

Case Report**Leptomeningeal Metastasis from Colorectal Cancer Treated with Folinic Acid, Fluorouracil, and Oxaliplatin Chemotherapy Plus Bevacizumab: A Case Report**

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Leptomeningeal metastasis (LM) from colorectal cancer is rare. LM is characterized by rapid progression, making diagnosis and treatment challenging, and are associated with a poor prognosis. A 63-year-old man undergoing chemotherapy with bevacizumab for colorectal cancer was admitted to our hospital with loss of appetite. On admission, he experienced frequent episodes of loss of consciousness. Imaging to identify the underlying cause revealed no abnormalities. Cytological examination of cerebrospinal fluid confirmed LM. Because of worsening symptoms, the patient had difficulty communicating, thus preventing continuation of chemotherapy. He died at 3 weeks post-admission. In patients with cancer who exhibit central nervous system symptoms without abnormal imaging findings, LM should be considered even if the primary tumor is in the transverse colon. In such cases, cytological examination of cerebrospinal fluid and imaging studies should be conducted. This rare case of LM from colorectal cancer after resection and chemotherapy with molecularly targeted agents yielded insights that might guide future treatment strategies.

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Introduction

Leptomeningeal metastasis (LM), defined as malignant infiltration of the pia mater and arachnoid membrane, develops in approximately 5% of patients with cancer and has a poor prognosis and limited treatment options^{1–5}. Although rare, LM is increasingly being detected in patients with melanoma^{6,7}, lung cancer^{8–10}, and advanced breast cancer^{11,12}. However, in the few case reports that have described LM from colorectal cancer, all patients had poor outcomes.

Case Report

A 63-year-old man with no relevant medical history presented to Kamisu Saiseikai Hospital with constipation and appetite loss. Initial abdominal CT revealed colonic obstruction, which was treated with colonoscopic retrograde bowel drainage. Contrast-enhanced CT of the abdomen revealed wall-thickening in the transverse colon, with a narrowed lumen and multiple lymphadenopathies (**Figure 1A and 1B**). No liver or lung metastases were observed, but the para-aortic and supraclavicular lymph nodes were swollen. Colonoscopic biopsy revealed poorly differentiated adenocarcinoma of the transverse

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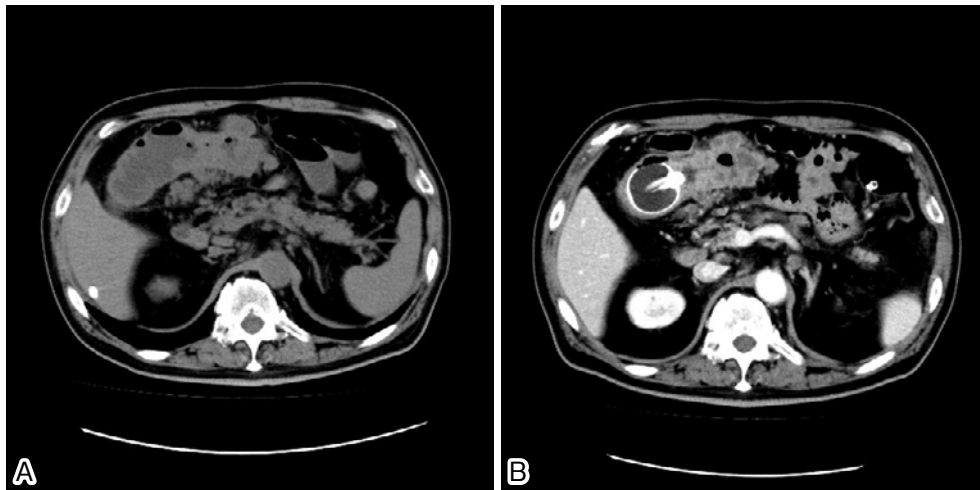


Figure 1 (A) Abdominal simple CT (B) and contrast-enhanced CT showing thickening of the transverse colon wall, with a narrowed lumen and multiple lymphadenopathies in the abdominal region

colon. His preoperative carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were elevated: 62.9 ng/mL (normal: <5 U/mL) and 1,995.8 U/mL (normal: <37 U/mL), respectively. He was diagnosed with T4aN2bM1b stage IVB (UICC for International Cancer Control TNM classification) poorly differentiated adenocarcinoma of the transverse colon and underwent palliative partial colectomy (**Figure 2A and 2B**). Further analysis revealed wild-type *RAS*, mutant *BRAF*, and heterozygous *UGT1A1* in the tumor tissue. He received 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX) plus bevacizumab chemotherapy. After four cycles of chemotherapy, the para-aortic and subclavian lymph node metastases showed a partial response according to the guidelines for evaluating the response to treatment of solid tumors (**Figure 3C and 3D**). Both CEA and CA19-9 levels decreased to levels below those before chemotherapy (2.4 and 25.2 U/mL, respectively).

After six cycles of chemotherapy, the patient was admitted to our hospital for general fatigue and anorexia; he was conscious, showed no signs of meningeal irritation, and was ambulatory. On day 6 after admission, he lost consciousness for a few minutes, with no headache or vomiting after regaining consciousness. Thereafter, the frequency and duration of loss of consciousness increased, and his activities progressively worsened. Serum CEA and CA19-9 were markedly elevated at 14.6 and 3,299.8 U/mL, respectively, but laboratory tests showed no abnormalities that could explain his altered consciousness. Chest and abdominal CT revealed no recurrence or metastasis of colorectal cancer, and brain CT and MRI findings showed no evidence of cerebral hemorrhage or

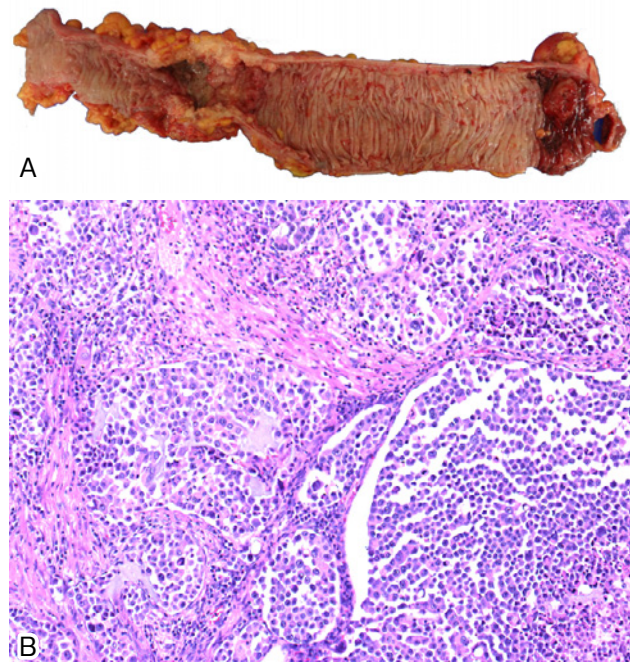


Figure 2 Representative histology of cancer of the transverse colon
(A) Surgical excision specimen containing the tumor. (B) High-magnification view (×100 magnification) showing the predominant histology of poorly differentiated adenocarcinoma in the transverse colon.

infarction. Contrast-enhanced CT (**Figure 4A**) and simple MRI (**Figure 4B**) did not suggest brain metastases, and there were no signs of hydrocephalus or ventricular enlargement. Electroencephalography revealed no specific findings. A lumbar puncture was performed, and cytopathology of the cerebrospinal fluid (CSF) revealed adenocarcinoma cells (**Figure 5**), indicating a rare type of me-

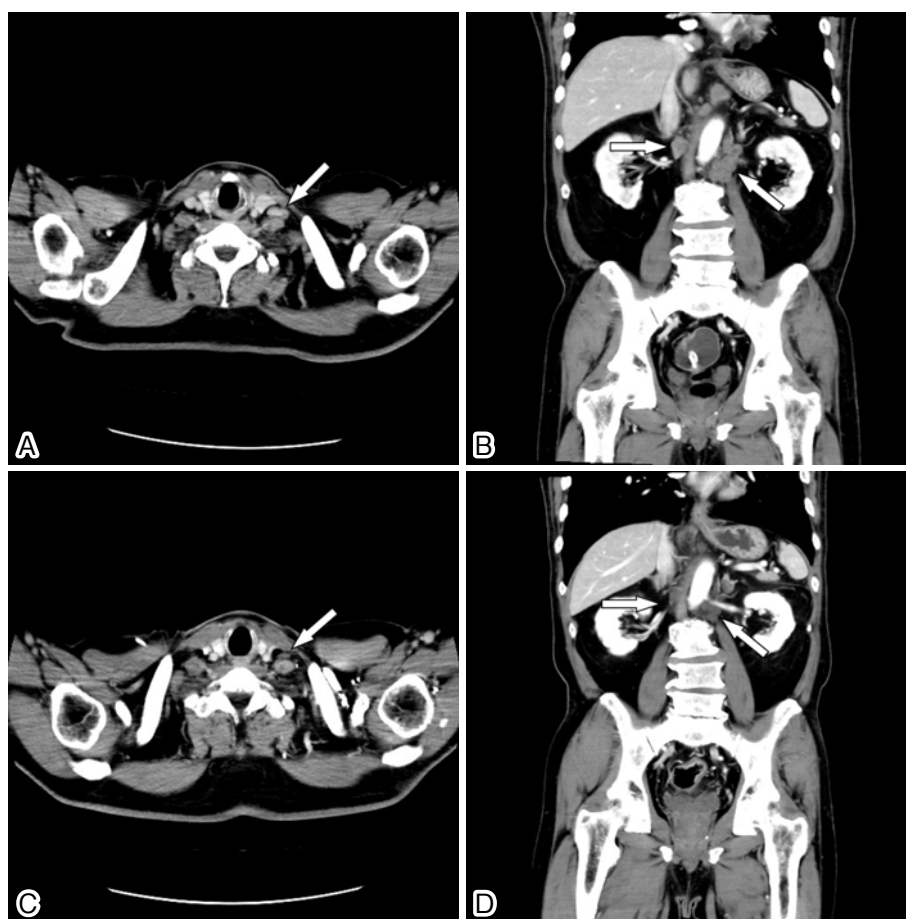


Figure 3 CT image comparison before (A, B) and after (C, D) chemotherapy (A, C) Subclavian lymph nodes and (B, D) para-aortic lymph nodes were smaller after four chemotherapy cycles than before treatment (arrows), indicating a partial response to chemotherapy.

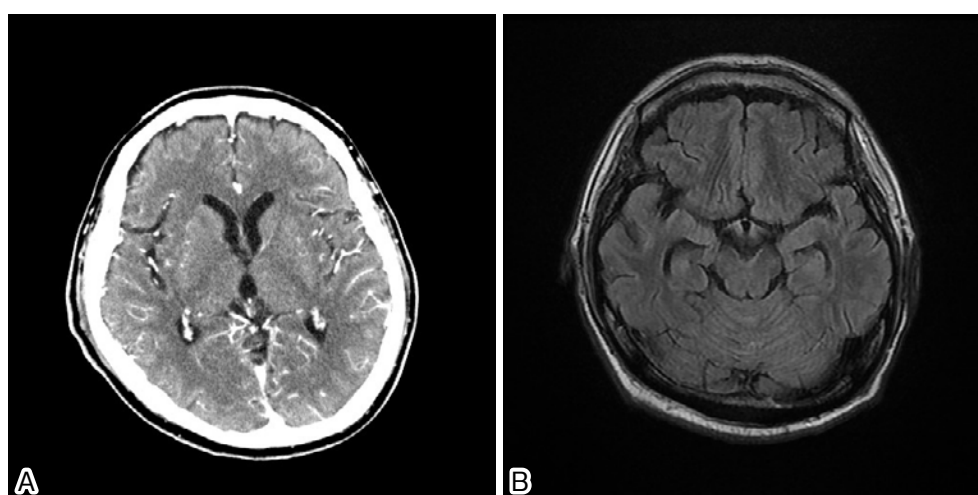


Figure 4 Head CT and MRI findings (A) Head contrast-enhanced CT showing no evidence of brain metastasis or findings suggestive of impaired cerebral spinal fluid (CSF) resorption. (B) Fluid-attenuated inversion recovery (FLAIR) MRI of the head showing no evidence of brain metastasis or hydrocephalus.

tastatic cancer. His level of consciousness and ability to communicate deteriorated, making it difficult to continue chemotherapy. Three weeks after admission to our hospital, the patient died of cachexia.

All procedures were performed in accordance with the principles of the 1964 Declaration of Helsinki and its

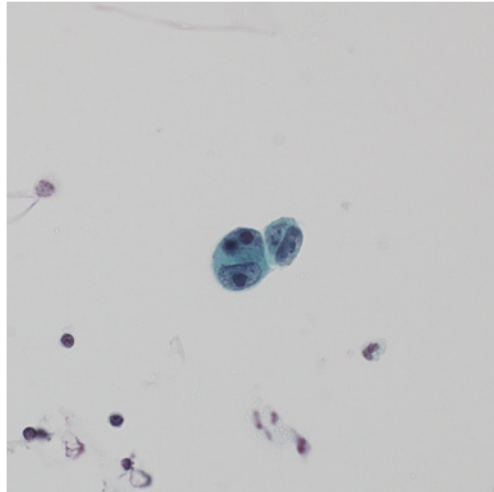


Figure 5 Cytology of cerebrospinal fluid showing atypical epithelial cells (×400)
Representative Papanicolaou staining of adenocarcinoma cells in cerebrospinal fluid.

later amendments. Informed consent was obtained from the patient's family for inclusion in the study.

Discussion

This rare case of LM originated from a poorly differentiated adenocarcinoma of the transverse colon. Studies published from January 2000 through December 2024 were reviewed by searching the Ichushi-Web database of the Japanese Medical Abstract Society (<http://login.jama.s.or.jp/>) and PubMed using "leptomeningeal metastasis" and "colorectal cancer" as key words. Case reports and full-text or abstract reviews were also included. Seventeen cases of LM from colorectal cancer, including our case, have been reported in the English literature (**Table 1**)^{13–28}. Retrospective reviews of medical records from a single institution were excluded because they lacked detailed information on the individual cases²⁹. Among the 17 reported patients, 70% were men, and the median age was 54 years (range, 25–77 years). Primary tumors were in the rectum (n = 5), sigmoid colon (n = 2), transverse colon (n = 4), right colon (n = 4), or unknown (n = 2). Analysis of tumor histology revealed signet ring cell carcinoma (n = 9), poorly differentiated adenocarcinoma (n = 4), and unknown type (n = 4). No well-

Table 1 Cases of leptomeningeal metastasis from colon cancer

No.	Authors	Sex	Age	Location	Pathology	Surgery	Chemotherapy	MRI	CSF	Survival	Genes
1	Nagashima et al. ¹³	M	59	A	por.	None	None	Abnormal	Positive	8 days	NA
2	Sartore-Bianchi et al. ¹⁴	M	43	R	por.	Performed	5-fluorouracil	NA	Positive	NA	NA
3	Suzuki et al. ¹⁵	F	60	R	por.	Performed	None	Abnormal	Positive	4 months	NA
4	Longo et al. ¹⁶	M	41	NA	sig.	Performed	FOLFOX	Abnormal	Negative	15 days	NA
5	Chadha et al. ¹⁷	F	45	C	sig.	Performed	FOLFILI	Abnormal	Positive	2 months	NA
6	Crncevic-Urek et al. ¹⁸	F	61	A	NA	NA	NA	Abnormal	Positive	NA	NA
7	Bruce et al. ¹⁹	M	65	R	NA	Performed	NA	Normal	Positive	NA	NA
8	Yildirim et al. ²⁰	M	58	T	sig.	Performed	5-fluorouracil	Abnormal	Positive	2 months	NA
9	Lahiri et al. ²¹	M	72	T	NA	None	None	Abnormal	Positive	19 days	NA
10	Kato et al. ²²	F	77	NA	NA	None	None	Abnormal	Positive	6 weeks	NA
11	Kleinfeld et al. ²³	M	49	T	sig.	None	None	Abnormal	Positive	6 weeks	NA
12	Mohebi et al. ²⁴	M	50	S	sig.	Performed	FOLFOX	Abnormal	Negative	3 weeks	NA
13	Assi et al. ²⁵	M	54	S	sig.	Performed	FOLFOX	Abnormal	Positive	6 weeks	NA
14	Lusilla and de Tomas ²⁶	M	25	R	sig.	Performed	NA	Abnormal	Positive	11 months	NA
15	Zeeneldin et al. ²⁷	M	42	R	sig.	None	CapeOX	Abnormal	None	3 weeks	NA
16	Smilde et al. ²⁸	F	51	A	sig.	None	CapeOX plus Bmab	Abnormal	Positive	11 months	BRAF-mutation
17	Hayakawa et al.	M	63	T	por.	Performed	FOLFOX plus Bmab	Normal	Positive	3 weeks	BRAF-mutation

por.: poorly differentiated adenocarcinoma; sig: signet ring cell carcinoma; Bmab: bevacizumab; CapeOX: capecitabine and oxaliplatin; CSF: cerebral spinal fluid; FOLFILI: 5-fluorouracil, folinic acid, and irinotecan; FOLFOX: 5-fluorouracil, folinic acid, and oxaliplatin; MRI: magnetic resonance imaging; NA: Not applicable.

differentiated or moderately differentiated adenocarcinomas were reported. Signet ring cell carcinoma may be an independent histological type of colorectal cancer, with a different biological behavior and molecular profile from highly/moderately differentiated adenocarcinomas^{30–33}. In the reported LM cases, the most common primary histology was signet ring cell carcinoma. Ten patients underwent primary tumor resection and nine received chemotherapy before the diagnosis of LM. Outcomes for LM originating from colorectal cancer were poor (median survival time, 7 weeks from onset of neurological symptoms).

Several mechanisms are believed to be involved in LM pathophysiology but have not been examined systematically⁵. Because of its poor prognosis, early diagnosis and treatment is crucial and may improve activities of daily living and extend survival^{12,3,5,28,30}.

The gold standard for diagnosis includes CSF cytology or MRI^{34–36}. MRI showed no metastatic findings in brain parenchyma. Positive MRI findings were defined as those suggestive of LM, such as leptomeningeal linear enhancement, brain parenchyma enlargement, and cerebellum and cranial nerve enhancement (particularly VII and VIII), whereas positive CSF findings were defined as malignant cells in the CSF. MRI and CSF cytology showed diagnostic sensitivities of approximately 82% and 87%, respectively (Table 1). If either test result was positive, the diagnostic rate was set to 100%. In some cases, CSF cytology was negative (cases 4 and 12), for which detailed neurological and LM findings from MRI studies were sufficient for diagnosis³⁷. In such cases, contrast-enhanced rather than simple MRI was used. Retrospectively, simple head MRI alone was insufficient in our patient, and gadolinium-enhanced MRI should have been performed. However, gadolinium-enhanced MRI alone is insufficient; if either test result is positive, the diagnostic rate is 100% (Table 1). Therefore, both examinations must be performed to accurately diagnose LM.

Recently, systemic chemotherapy with molecularly targeted agents, including anti-vascular endothelial growth factor (VEGF) therapy, has been used for colorectal cancer and is based on the presence of *RAS* or *BRAF* mutations³⁸. The effectiveness of molecularly targeted agents for LM was confirmed in breast cancer, and systemic chemotherapy combined with anti-VEGF therapy may improve outcomes for patients with LM³⁹. Although chemotherapy with molecularly targeted agents is beneficial for patients with colorectal cancer with poor performance status⁴⁰, the efficacy of anti-VEGF therapy is unknown in

cases of LM from colorectal cancer. Genetic mutation testing was performed in two cases, including ours (cases 14 and 15 in Table 1). *BRAF* mutations, which are rare in colorectal cancer (approximately 6% of all advanced colorectal cancers), have also been detected. A meta-analysis of patients with *BRAF* mutation-positive colorectal cancer found that FOLFOX and bevacizumab chemotherapy was the optimal primary chemotherapy⁴¹, and this regimen was used in our patient.

In this rare case of LM with a rapidly fatal course after palliative resection of primary colorectal cancer, use of FOLFOX and bevacizumab chemotherapy reduced extramedullary lesions but not intramedullary lesions. Further clinical studies of LM from colorectal cancer should attempt to evaluate genetic mutations and the therapeutic effects of molecularly targeted agents.

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