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Case report

# Pathological complete response after neoadjuvant chemotherapy with FOLFOX for locally advanced sigmoid colon cancer with diverticulitis: A case report

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ABSTRACT

*Introduction and importance:* The standard treatment for locally advanced colon cancer (LACC) without distant metastasis is curative surgery followed by adjuvant chemotherapy, but the long-term outcomes of this strategy are not satisfactory. Neoadjuvant chemotherapy (NAC) is a promising novel option to overcome this issue. Tumor regression is an expected effect of NAC for LACC, but pathological complete response (pCR) is rare. In this report, we present a rare case of pCR after NAC with FOLFOX for LACC in the sigmoid colon.

*Presentation of case:* A 66-year-old woman presented to our hospital with fever and abdominal pain. The diagnosis was LACC in the sigmoid colon with possible invasion of the uterus and pelvic wall, stage IIIC (T4bN1bM0). Furthermore, the tumor was complicated by diverticulitis. A colostomy was performed, followed by NAC with FOLFOX. Six cycles were completed without significant adverse events, and the lesion shrunk remarkably. We performed a curative sigmoidectomy without any postoperative complications. Pathological examination revealed no viable cancer cells, indicating pCR.

*Discussion:* To the best of our knowledge, this is the first report of pCR after NAC for LACC complicated by diverticulitis. Colostomy before NAC, regimen, and cycle of NAC may be the key to this favorable course.

*Conclusion:* We present a rare case of pathological complete after neoadjuvant chemotherapy with FOLFOX for locally advanced colon cancer in the sigmoid colon complicated by diverticulitis. Our experience may be valuable in determining the optimal treatment strategy for LACC complicated by diverticulitis.

## 1. Introduction

The standard treatment for locally advanced colon cancer (LACC) without distant metastasis is curative surgery followed by adjuvant chemotherapy (ACT), but the long-term outcome of this strategy is not satisfactory. High local and distant recurrence rates of 15–43% have been reported [1,2]. A novel strategy is warranted, and neoadjuvant chemotherapy (NAC) may be a promising option. Tumor regression is an expected effect of NAC for LACC; previous research indicates a promising regression rate of 31–44% but a low pathological complete response (pCR) of 2–8% [3,4]. Even in whole colorectal cancer, only a few case reports of pCR after NAC have been published [5,6].

In this report, we present a rare case of pCR after NAC with FOLFOX for LACC in the sigmoid colon. Furthermore, the tumor was complicated by diverticulitis. This situation typically warrants exclusion from clinical trials, and to the best of our knowledge, this is the first case report of pCR after NAC for LACC complicated by diverticulitis. This work is reported in line with the SCARE criteria [7].

## 2. Presentation of case

A 66-year-old woman presented to our hospital with a maximum fever of 38.8 °C and lower abdominal pain. Her medical history included an appendectomy and cesarean section. Her white blood cell count, C-reactive protein level, and carcinoembryonic antigen (CEA) level were 7600 cells/μL, 2.36 mg/dL, and 235.3 ng/mL, respectively. Colonoscopy revealed advanced cancer in the sigmoid colon, and biopsy revealed a tubular adenocarcinoma with a RAS mutation (Fig. 1). Computed

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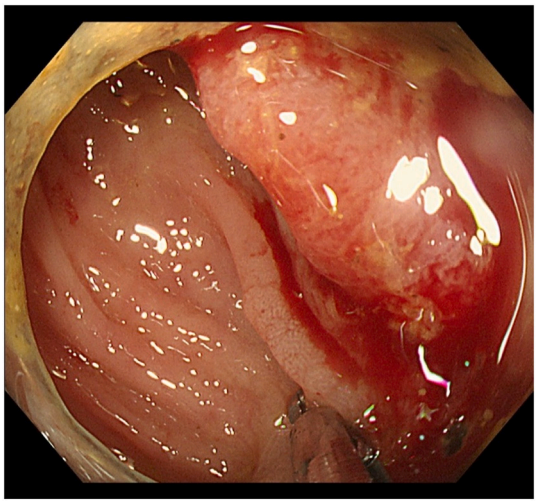

**Fig. 1.** Colonoscopy at the time of diagnosis.
Colonoscopy revealed advanced cancer in the sigmoid colon.

tomography revealed a large tumor extending into the pelvis, possibly invading the uterus and pelvic wall, and complicated by diverticulitis (Fig. 2). Metastasis was suspected in the enlarged regional lymph nodes, but no distant metastasis was identified. The diagnosis was LACC in the sigmoid colon complicated by diverticulitis, stage IIIC (T4bN1bM0) according to the 8th Union for International Cancer Control classification.

We performed a laparoscopic loop colostomy of the right transverse colon along with antimicrobial treatment. The findings supportive of diverticulitis disappeared, and we started NAC 4 weeks after the colostomy. The regimen was mFOLFOX6 consisting of oxaliplatin 85 mg/m$^2$, l-leucovorin 200 mg/m$^2$, and 5-fluorouracil (5-FU) 400 mg/m$^2$ intravenously on day 1, followed by continuous intravenous 5-FU 2400 mg/m$^2$ for 46 h, every 2 weeks. Six cycles were completed without significant adverse events. After chemotherapy, the tumor shrank remarkably, and there were no findings of invasion of the uterus and pelvic wall (Fig. 3). The enlarged lymph nodes also shrank, and the CEA level reduced from 235.3 to 9.4 ng/mL. Pre-operative re-staging revealed that the tumor stage was T4aN0M0. We performed curative open sigmoidectomy and stoma closure 5 weeks after the last cycle of FOLFOX. Intraoperatively, only inflamed adhesions were observed between the tumor and uterus, and between the tumor and pelvic wall. The adhesions were easily detached and were not likely involved with the cancer. Therefore, we performed only sigmoidectomy without combined

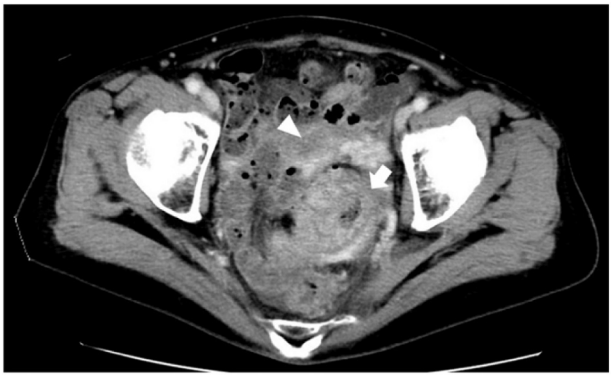

**Fig. 2.** Computed tomography at the time of diagnosis.
At diagnosis, computed tomography revealed a large tumor in the sigmoid colon complicated with diverticulitis (arrow), which extended into the pelvis and possibly invaded the uterus (arrowhead) and pelvic wall (T4bN1bM0).

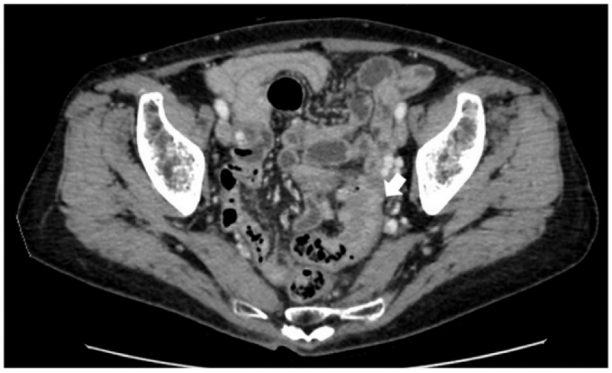

**Fig. 3.** Computed tomography after neoadjuvant chemotherapy.
After neoadjuvant chemotherapy, the lesion shrunk remarkably (arrow).

resection of other organs. We also performed standard regional lymphadenectomy with high ligation of the inferior mesenteric artery.

Only an ulcer scar and numerous diverticula were identified in the specimen (Fig. 4). Pathological findings revealed granulomas, suggestive of past diverticulitis, and the absence of viable cancer cells in the primary lesion (Fig. 5). Furthermore, no metastasis was observed in the 19 harvested lymph nodes; therefore, the effect of NAC was considered to be pCR. The patient's postoperative course was uneventful. We suggested another six cycles of adjuvant FOLFOX, but the patient refused because of non-specific postoperative fatigue. No recurrence was observed 10 months after the curative surgery.

## 3. Discussion

Neoadjuvant chemotherapy (NAC) is now a common treatment for upper gastrointestinal malignancies [8,9]. Although NAC is not the standard treatment for LACC, many previous studies have proposed NAC as a novel promising option to overcome the poor prognosis of LACC [3,4,10,11]. The FOxTROT trial reported a higher complete resection rate with sufficient margins using NAC than ACT (96% vs. 80%) without any increased postoperative complications [3]. This result is very attractive because it is well known that an insufficient resection margin leads to a poor prognosis in colorectal cancer [12–14]. Furthermore, an observational study reported improved overall survival with NAC compared with ACT, particularly in patients with stage T4b disease, and the National Comprehensive Cancer Network (NCCN) guidelines now consider NAC as a viable option for T4b LACC [10,11]. Therefore, we selected NAC for our patient.

In this case, the tumor was complicated by diverticulitis. Colon diverticulitis is a common disease that can coexist with malignancy, but the management of LACC complicated by diverticulitis is often complicated. Inflammation makes surgery quite difficult because the

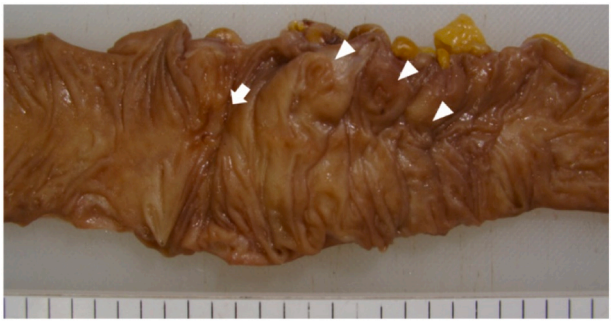

**Fig. 4.** Surgical specimen.
Only the ulcer scar (arrow) and numerous diverticula (arrowhead) were identified in the specimen.

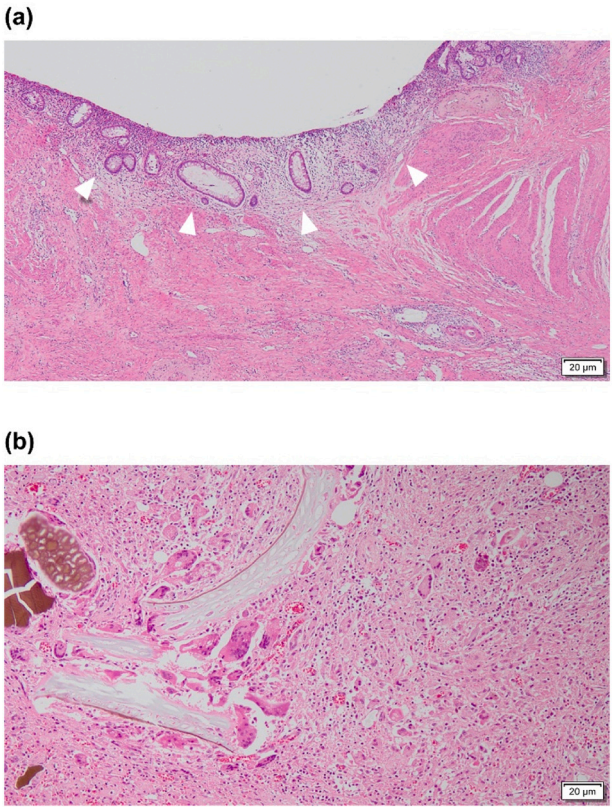


**Fig. 5.** Pathological findings.
Pathological findings revealed no viable cancer cells in the ulcer scar (arrowhead) (a), but granulomas were observed, which suggested past diverticulitis (b).

weakened tissue is difficult to manage and an accurate resection line is difficult to identify. In such situations, NAC may be useful because of the direct effect of chemotherapy and the waiting time to eliminate the inflammation. Although the risk of diverticulitis-related adverse events (i.e., recurrent inflammation and perforation) was a serious concern, we completed the planned chemotherapy without significant adverse events. In this patient, the indication for colostomy was controversial because symptoms of bowel obstruction were absent. However, a colostomy may be helpful for the rapid and complete control of inflammation,and most importantly, to prevent diverticulitis-related events during chemotherapy. Furthermore, we started NAC more than 4 weeks after the onset of diverticulitis. It may be safe to have enough time between the onset of diverticulitis and chemotherapy initiation to reverse the inflammation completely. However, this decision should consider the cancer progression during the waiting time.

We performed six cycles of FOLFOX, but the regimen and cycle of NAC for LACC remain controversial. In the NCCN guidelines, FOLFOX or CapeOX (capecitabine plus oxaliplatin) is considered a viable regimen, but the number of cycles is not specified. Previous studies administered three or four cycles of FOLFOX to balance the expected effect of chemotherapy with the risk of NAC-related adverse events and postoperative complications [3,4]. However, the PRODIGE 22 trial failed to reveal an improved major response rate in NAC compared with ACT, which was the primary endpoint of this trial, and the investigators discussed that the limited cycle of NAC might have been responsible for this negative result [4]. More cycles may be considered depending on the clinical situation.

The possibility of additional effects of molecular targeted agents in NAC is another interesting topic. In patients with RAS mutations, the use of vascular endothelial growth factor (VEGF) inhibitors can be considered, but previous research in rectal cancer reported this matter in a negative light [15,16]. In the trial of NAC for locally advanced rectal cancer (LARC), FOLFOX plus bevacizumab (*Bmab*) yielded promising results, but cardiac adverse events and postoperative death were observed. The investigators discussed the possibility that the use of *Bmab* contributed to these events and decided not to use *Bmab* in future research [15]. Furthermore, N-SOG 03, a trial utilizing CapeOX plus *Bmab* as NAC for LARC, also reported promising findings, but a high anastomotic leakage rate of 27.8% called for reconsideration of the use of *Bmab* in NAC [16]. In addition, regarding the negative result of adding *Bmab* to conventional regimens (i.e., FOLFOX or CapeOX) in ACT for colon cancer, VEGF inhibitors may be unnecessary as NAC in colorectal cancer [17]. However, this matter remains controversial because the situation and purpose of NAC are not always the same as that of ACT.

## 4. Conclusion

We present a rare case of pathological complete response after neoadjuvant chemotherapy with FOLFOX for locally advanced colon cancer in the sigmoid colon complicated by diverticulitis. Six cycles of neoadjuvant FOLFOX were completed without significant adverse events, and the postoperative course was uneventful. Colostomy before NAC and the regimen and cycle of NAC may be key to this favorable course. Although this is a single-case report and it is generally controversial whether pCR after NAC leads to improved long-term outcomes in LACC, our experience may be valuable in determining the optimal treatment strategy for LACC complicated by diverticulitis.

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## Ethical approval

Not applicable.

## 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.

## Author contributions

Yusuke Asada: partook in all aspects of this study: management of the patient, conceptualization of the report, and writing of the draft.
Katsuya Chinen: reported the pathological findings.
Ken Yamataka and Jo Tokuyama: managed the patient.
Naoto Kurihara and Shuhei Iida: managed the patient and supervised.

## Registration of research

Not applicable.

## Guarantor

Yusuke Asada.

## Provenance and peer review

Not commissioned, externally peer reviewed.

## Declaration of competing interest

None.

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