other data which indicated the effect of the decrease of VEGF by cetuximab. Moreover, cetuximab might prolong wound healing time, which itself may cause perforation because of pre-existing ulcer[21].

Nevertheless, in our case, EGD revealed only atrophic gastritis before we started cetuximab plus mFOLFOX6, and the duodenal perforation occurred during chemotherapy. There was the possibility of the duodenal ulcer perforation caused by Helicobactor pylori, but H. pyloli test was not examined in this case. We should had performed H. pyloli test at the event of duodenal perforation, and eradicated H. pyloli if H. pyloli test was positive. Although we could not assured that duodenal ulcer caused the bowel perforation, we prophylactically administrated to her proton pump inhibitor in a hospital and H2-blocker at the time of discharge, so she took H2-blocker during chemotherapy.

Except for our case, to date, there have been 11 reported cases of gastrointestinal perforation during

cetuximab administration in Japan[22]. However, the reports of these cases have not included detailed clinical courses, risk factors, treatment method, prognosis.

In our case, at first we proposed to change another regimen or chemotherapy without cetuximab to her, but she desired to receive the same chemotherapeutic regimen because of the effectiveness in first line chemotherapy and the possibility of insufficient effect in second line chemotherapy. We discussed continuing chemotherapy with her, on the condition that the possibility of bowel perforation caused again, we started second cetuximab puls FOLFOX treatment and prophylactically administrated anti-ulcer agent under informed consent. We administrated to her the same chemotherapeutic regimen and dose until progressive disease was observed, and duodenal perforation fortunately did not occur again.

Hapani S et al reported that identifying patients at high risk of gastrointestinal perforation would be important before chemotherapy with bevacizumab[17]. Careful assessment of the patient's history should include looking for the evidence of past diverticulitis and peptic ulcer, irradiation exposure, recent colonoscopy, bowel obstruction, previous polysurgeries, so physicians should be careful to detect any signs of bowel perforation as early as possible after chemotherapy. The mortality rate of gastrointestinal perforation was 21.7% among patients receiving bevacizumab. Therefore, if gastrointestinal perforation is detected during chemotherapy, first of all the prompt surgical treatment is warranted. We should certainly close via suturing the perforated site and cover with an omental flap, or create only stoma without intestinal anastomosis. In any case, it is important to carry out prudent surgical procedures and intensive postoperative managements for improving the survival rate. On the other hand, non-operative treatment such as bowel rest and intravenous fluid and antibiotics might be a viable approach for some patients with the stability of vital signs and examination findings[17]. As duodenal perforation had occurred during mFOLFOX6 plus cetuximab in our case, we should had changed the causal chemotherapeutic regimen. We should be discreet in re-starting the same chemotherapy, and administrate FOLFIRI regimen alone without cetuximab and/or bevacizumab.

Though our patient was satisfied with the improvement in her abdominal paraneoplastic symptom such as pain, we always remember the possibility of serious side effects and adverse events during the administration of mFOLFOX6 plus cetuximab too.

CONCLUSION

In general, it has been reported that chemotherapy with cetuximab regimen is associated with some adverse events such as hematotoxicity, skin toxicity and hypersensitivity reaction. Here, we experienced a rare case of duodenal perforation that might have been associated with mFOLFOX6 plus cetuximab. We suggest that bowel perforation should be considered if a patient who is receiving chemotherapy for colorectal cancer develops sudden abdominal pain.

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