Treatment of Rectal Cancer-Induced Disseminated Carcinomatosis of the Bone Marrow with FOLFOX plus Cetuximab and Panitumumab

Takehito Ehara     Masato Kitazawa     Nao Hondo     Shugo Takahata
Yuta Yamamoto     Makoto Koyama     Motohiro Okumura
Satoshi Nakamura     Shigeo Tokumaru     Futoshi Muranaka
Yusuke Miyagawa     Yuji Soejima

Department of Surgery, Shinshu University School of Medicine, Matsumoto, Japan

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Abstract
Disseminated carcinomatosis of the bone marrow (DCBM) in colorectal cancer is an extremely rare complication with a poor prognosis. Here, we report a case of DCBM due to rectal cancer successfully treated with a combination of FOLFOX and an anti-epidermal growth factor receptor (EGFR) agent. The patient was a 38-year-old man diagnosed with rectal cancer with multiple bone and para-aortic lymph node metastases complicated by disseminated intravascular coagulation (DIC). He first recovered from DIC following cotreatment with FOLFOX and cetuximab; subsequently, the second attack was successfully treated with FOLFOX plus panitumumab. His initial condition was extremely poor, but he survived with two FOLFOX plus anti-EGFR regimens and died 333 days after introduction of chemotherapy.

Introduction
Disseminated carcinomatosis of the bone marrow (DCBM) is characterized by diffuse organ infiltration centered on the bone marrow and is a type of cancer metastasis frequently associated with disseminated intravascular coagulation (DIC) [1, 2]. Most primary lesions associated with DCBM are observed in gastric, prostate, and breast cancer, whereas it is rare
in colorectal cancer [3, 4]. The prognosis of DCBM without chemotherapy is reported to be extremely poor [5].

Herein, we report a case of DCBM due to rectal cancer successfully treated with FOLFOX plus an anti-epidermal growth factor receptor (EGFR) agent, cetuximab (Erbitux®, Merck Biopharma, Darmstadt, Germany), as a first-line chemotherapy and FOLFOX plus another anti-EGFR agent, panitumumab (Vectibix®, Takeda Pharmaceutical, Tokyo, Japan), as the fourth-line chemotherapy.

**Case Report**

The patient was a 38-year-old man who had previously visited another hospital because of pain in his lower back and lower extremities. His Eastern Cooperative Oncology Group (ECOG) performance status was 3 and his axillary temperature was 38.9°C. There was no abnormal finding in the abdomen or subcutaneous hemorrhage. Blood test results revealed a decreased red blood cell count, hemoglobin level, and platelet count – 380 × 10^4/μL, 10.6 g/dL, and 12.5 × 10^3/μL, respectively – while the white blood cell count increased to 12,600/μL. Analysis of the patient’s coagulation system revealed a prolonged prothrombin time/international normalization ratio (14.0 s/1.23) and increased levels of fibrinogen (491 μg/mL) and D-dimer (90.9 μg/mL). Serum biochemistry test results revealed elevated levels of lactate dehydrogenase (LDH) at 5,850 IU/L, alkaline phosphatase (ALP) at 3,475, and aspartate aminotransferase (AST), alanine aminotransferase (ALT), and C-reactive protein (CRP) at 92, 336, and 28.13 mg/dL, respectively. The serum level of carcinoembryonic antigen (CEA) was elevated at 13.6 ng/mL. The CT showed wall thickness with contrast effect located in the upper rectum (Fig. 1A) and in the para-aortic lesion (Fig. 1C). Furthermore, the CT showed osteolytic changes in multiple bones including the vertebrae (arrows in D), sacrum, and iliac bones (arrows in E).

**Fig. 1.** A CT shows wall thickness with contrast effect in the upper rectum (arrow). B, C CT shows multiple lymph node enlargement beside the rectum (arrows in B) and in the para-aortic lesion (arrows in C). D, E CT shows osteolytic changes in multiple bones including the vertebrae (arrows in D), sacrum, and iliac bones (arrows in E).
changes in multiple bones including the sacrum, ilium, and vertebrae (Fig. 1D,E). The colonoscopy showed elevated lesion in the upper rectum without stenosis (Fig. 2A). A tumor biopsy specimen from the patient displayed a poorly differentiated adenocarcinoma with a mucinous component. Bone scintigraphy revealed abnormal diffuse accumulation in the cranial bone, spine, shoulder blade, right clavicle, and pelvic bone and bilaterally in ribs and femur (Fig. 2B). The patient was diagnosed with diffuse bone marrow metastasis originating from rectal cancer.

The patient’s condition was very poor with platelet counts declining >30% within 24 h meeting the criteria of acute DIC. However, the patient’s condition did not meet the criteria for a safe initiation of chemotherapy because his performance status was 3, and he had thrombopenia, and high AST and ALT levels. Capecitabine plus oxaliplatin (CapeOX) was administered without dose reduction along with recombinant human-soluble thrombomodulin (Recomodulin®, Asahi Kasei Pharma, Tokyo, Japan). The patient’s symptoms gradually improved and his abnormal laboratory findings of D-dimer, ALP, LDH, and CEA levels rapidly decreased with the treatment; he recovered from the DIC (Fig. 3).

The RAS gene was identified as wild type; therefore, the second chemotherapy regimen was changed to FOLFOX plus cetuximab and, subsequently, the CT showed markedly reduced para-aortic lymph nodes (Fig. 4A, B). After the eighth course of FOLFOX plus cetuximab, the patient developed a high fever, the lower back pain recurred, and the CT showed enlarged para-aortic lymph nodes. The patient was administered two courses of FOLFIRI plus aflibercept and one course of regorafenib, but neither had any effect. The CT showed increased para-aortic lymph node metastasis (Fig. 4C), the blood test results indicated that his condition had worsened, and DIC recurred. Three treatment options, i.e., TAS102 (Lonsurf®, Taiho

![Fig. 2. A Colonoscopy shows elevated lesion in the upper rectum without stenosis. B Bone scintigraphy shows abnormal diffuse accumulation in the cranial bone, spine, shoulder blade, right clavicle, and pelvic bone, and bilaterally in ribs and femur.](image-url)
pharma, Tokyo, Japan), FOLFOX plus panitumumab, and best supportive care, were proposed to the patient, and he selected FOLFOX plus panitumumab.

Subsequently, the patient’s condition improved again, and he recovered from the DIC after one course of FOLFOX plus panitumumab. After two courses of chemotherapy, his CT showed para-aortic lymph node shrinkage (Fig. 4D) and decreased tumor marker levels (Fig. 3). However, after four courses, the patient became septic with high fever and back pain. His CT showed a retroperitoneal abscess, enlarged para-aortic lymph nodes, and mediastinal lymph nodes metastasis.

We searched for cancer gene mutations using next-generation sequencing (tumor-profiling multiplex gene panels) and the results revealed mutations in the breast cancer (BRCA) gene. Based on the test result, olaparib (Lynparza®, AstraZeneca, Cambridge, UK) was administered orally for 2 weeks; however, tumor marker levels were persistently elevated and the CT revealed no changes in the metastatic lymph node lesions. His condition rapidly worsened and he died 333 days after the initiation of chemotherapy.

**Discussion**

The relationship between bone metastasis of malignant tumors and hematological abnormalities is well known. Jarcho [5] first reported diffusely infiltrative scirrhou£s gastric cancer characterized by diffuse bone marrow metastasis, anemia, thrombocytopenia, and bleeding tendency in 1936. Brain et al. [6] demonstrated the relationship between mucin-producing adenocarcinoma, DIC, and microangiopathic hemolytic carcinoma in 1970.
Hayashi et al. [7] reported 40 cases of patients who presented with diffuse bone marrow metastasis and defined DCBM as a wide range of hematogenous and lymphatic metastases, causing bleeding tendencies due to DIC and hemolytic anemia. In that study, 37 of the 40 cases (92.5%) were due to gastric cancer while one each was due to prostate, gallbladder, and ovarian cancer with unknown primary lesion, but no case of colorectal cancer was reported. A review of the literature revealed that DCBM in colorectal cancer is particularly rare and only 10 cases have been reported previously (Table 1) [8–17]. The average age of the patients was 61.0 years (men, 9 cases; women, 2 cases). The primary tumor was commonly located in the rectum ($n = 6$, 54.5%), sigmoid colon ($n = 2$), ascending ($n = 1$), transverse ($n = 1$), and right side (no detailed site was noted) of the colon ($n = 1$).

The histological subtypes were signet ring-like cell adenocarcinoma ($n = 3$), poorly differentiated adenocarcinoma ($n = 3$), mucinous adenocarcinoma ($n = 2$), moderately differentiated adenocarcinoma ($n = 2$), and well differentiated ($n = 1$). The peripheral blood test findings revealed a low average platelet count ($9.1 \times 10^4/\mu L$). Generally, anticoagulation therapy, blood transfusion, and protease inhibitors have been used to treat DIC. Chemotherapy is usually not feasible in patients with DCBM because of their poor general condition at diagnosis with anemia, thrombocytopenia, elevated AST and ALT, and DIC. No chemotherapy was administered to 3 of 11 patients, with a mean survival time (MST) of only 15.6 days.

In contrast, 8 patients who had received some chemotherapy showed a significantly longer MST (273.5 days). Seven patients who had received chemotherapy with oxaliplatin (FOLFOX/CapeOX) showed an MST of 305.3 days. Four patients who received molecular-targeted agents (bevacizumab, cetuximab, and panitumumab) had prolonged survival time (377.0 days) compared with those who did not receive molecular-targeted agents (196.0 days). Our patient was successfully treated with FOLFOX plus an anti-EGFR agent, cetuximab, as the first-line chemotherapy, followed by reintroduction of FOLOFOX plus another anti-EGFR agent, panitumumab, as the fourth-line chemotherapy. To the best of our knowledge,
| First author [Ref] | Year | Age, years | Gender | Primary site | Histology | PT, s | PT-INR | D-dimer, μg/dL | Plt, ×10⁴/μL | Onset | Treatment | Prognosis, days |
|-------------------|------|------------|--------|--------------|-----------|-------|--------|----------------|-------------|-------|-----------|----------------|
| Yoshioka [8]      | 1992 | 62         | male   | rectum       | mod       | 13.3  | -      | -              | 7.1         | primary | anti-DIC   | succumbed (12) |
| Huang [9]         | 2005 | 79         | male   | rectum       | mod       | 21.2  | -      | >1,050         | 5.8         | primary | anti-DIC   | succumbed (83) |
| Misawa [10]       | 2008 | 51         | male   | ascending colon | sig   | -     | -      | 61.5          | 12.9        | primary | anti-DIC   | succumbed (25) |
| Naito [11]        | 2014 | 61         | male   | transverse colon | sig | 21.8  | 1.98  | -              | 8.6         | primary | anti-DIC   | alive (118)      |
| Nakashima [12]    | 2014 | 65         | male   | rectum       | muc      | -     | -      | -              | 7.9         | primary | CapeOX+Bmab | succumbed (228) |
| van Bunderen [13] | 2014 | 65         | female | sigmoid colon | sig   | 19.2  | 66     | 14.45         | 12.7        | primary | CapeOX    | succumbed (210) |
| Lim [14]          | 2014 | 74         | female | right-sided colon | sig | 18.2  | 1.5   | -              | 0.4         | recurrence | anti-DIC | succumbed (10)     |
| Hanamura [15]     | 2016 | 60         | male   | sigmoid colon | por     | -     | 1.39  | 168.17        | 0.5         | primary | mFOLFOX6, CapeOX | succumbed (100) |
| Takeyama [16]     | 2017 | 65         | male   | rectum       | mod     | 15.8  | -      | 124.8         | 3.4         | recurrence | anti-DIC | succumbed (263) |
| Nakamura [17]     | 2017 | 51         | male   | rectum       | por     | -     | 1.65  | -              | 11.4        | primary | anti-DIC, 5FU/LV | succumbed (498) |
| Present case      | 2019 | 38         | male   | rectum       | por     | 14    | 1.23  | 90.9          | 12.5        | primary | anti-DIC, CapeOX, mFOLFOX6+Pmab | succumbed (333) |

PT, prothrombin time; PT-INR, prothrombin time/international normalization ratio; Plt, platelet.
this is likely the first case report of reintroduction of FOLFOX plus an anti-EGFR agent as a successful treatment of DCBM.

The RE-OPEN study demonstrated the effect of reintroduction of oxaliplatin in patients with advanced colorectal cancer previously treated with oxaliplatin and irinotecan [18]. Reintroduction of anti-EGFR antibodies has also been reported to be effective [19, 20]. However, effective reintroduction of oxaliplatin and anti-EGFR agents has been limited to patients treated for a duration of 6 months because of discontinuation and reintroduction in these reports. Recently, the REVERCE Study demonstrated that anti-EGFR treatment after regorafenib prolonged the overall survival more than the current standard sequence of treatment with an anti-EGFR agent followed by regorafenib [21]. Furthermore, preclinically, Napolitano et al. [22] reported that regorafenib overcame anti-EGFR antibody resistance of colorectal cancer by blocking the mitogen-activated protein kinase (MAPK) and AKT pathways. In this present case, pretreatment with regorafenib may have overcome the resistance to the anti-EGFR agents.

Conclusion

This case study revealed that FOLFOX plus anti-EGFR agents was effective in a patient with colorectal cancer with DIC. Therefore, reintroduction of FOLFOX plus an anti-EGFR agent may be a feasible treatment option for this class of patients.

Statement of Ethics

Written ethical approval for the publication on the present case report was obtained from the patient.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

All authors were involved in the preparation of the manuscript. Takehito Ehara, Nao Hondo, Shugo Takahata, Yuta Yamamoto, and Makoto Koyama collected the data, and Masato Kitazawa, Yusuke Miyagawa, and Yuji Soejima wrote the manuscript. Shugo Takahata, Yuta Yamamoto, Makoto Koyama, Motohiro Okumura, Nakamura Satoshi, Shigeo Tokumaru, and Futoshi Muranaka were involved in the treatment of the patient. All authors read and approved the final manuscript.
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