INTRODUCTION

Disseminated carcinomatosis of the bone marrow (DCBM) is defined as solid cancer metastasizing to the bone marrow. DCBM can lead to dysfunction of several organs. In most cases, patients die within a short period before any effective medication can be initiated. The primary solid cancer in DCBM cases originates from the stomach; rarely is the origin from the colon or rectum.\(^1\)

We report a rare case of a Japanese man who developed DCBM originating from rectal adenocarcinoma and survived for almost 1 year on chemotherapy and supportive medication.

CASE REPORT

A 66-year-old man with a cough lasting about three weeks presented to a nearby clinic. He was prescribed oral medications (cough suppressant, antibiotics, and expectorant), but his symptoms gradually worsened. A month after the first round of medication, he developed dyspnea. He presented to our hospital for a detailed examination and was admitted for type 1 respiratory failure. At presentation, his blood pressure was 139/89 mm Hg, pulse rate 106/min, body temperature 36.1\(^{\circ}\)C, respiratory rate 24/min, and oxygen saturation 95% (reservoir mask 6 L/min). Blood examination demonstrated a white blood cell count of 4700/
mm$^3$, hemoglobin concentration of 14.1 g/dL, platelet count of 10 000/mm$^3$, alkaline phosphatase (ALP) level of 576 IU/L, lactate dehydrogenase (LDH) level of 6227 IU/L, carcinoembryonic antigen (CEA) level of 163.4 ng/mL, fibrin/fibrinogen degenerative product level of 371.5 μg/mL, prothrombin time of 18.0 seconds (39%), C-reactive protein level of 2.2 mg/dL, and procalcitonin level of 0.28 ng/mL (Table 1). Computed tomography showed increased thickness of the rectal wall. The hilar, mediastinal, paraaortic, iliac, and mesenteric lymph nodes were swollen. Pleural effusion and ascites were not detected, and tumor-like lesions were not observed in any other organ except the rectum (Figure 1).

Thrombomodulin 25 600 U × 32 days, red blood cells transfusion 2 U × 9 days, and platelet transfusion 10 U × 21 days were administered because the patient was in a disseminated intravascular coagulation (DIC) state. Colonoscopy revealed a reddish, easily bleeding, and elevated lesion at the rectosigmoid junction (Figure 2). The biopsy specimen obtained from the lesion showed adenocarcinoma (moderately differentiated tubular adenocarcinoma and poorly differentiated adenocarcinoma) (Figure 3).
After admission, the laboratory data showed progressive pancytopenia (white blood cell count, 1900/mm³; hemoglobin concentration, 7.9 g/dL; and platelet count, 15,000/mm³). Bone marrow aspiration showed an adenocarcinoma with ductal formation in the bone marrow. The tumor immunoreactivities were positive for AE1/AE3, CK20, CEA, and CDX2, and negative for CK5/6, CK7, TTF-1, CA19-9, PAX8, PSA, chromogranin A, and synaptophysin. This indicated that the adenocarcinoma was metastasized from the colon or rectum (Figures 4, 5, 6, 7). We diagnosed the patient with DCBM from rectal cancer with a DIC state.

Chemotherapy (mFOLFOX6 therapy) was started 12 days after admission with pegfilgrastim 3.6 mg, in addition to thrombomodulin and platelet transfusion. Steroid pulse therapy was also administered due to the possibility of hemophagocytic syndrome.

The patient's general condition, including respiratory symptoms and blood examination outliers, gradually
| Case | Reporter | Age | Sex | Year | Primary lesion | Histopathology | Chief complaint |
|------|----------|-----|-----|------|----------------|----------------|----------------|
| 1    | Our case | 66  | M   | 2020 | Rectum         | tub2-por       | Dyspnea        |
| 2    | Miyazaki | 72  | M   | 2019 | Ascending colon| sig > por      | None           |
| 3    | Mori     | 66  | M   | 2018 | Rectum         | por-tub2       | Loose stool    |
| 4    | Takeyama | 65  | M   | 2017 | Rectum         | adenocarcinoma | Anal bleeding  |
| 5    | Yoshida  | 61  | M   | 2016 | Transverse colon| sig             | None           |
| 6    | Sawazaki | 77  | M   | 2015 | Rectum         | sig            | Bloody stool   |
| 7    | van Bunderen CC | 65 | F  | 2014 | unclear | Adenocarcinoma | Headache, spontaneous hematomas, |
| 8    | Naito    | 61  | M   | 2014 | Transverse colon| sig             | High levels of LDH, ALP |
| 9    | Nakashima| 65  | M   | 2014 | Rectum         | Adenocarcinoma | Melena and low back pain |
| 10   | Uefuji   | 32  | M   | 2011 | Sigmoid colon  | por            | Back pain, abdominal pain |
| 11   | Sakizaki | 45  | M   | 2011 | Descending colon| por            | Back pain      |
| 12   | Hamaguchi| 76  | M   | 2011 | Rectum         | tub2           | Constipation, abdominal pain |
| 13   | Higashiyama | 71 | M  | 2011 | Rectum         | por            | Constipation   |
| 14   | Nonaka   | 45  | F   | 2010 | Rectum         | por            | Back pain, bloody stool |
| 15   | Shimizu  | 65  | M   | 2009 | Ascending colon| tub2, por      | Back pain, fever, appetite loss |
| 16   | Hikita   | 59  | M   | 2009 | Sigmoid colon  | Adenocarcinoma | Bloating       |
| 17   | Misawa   | 51  | M   | 2008 | Ascending colon| sig            | Back pain      |
| 18   | Nakazaki | 26  | F   | 2007 | Transverse colon| por            | Constipation   |
| 19   | Kosuge   | 59  | F   | 2007 | Transverse colon| por            | Dyspnea, headache |
| 20   | Oonishi  | 21  | F   | 2007 | Transverse colon| sig            | Abdominal pain, diarrhea |
| 21   | Tazima   | 48  | M   | 2006 | Ascending colon| sig            | Abdominal pain |
| 22   | Nagashima| 74  | F   | 2005 | Ascending colon| tub1           | Back pain      |
| 23   | Makino   | 55  | F   | 2005 | Sigmoid colon  | sig            | Back pain      |
| 24   | Hirokawa | 70  | F   | 2003 | Rectum, Transverse colon | por, tub2 | Back pain |
| 25   | hirose   | 37  | M   | 2002 | Rectum         | muc            | Back pain      |
| 26   | Nakazawa | 57  | F   | 2002 | Ascending colon| tub1           | Back pain, vomit |
| 27   | Yoshioka | 62  | M   | 1992 | Rectum         | tub2           | Paresis of the legs and a bleeding tendency |
| Diagnosis of DCBM | Chemotherapy | Side effect | Anti-DIC therapy | Prognosis |
|------------------|--------------|-------------|-----------------|-----------|
| Bone marrow aspiration | mFOLFOX6 + Pmab | Neuropathy | Thrombomodulin, blood transfusion | Died (333 d) |
| Bone scintigraphy, bone marrow biopsy | — | — | — | Died (14 d) |
| PET | mFOLFOX6 + Pmab $\rightarrow$ FOLFIRI $\rightarrow$ XELOX + Bmab $\rightarrow$ regorafenib | Neuropathy | Thrombomodulin, anti thrombin | Died (600 d) |
| Bone marrow biopsy | mFOLFOX6 | None | Thrombomodulin, nafamostat mesilate, transfusion | Died (263 d) |
| Bone marrow aspiration, PET | XELOX + Bmab | — | Thrombomodulin | Died (7 M) |
| Bone marrow aspiration and biopsy | — | — | Blood transfusion | Died (74 d) |
| Bone marrow aspiration and biopsy | XELOX | Neuropathy | — | Died (8 M) |
| Bone marrow aspiration, PET | XELOX + Bmab | — | Thrombomodulin | ? |
| Bone marrow aspiration, bone scintigraphy | mFOLFOX6 + Bmab | General fatigue | Transfusion, gabexate mesilate | Died (128 d) |
| MRI | mFOLFOX6 $\rightarrow$ FOLFIRI | — | Synthetic protease inhibitor, blood transfusion | Died (8 M) |
| PET | mFOLFOX6 $\rightarrow$ FOLFIRI | — | Synthetic protease inhibitor, blood transfusion | Died (230 d) |
| PET | — | — | Unclear | Died (26 d) |
| Bone marrow aspiration, bone scintigraphy | mFOLFOX6 | Thrombocytopenia | Danaparoid sodium | Alive (5 M) |
| PET, MRI | mFOLFOX6 + Bmab | Neuropathy | Synthetic protease inhibitor, blood transfusion | Alive (210 d) |
| Bone marrow aspiration, bone scintigraphy | — | — | Unclear | Died (3 M) |
| Bone marrow aspiration, bone scintigraphy | — | — | — | Died (9 d) |
| MRI | — | — | Heparin, gabexate mesilate | Died (25 d) |
| Bone scintigraphy | UFT/LV + CPT-11 | — | Danaparoid sodium | Died (6 M) |
| Bone marrow biopsy, MRI | MTX/5FU | — | Synthetic protease inhibitor, blood transfusion | Alive (36 d?) |
| MRI | MTX/5FU | — | — | Died (2 M) |
| Bone scintigraphy | — | — | Synthetic protease inhibitor | Died (2 M) |
| MRI, bone scintigraphy | — | — | — | Died (50 d) |
| Bone scintigraphy | — | — | — | Died (21 d) |
| Bone marrow aspiration | — | — | Unclear | Died (58 d?) |
| MRI, bone scintigraphy | 5-FU | — | Unclear | Died (3 M) |
| Bone marrow biopsy, bone scintigraphy | — | — | — | Died (1 M?) |
| Pathological anatomy | — | — | Heparin, synthetic protease inhibitor, anti thrombin | Died (12 d) |
improved. No remarkable side effects were observed, except for mild numbness of the limbs.

We thought that he could continue chemotherapy as an outpatient; therefore, he was discharged 75 days after admission.

mFOLFOX6 therapy was continued; we checked blood LDH levels every 2 weeks; the levels shifted slightly to the higher side compared to the normal range. However, after 10 courses, the blood LDH levels were found to be elevated. We added panitumumab 380 mg/course to the mFOLFOX6 therapy 170 days after the first admission because the KRAS gene of the tumor was the wild type. The patient’s general condition was stable, and the tumor size and lymph node swelling reduced. The patient experienced fever; after 2 days he felt general fatigue and appetite loss. Therefore, he was re-admitted to our hospital 306 days after the first admission. The reason for his condition was considered to be an exacerbation of cancer, and chemotherapy with thrombomodulin and platelet transfusion was administered after admission. However, his general condition gradually deteriorated, and he died due to the cancer progression 333 days after the first admission.

3 | DISCUSSION

Cancer metastasizes to several organs but rarely to the bone marrow. DCBM is defined as solid cancer metastasizing to the bone marrow, resulting in several organs’ dysfunction.²,³ Cases of DCBM metastasizing from the lung, breast, or prostatic gland have been reported.⁴ However, cases of DCBM metastasizing from the colon or rectum are rare. Long-term survival with medication, as in our case, is particularly rare.

Anemia, back pain, and bleeding tendency are the triad of the DCBM.³ Elevated ALP or LDH levels, erythroblastic anemia, microangiopathic hemolytic anemia, or DIC is sometimes observed.

In this case, the patient did not have anemia or back pain, but the laboratory data showed an elevated blood LDH level, multiple organ dysfunction, and bleeding tendency due to DIC. However, the bone marrow aspiration contributed to the diagnosis of DCBM.

The diagnosis rate of DCBM through bone marrow aspiration was reported as 25%-31.6% in a previous report.⁵ Some cases were diagnosed as having no malignancy on bone marrow aspiration but were diagnosed with DCBM based on other investigations.¹⁶ The diagnosis rate of DCBM with bone scintigraphy has been reported to be almost 100%.⁷ However, this study was performed in a single hospital. In cases of trabecular or micrometastasis, bone scintigraphy is occasionally negative. In these cases, magnetic resonance imaging or ¹⁸F-fluorodeoxyglucose positron emission tomography/computerized tomography was useful to finalize the diagnosis.⁸

A review of case reports of DCBM originating from colon or rectal cancer is shown in Table 2. These cases were obtained through a search of PubMed from 1946 to 2019 using the following search terms: “Disseminated carcinomatosis of the bone marrow” and “rectum”, “Disseminated carcinomatosis of the bone marrow” and “rectal”, or “Disseminated carcinomatosis of the bone marrow” and “colon”. Besides, Japanese cases were obtained through a search of the Japana Centra Revuo Medicina Web from 1977 to 2019 using the search terms described above in Japanese and a manual search (some cases with unclear details were not included). Regarding the organization type of the primary tumor, most of them showed a poor degree of differentiation, such as poorly differentiated adenocarcinoma and signet ring cell carcinoma. Many cases were recently diagnosed as having DCBM through bone marrow aspiration. The patients died within 3 months in many cases, but a few patients who received chemotherapy survived for more than 6 months. These long-term survival patients also received anti-DIC therapy (except in one case). On the other hand, patients who received anti-DIC therapy without chemotherapy did not survive for long. Because the extrinsic coagulation cascade is activated by coagulation-activating substances from tumor cells or cytokines such as IL-6 and TNF-α in the DIC state with DCBM, administration of thrombomodulin before chemotherapy probably suppressed the DIC state.⁹ Both bleeding tendency caused by a DIC state and bone marrow suppression with chemotherapy are high-risk treatments, but long-term survival is difficult without them. Molecular target drugs have been authorized since 2007 in Japan. Patients who underwent chemotherapy with these drugs survived for longer periods. In other organs, the patients with DCBM and DIC from breast cancer were reported to have a longer survival period with chemotherapy using molecular target drugs; the therapy was particularly useful in oncologic emergency states.¹⁰,¹¹ The side effects of chemotherapy for DCBM from the colon or rectal cancer were found to be mild. Peripheral neuropathy in 4 cases and general fatigue in 1 case were mild and did not significantly affect the patient.

Apart from the abovementioned medications, very few effective treatments are available for DCBM. Chemotherapy with bisphosphonate prolonged patient survival in a report of DCBM originating from gastric cancer. Bisphosphonate suppresses bone absorption; the resulting reduction in the supply growth factors from the bone suppresses the tutor growth.¹² Therefore, bisphosphonate may be effective for treating DCBM from the colon or rectal cancer.

On the premise of sufficient informed consent, aggressive chemotherapy with anti-DIC therapy can improve the prognosis of DCBM from the colon or rectal cancer.

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CONFLICT OF INTEREST
The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS
KY: participated in the management of this patient, wrote the manuscript. TO and TT: participated in the management of this patient. SK, YS, TS, and TM: helped in writing the manuscript. CI: advised on pathological results. YS and SF: helped in writing and supervised the manuscript.

ETHICAL APPROVAL
Informed consent for his case to be published was obtained from a relative, because the patient was dead.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, [Kenta Yoshida], upon reasonable request.

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