

Long-term survival after a favorable response to anti-EGFR antibody plus chemotherapy to treat bone marrow metastasis: a case report of *KRAS*-wildtype rectal cancer

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Abstract: Bone marrow metastasis is a rare consequence of colorectal cancer that results in a poor prognosis; few reports describe a favorable response to doublet chemotherapy combined with targeted therapy, which is currently the standard treatment. We experienced a case where anti-epidermal growth factor receptor (EGFR) antibody produced a marked anti-tumor response to bone marrow metastasis that led to long-term survival. A 51-year-old man was diagnosed with a primary *KRAS*-wildtype rectal cancer with multiple metastases, including the bone marrow. Disease control was achieved for 10.8 months following chemotherapy with a modified FOLFOX6 regimen combined with an anti-EGFR antibody. He died of cancer 22.7 and 16.6 months after disease onset and first-line chemotherapy, respectively. This case shows that early tumor shrinkage and deepness of response to the anti-EGFR antibody were observed even in a patient with bone marrow metastasis. Anti-EGFR antibody therapy should therefore be considered even when a patient's medical condition appears to be poor owing to bone marrow metastasis. Moreover, tumors that are likely to be sensitive to chemotherapy, such as *RAS*-wildtype colorectal cancers, can be considered for anti-EGFR antibody therapy even if the patient is considered unfit for chemotherapy.

Keywords: colorectal cancer, anti-epidermal growth factor receptor antibody, molecular targeted therapies, disseminated intravascular coagulation, standard of care

Introduction

Bone marrow metastasis of colorectal cancer is rare, and the prognosis is poor.^{1,2} Previous case reports suggest that administering chemotherapy would be beneficial even in the event of bone marrow metastasis; however, such approaches only prolong overall survival for a short period.^{3–5} Even if it is beneficial, metastasis to the bone marrow often causes detrimental clinical manifestations such as myelosuppression or disseminated intravascular coagulation (DIC), causing hesitation to administer chemotherapy.³ We report a patient with primary *KRAS*-wildtype rectal cancer and bone marrow metastasis who was in poor medical condition before starting treatment. Chemotherapy combined with anti-epidermal growth factor receptor (EGFR) antibody showed a clinically significant response. Clinical symptoms also improved, and the patient survived for 16.6 months after the first-line chemotherapy.

Case

A 51-year-old man began experiencing back pain in May 2014. Myelofibrosis was suspected because of the significant signal change in the spinal body on magnetic resonance

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imaging (MRI) and dry-tap bone marrow aspiration. He did not have a *Janus Kinase 2 (JAK2)* mutation.

The patient was administered analgesic agents for 4 months until blood examination showed a worsening of anemia, emergence of nucleated erythrocytes, and a left shift of leukocytes. Adenocarcinoma (well-to-moderately differentiated) was observed in a bone marrow biopsy specimen obtained in September 2014. A subsequent colonoscopy revealed a circumferential diffuse infiltrative lesion in the rectum (Ra-Rb) causing a narrowing of the lumen; a biopsy showed poorly differentiated adenocarcinoma. Imaging examinations (computed tomography [CT], MRI, and positron-emission tomography-CT) at the time of the onset of back pain had not shown any suspicious lesions, but re-examination in September and October showed a rectal tumor with multiple metastatic lesions (bone, liver, left pararenal gland, peritoneum, and pleura; Figure 1); the cancer was diagnosed as clinical stage T4N0M1 (*Union for International Cancer Control*, 7th edition).⁶

The patient underwent ureteral stenting for hydronephrosis due to ureteral stricture, as well as emergency surgical decompression and colostomy for colon obstruction caused by the primary tumor and severe peritoneal metastasis. The

patient's condition deteriorated most severely on postoperative day (POD) 3; his Eastern Cooperative Oncology Group performance status (PS) was 3, and he experienced a recurrent fever $>39^{\circ}\text{C}$ due to rhabdomyolysis, sepsis, and the neoplasm. Blood tests at POD 3 showed prothrombin time-international normalized ratio (PT-INR) 1.65 (6.8 s prolonged), fibrin and fibrinogen degradation product (FDP) 73.5 mg/L, creatine kinase (CK) 15.45 $\mu\text{kat/L}$ (925 U/L), lactate dehydrogenase (LDH) 61.71 $\mu\text{kat/L}$ (3,695 U/L), C-reactive protein (CRP) 313.91 nmol/L (32.96 mg/dL), procalcitonin 1.81 $\mu\text{g/L}$, white blood cell (WBC) count $13.05 \times 10^9/\text{L}$, hemoglobin 65 g/L, and platelet count $114 \times 10^9/\text{L}$. DIC treatment (including recombinant human thrombomodulin), antibacterial and antifungal agents, and red blood cell transfusion, improved the patient's blood test results as follows: PT-INR 1.39 (4.7 s prolonged), FDP 44.5 mg/L, CK 1.95 $\mu\text{kat/L}$ (117 U/L), LDH 6.03 $\mu\text{kat/L}$ (361 U/L), CRP 118.38 nmol/L (12.43 mg/dL), WBC $5.76 \times 10^9/\text{L}$, hemoglobin 85 g/L, and platelet count $114 \times 10^9/\text{L}$. However, his eligibility for chemotherapy remained uncertain. Surgery was deemed to be the principal cause of rhabdomyolysis, and recurrent fever was eventually diagnosed as neoplastic fever after no bacterial growth was observed in culture tests. Prompt relief from pyrexia was achieved with naproxen.

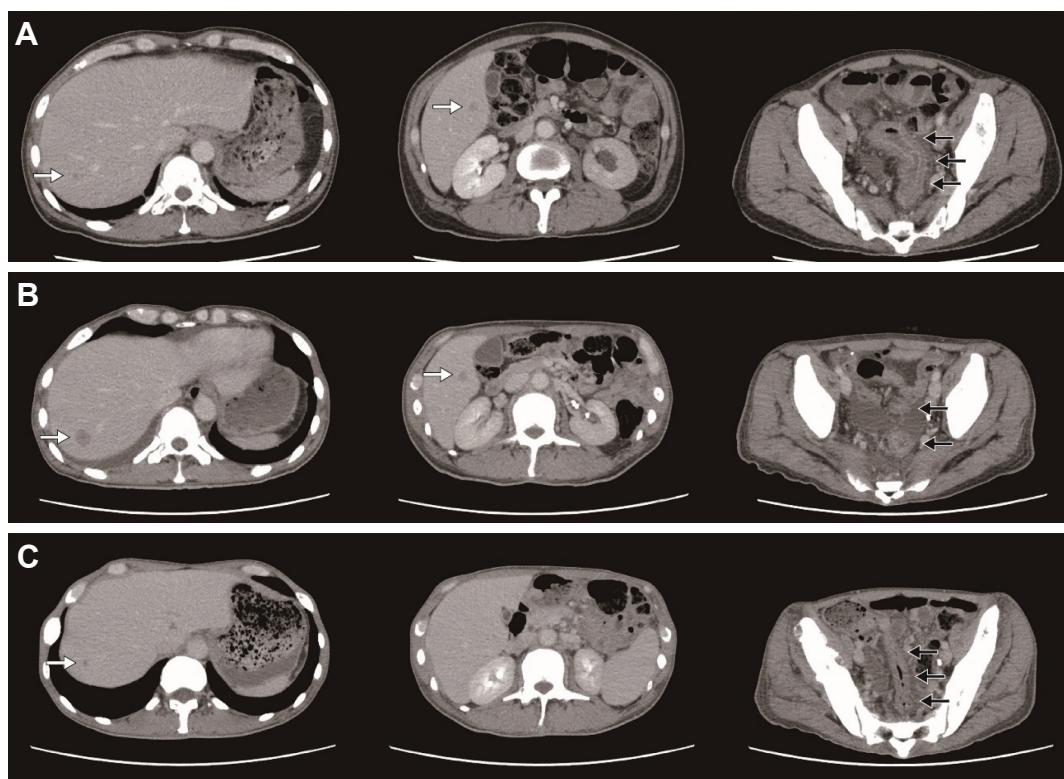


Figure 1 Computed tomography (CT) image before and after the chemotherapy. (A) CT performed before the first-line chemotherapy administration (September 2014). (B) CT performed following two cycles of first-line chemotherapy and before commencing second-line therapy. (C) CT performed 4 weeks after the initiation of anti-EGFR antibody combined second-line chemotherapy. The black arrows show the primary lesion, while the white arrows denote the liver metastases.

Table 1 Chemotherapy agent and dose intensity of each regimen

Regimen ^a	Cycles	Duration (months)	Relative dose intensity of each chemotherapy agent (%) ^b						RTDI (%) ^b
			5-FU (bolus)	5-FU (civ)	L-OHP	CPT-11	Anti-EGFR antibody	Bevacizumab	
sLV5FU2	2	1.0	93.3	93.3	–	–	–	–	93.3
mFOLFOX6 + panitumumab	3	1.7	79.2	79.2	79.2	–	52.8	–	72.6
mFOLFOX6 + cetuximab	17	9.0	41.9	86.5	11.2	–	84.0	–	55.9
FOLFIRI + bevacizumab	10	4.8	35.3	84.2	–	89.2	–	47.2	64.0

Notes: ^asLV5FU2: levoleucovorin 200 mg/m² IV on day 1 followed by 5-FU IV bolus 400 mg/m² and then 2,400 mg/m² continuous IV (CIV) over 46 hours, repeated every 2 weeks. mFOLFOX6 + EGFR antibodies: oxaliplatin 85 mg/m² IV and levoleucovorin 200 mg/m² IV on day 1, followed by 5-FU IV bolus 400 mg/m² and then 2,400 mg/m² CIV over 46 hours, with either cetuximab 400 mg/m² IV for first infusion and consecutive 250 mg/m² weekly or panitumumab 6 mg/kg IV administration, repeated every 2 weeks. FOLFIRI + bevacizumab: irinotecan 150 mg/m² IV and levoleucovorin 200 mg/m² IV on day 1, followed by 5-FU IV bolus 400 mg/m² and then 2,400 mg/m² CIV over 46 hours, with bevacizumab 5 mg/kg IV, repeated every 2 weeks. ^bRatio of actual (average dose intensity over the actual treatment duration) over planned (total) dose intensity. Dash denotes agents that were not included in the regimen.

Abbreviations: 5-FU, 5-fluorouracil; civ, continuous infusion; L-OHP, oxaliplatin; CPT-11, irinotecan; EGFR, epidermal growth factor receptor; RTDI, relative total dose intensity; sLV5FU2, simplified biweekly infusional 5-FU/leucovorin; mFOLFOX6, modified FOLFOX 6; IV, intravenous infusion.

We administered chemotherapy in the form of infusional 5-fluorouracil (5-FU) plus levoleucovorin. Details of the chemotherapy regimens are shown in Table 1. CT after two cycles of chemotherapy showed progressive disease with worsening liver metastasis (Figure 1). Despite disease progression, the patient's PS score had improved to 2 owing to the amelioration of rhabdomyolysis and recurrent fever. Additionally, molecular testing at this time showed no *KRAS* mutation. Thus, he was administered modified FOLFOX6 combined with anti-EGFR antibody therapy as a second-line therapy. CT after two cycles showed a partial response; his primary lesion and liver metastasis shrank, and pleural effusion and ascites decreased (Figure 1). Furthermore, his

PS score improved to 1, leukoerythroblastosis disappeared, and red blood cell transfusion was no longer required because his anemia improved. Moreover, his tumor markers normalized, as shown in Figure 2. Observed adverse events (per the *Common Terminology Criteria for Adverse Events* version 4.0)⁷ were as follows: rash (grade 2), paronychia (grade 2), peripheral neuropathy (grade 2), fatigue (grade 2), neutrophil count decrease (grade 3), anemia (grade 3), platelet count decrease (grade 2), and hypomagnesemia (grade 1). We switched the anti-EGFR antibody from panitumumab to cetuximab owing to the development of a rash; we did not wish to discontinue anti-EGFR antibody therapy outright.

The patient performed well for 20 cycles (10.8 months) until CT showed worsening of the primary lesion and liver metastases. The patient then received FOLFIRI plus bevacizumab as a third-line therapy; response lasted for nine cycles (4.8 months) until bone marrow metastasis progressed and leukoerythroblastosis and anemia relapsed, necessitating red blood cell transfusion. He died following the progression of the left pararenal gland metastasis, impairment of renal function, and uncontrollable hemorrhage 22.7 months after diagnosis and 16.6 months after commencing first-line therapy.

The patient's next of kin provided written informed consent for the publication of this case report.

Discussion

To our knowledge, no *KRAS*-wildtype rectal cancer patients with initial findings of bone marrow metastasis were previously reported to have survived long-term after responding to anti-EGFR antibody therapy combined with doublet chemotherapy (the standard treatment). Even if bone marrow metastasis causes clinical deterioration, such

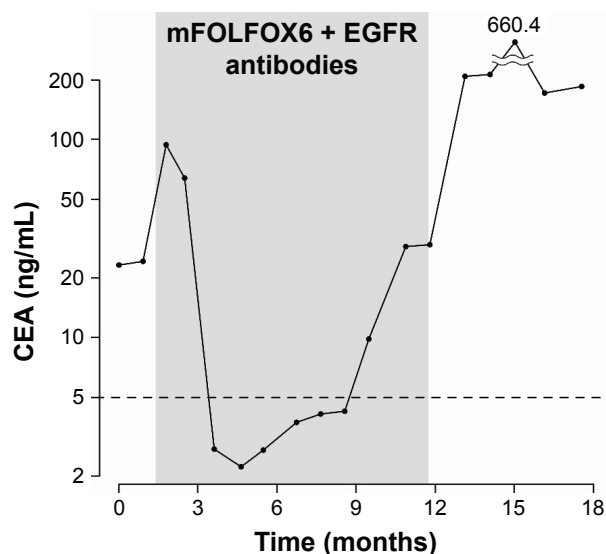


Figure 2 Changes in serum carcinoembryonic antigen levels. The time highlighted in gray corresponds to the period during which mFOLFOX6 + EGFR antibodies (three cycles of panitumumab and 17 cycles of cetuximab) were administered. The horizontal dotted line shows the cutoff level of serum CEA.

Abbreviations: mFOLFOX6, modified FOLFOX 6; EGFR, epidermal growth factor receptor; CEA, carcinoembryonic antigen.

patients are considered eligible for chemotherapy according to European Society for Medical Oncology consensus guidelines for colorectal cancer.⁸ There are several reports on the benefit of chemotherapy against metastatic colorectal cancer in the bone marrow.^{3–5} However, there is no English language literature reporting anti-EGFR antibody therapy to be effective against bone marrow metastasis of colon cancer. Clinical symptoms caused by bone marrow metastasis significantly improved following anti-EGFR antibody therapy in our patient, who survived for more than 22 months. A strong cytoreduction effect and early tumor shrinkage due to anti-EGFR antibody treatment have been observed in bone marrow metastases of *RAS*-wildtype colorectal cancers;⁹ we suspect that the favorable clinical response in our patient was likely due to such cytoreduction of the bone marrow metastatic lesion.

Our patient was a man with rectal cancer, and favorable response to treatment was expected^{10,11} as anti-EGFR antibody therapy shows relatively favorable response in *RAS*-wildtype colorectal cancer patients, especially men.¹⁰ Our patient provided an example of this notion being true even for cases with bone marrow metastasis that exhibit poor clinical features such as myelosuppression, hemorrhagic diathesis, and/or poor PS. Clinicians are often hesitant to administer chemotherapy to patients with bone marrow metastasis because of their poor prognoses and a high risk of rapid deterioration. In our case, no serious hematological or non-hematological adverse events occurred; peripheral blood findings improved (ie, leukoerythroblastosis disappeared), the rash was tolerable upon switching panitumumab to cetuximab, and peripheral neuropathy and fatigue were managed by reducing the dose (Table 1). It was unclear whether the uncontrollable hemorrhage that led to death was itself caused by hemorrhagic diathesis due to bone marrow metastasis, or was an adverse event following anti-vascular endothelial growth factor (VEGF) antibody administration. However, clinicians usually avoid administering anti-VEGF antibody to colorectal cancer patients with bone marrow metastasis if their conditions deteriorate, because life-threatening adverse events such as hemorrhagic or thromboembolic events as well as gastrointestinal perforation have been reported. Anti-EGFR antibody, which has milder adverse events whether administered alone or with other regimens, is recommended in patients with myelosuppression or poor PS owing to bone marrow metastasis when possible.

Conclusion

Anti-EGFR antibody therapy, with or without chemotherapy, appears to benefit colorectal cancer patients with bone marrow metastasis, for which the prognoses and general conditions tend to be poor. Moreover, patients likely to show a favorable response, namely, men with *RAS*-wildtype, ought to be considered for anti-EGFR antibody therapy, even for seemingly unfit cases.

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Disclosure

The authors declare no conflicts of interest in this work.

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