A Report of Disseminated Carcinomatosis of the Bone Marrow Originating from Transverse Colon Cancer Successfully Treated with Chemotherapy Using XELOX plus Bevacizumab

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Key Words
Disseminated carcinomatosis of bone marrow · Chemotherapy · Transverse colon cancer · Disseminated intravascular coagulation

Abstract
A 61-year-old male, who had been admitted to another hospital due to disseminated intravascular coagulation (DIC), was referred to our hospital. Total colonoscopy, abdominal dynamic CT and positron-emission tomography revealed bone metastasis and multiple lymphocytic metastases from transverse colon cancer in addition to disseminated carcinomatosis of the bone marrow (DCBM). We immediately performed chemotherapy with XELOX + bevacizumab and denosumab against DCBM from transverse colon cancer in order to avoid radical surgery. In addition, we initiated the administration of recombinant human soluble thrombomodulin for 1 week to treat DIC. The patient was able to tolerate and receive 4 cycles of chemotherapy without any severe side effects. After receiving the 4 cycles of treatment, he recovered from DIC, and the bone and multiple lymphocytic metastases disappeared.
Introduction

Disseminated carcinomatosis of the bone marrow (DCBM) is often associated with disseminated intravascular coagulation (DIC), and both are associated with poor prognoses. Most cases of DCBM are derived from gastric cancer; however, DCBM originating from colorectal cancer is relatively rare.

We herein report a case of DCBM originating from transverse colon cancer that was successfully treated with chemotherapy using XELOX + bevacizumab (BV) and recombinant human soluble thrombomodulin (rhTM).

Case Report

A 61-year-old male showed high levels of lactase dehydrogenase and alkaline phosphatase at a health checkup. He went to the clinic for an assessment of his general condition, and multiple lymphocytic metastases on an abdominal ultrasound and an elevation of the carcinoembryonic antigen level were detected. At the time of the medical visit, the patient only had back pain and did not report any inconveniences in his daily life activities. He had a history of hyperlipidemia and hypertension. When he came to our hospital, his peripheral blood examination showed multiple abnormal values (table 1). In addition, we diagnosed the patient with DIC (based on the DIC score calculated according to the DIC diagnostic criteria issued by the Japanese Association of Acute Medicine). A total colonoscopy (TCS) showed a stenosis of the transverse colon (fig. 1), and a signet ring cell carcinoma was detected on a biopsy. We found that the cancer was present throughout the transverse colon on a barium enema (fig. 2). Furthermore, a CT detected multiple lymph node metastases. Fluorodeoxyglucose (FDG)-positron-emission tomography (PET) also detected multiple lymph node metastases in addition to multiple bone metastases (fig. 3a–c). We performed a bone marrow puncture in order to make a diagnosis of the tumor and ultimately diagnosed the patient with DCBM originating from colon cancer (fig. 4). The same day, he was admitted to our department for treatment. We immediately initiated treatment with emergency chemotherapy consisting of XELOX + BV with an elemental diet. To treat the bone metastasis, denosumab was administered at an interval of 1 month for a total of 3 times before reevaluating the tumor. In addition, we administered anticoagulation therapy with rhTM to treat DIC (resulting from DCBM) for 1 week. We continued the chemotherapy for 4 cycles without any severe adverse events; we then reevaluated the tumor. The carcinoembryonic antigen level consistently decreased from 1,382 to 69.1 ng/ml. Although the primary lesion did not change in size on TCS or barium enema (fig. 5), the multiple metastases in the bone and lymph nodes clearly disappeared on CT and PET-CT (fig. 6a–c). Furthermore, the patient recovered from DIC caused by DCBM following the administration of chemotherapy and rhTM. We considered performing a resection of the primary lesion in order to reduce the tumor volume and enable oral intake.

Discussion

A diffusely infiltrative carcinoma was first reported by Jarcho [1] in 1936. Hayashi et al. [2] conducted a study of DCBM among 40 cases of disseminated carcinoma in Japan. The authors reported that most of the DCBM cases derived from gastric cancer (over 90%). DCBM is associated with 3 major symptoms: anemia, back pain and bleeding tendencies. The
hematological and blood biochemical findings of DCBM demonstrate severe anemia, leukoerythroblastosis and elevated levels of alkaline phosphatase and lactase dehydrogenase. In addition, the disease often occurs in association with DIC due to invasive bone marrow, and the metastases in the bone marrow are diffusely infiltrative rather than exhibiting a nodular pattern.

On the other hand, colorectal cancer is relatively rare as an origin of DCBM, with only 27 cases having been reported between 1984 and 2013 in Japan (table 2) [3–28]. The average patient age in these cases is 55 years, and the disease is as common in males as it is in females. The major symptoms are also the same as those of general DCBM. The frequency of lesions in the rectal colon is slightly higher than that of other primary lesions. With respect to the histological diagnosis, poorly differentiated carcinoma (13 cases), signet ring cell carcinoma (6 cases) and mucin-forming carcinoma (3 cases) are the most frequently observed, accounting for approximately 81% of cases. Although many patients with DCBM originating from colorectal cancer do not survive more than 100 days, chemotherapy regimens such as folinic acid, fluorouracil and oxaliplatin (FOLFOX) or folinic acid, fluorouracil and irinotecan (FOLFIRI) clearly improve survival. Therefore, it is possible to survive for more than 200 days in some cases. However, it is difficult to improve the prognosis of patients with DCBM originating from signet ring cell carcinoma, and the duration of survival remains short despite treatment with chemotherapy.

The present patient had DCBM originating from transverse colon cancer that occurred in association with DIC. We administered emergency chemotherapy consisting of XELOX + BV and denosumab to treat the patient’s bone metastasis. In addition, we administered anticoagulation therapy with rhTM to treat DIC. The lymph node and bone metastases dramatically improved with these therapies and without any development of severe adverse events; the patient completely recovered from DIC. He survived for more than 100 days with a diagnosis of DCBM originating from signet ring cell carcinoma. To our best knowledge, this is the first report of such long-term survival. These results suggest that the administration of aggressive chemotherapy for DCBM originating from colon cancer may help to prolong overall survival.

We combined rhTM with chemotherapy to treat DIC resulting from DCBM in this case. Recently, rhTM has become widely used to treat DIC resulting from sepsis in Japan [29]. However, Akiyama et al. [30] reported that the use of anticoagulation therapy alone is not effective for DIC resulting from DCBM and recommended not only treatment against DIC, but also treatment with chemotherapy against the tumors of DCBM. Therefore, we considered chemotherapy to be the central therapy and used rhTM to support the chemotherapy.

The purpose of surgical resection of primary tumors is to prevent hemorrhaging, perforation and bowel obstruction. In many cases, it is not possible for patients to continue chemotherapy due to complications such as bleeding, perforation and bowel obstruction occurring without undergoing surgical resection of the primary tumor. Therefore, it is necessary to surgically remove the primary tumor in order to continue chemotherapy with few complications. In the past, some investigators have recommended performing a routine resection of the primary tumor in order to prevent the need for urgent surgical procedures due to local complications [31, 32]. Ru et al. [33] reported that 30 (29%) out of 103 patients who were initially treated without bowel resection required subsequent operations for palliation of complications. Recently, some authors have suggested the use of elective resection of asymptomatic colorectal cancers, at least in a subset of patients with less advanced stage IV disease [33, 34]. Other authors have suggested a deferring resection of minimally symptomatic colorectal tumors because most of these patients succumb to progressive systemic disease instead of the complications related to the intact primary
lesion [33, 35]. However, surgical resection may delay the start of chemotherapy [35]. Generally, an interval of 4 weeks is required between surgery and the start of chemotherapy regimens, such as FOLFOX, FOLFIRI or XELOX. In most clinical trials, patients who have undergone surgery within 4 weeks are excluded. However, there is no apparent evidence to support this delay. Metastatic tumors can enlarge rapidly before the start of chemotherapy, possibly resulting in death. Because the significance of the postoperative 4-week delay before the start of chemotherapy is unclear, we evaluated the feasibility and safety of administering chemotherapy early in patients who have undergone colorectal surgery for colorectal cancer with synchronous multiple distant metastases [36–38].

In conclusion, we herein reported a case in which combination chemotherapy with XELOX + BV, denosumab, and rhTM was administered to treat DIC resulting from DCBM of the transverse colon cancer. The patient successfully survived DCBM for more than 100 days from the start of chemotherapy. As previously noted and to the best of our knowledge, this is the first case report of such long-term survival in a patient with DCBM originating from colorectal cancer. We are now considering surgical intervention targeting the primary lesion.

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### Table 1. Blood biochemical findings

| Test  | Value          |
|-------|----------------|
| WBC   | 4,000/μl       |
| RBC   | 3.43×10^6/μl   |
| Hb    | 10 g/dl        |
| Ht    | 29.30%         |
| Plt   | 8.6×10^4/μl    |
| TBil  | 0.9 mg/dl      |
| AST   | 53 IU/l        |
| ALT   | 23 IU/l        |
| LDH   | 537 IU/l       |
| CK    | 508 IU/l       |
| ALP   | 1,379 IU/l     |
| γ-GTP | 13 IU/l        |
| CRP   | 0.9 mg/dl      |
| BUN   | 22 mg/dl       |
| Cr    | 1.78 mg/dl     |
| Na    | 138 mEq/dl     |
| K     | 3.9 mEq/dl     |
| Cl    | 100 mEq/dl     |
| Glu   | 155 mg/dl      |
| PT    | 21.8 s         |
| INR   | 1.98           |
| APTT  | 33.6 s         |
| AT III| 82%            |
| Fibrinogen | 51 mg/dl |
| AT III| 82%            |
| FDP   | 57 μg/dl       |
| CA19-9| 41 U/ml        |
| CEA   | 1,382.5 ng/ml  |
### Table 2. Characteristics of DCBM in patients with colorectal cancer (Japan 1984–2013)

| Characteristics | Patients, n | Chemotherapy | No. patients in chemotherapy | Survival | Outcome |
|-----------------|------------|--------------|------------------------------|----------|---------|
| **Age**         |            |              |                              |          |         |
| Median          | 55         |              |                              |          |         |
| Range           | 26–78      |              |                              |          |         |
| **Sex**         |            |              |                              |          |         |
| Male            | 16         |              |                              |          |         |
| Female          | 11         |              |                              |          |         |
| **Primary lesion** |        |              |                              |          |         |
| Cecum           | 2          |              |                              |          |         |
| Ascending colon | 5          |              |                              |          |         |
| Transverse colon| 4          |              |                              |          |         |
| Descending colon| 1          |              |                              |          |         |
| Sigmoid colon   | 4          |              |                              |          |         |
| Rectum          | 10         |              |                              |          |         |
| Anal            | 1          |              |                              |          |         |
| **Histology**   |            |              |                              |          |         |
| Well            | 2          | BSC          | 2                            | 52±2     | All dead|
| Moderately      | 2          | BSC          | 2                            | 20±9     | All dead|
| Poorly          | 13         | BSC          | 4                            | 47±14    | All dead|
|                |            | mFOLFOX6     | 3                            | 180±44   | 1 case alive|
|                |            | mFOLFIRI     | 1                            | 210      | alive    |
|                |            | mFOLFOX6/BV  | 1                            | 210      | alive    |
|                |            | MTX/5-FU     | 2                            | 124±79   | All dead|
|                |            | CPT11/CDDP   | 1                            | 84       | All dead|
|                |            | UFT/LV/CP11  | 1                            | 180      | All dead|
| Signet          | 6          | BSC          | 2                            | 22±1     | All dead|
|                |            | XELOX/BV     | 1                            | 118      | alive    |
|                |            | 5-FU         | 1                            | 90       | All dead|
|                |            | MTX/5-FU     | 1                            | 90       | All dead|
|                |            | CBDCA/5-FU   | 1                            | 90       | All dead|
| Mucinous        | 3          | BSC          | 2                            | 21±1     | All dead|
|                |            | 5-FU         | 1                            | 90       | All dead|
| Carcinoid       | 1          | BSC          | 1                            | 390      | All dead|

BSC = Best supportive care; MTX = methotrexate; 5-FU = fluorouracil; LV = leucovorin; CPT11 = irinotecan; CDDP = cisplatin; CBDCA = carboplatin; UFT = tegafur–uracil; XELOX = oxaliplatin + capecitabine.
Fig. 1. Complete stenosis of the transverse colon on TCS.

Fig. 2. Intense stenosis with transverse colon cancer observed during an enema.

Fig. 3. a–c. Multiple areas of metastatic lymph node invasion and bone metastasis on PET-CT.
Fig. 4. Biopsy of bone marrow. Metastasis from a signet ring cell carcinoma (HE. ×400).

Fig. 5. Stenosis of the transverse colon did not develop during the enema.

Fig. 6. a–c. Multiple areas of metastatic lymph node invasion and bone metastasis on PET-CT.